Biomedical Seasonal Update
2024

SMART MAGAZINE

Join us in this collection of interdisciplinary excellence, propeliling transformative progress at the science crossroads.

ON-STREAM MEDICAL ACADEMY OF RESEARCH AND TRANSLATION

SCIENCE MAGAZINE

EFFICIENCY
ACCURATE
INFLUENTIAL

PRODUER
Cylina Wang

DESIGNER
Sally Tao, Grace, Ruby, Lyra, Sophie, Ariel

WRITER
Evelyn, Olivia, Chris, Molly, Derek, Seraphina, Ariana, Zeke, Dora, Kita, Nox

EDITOR
=Hecate, Amanda, Zeke, Yates,

The ENGLISH VERSION

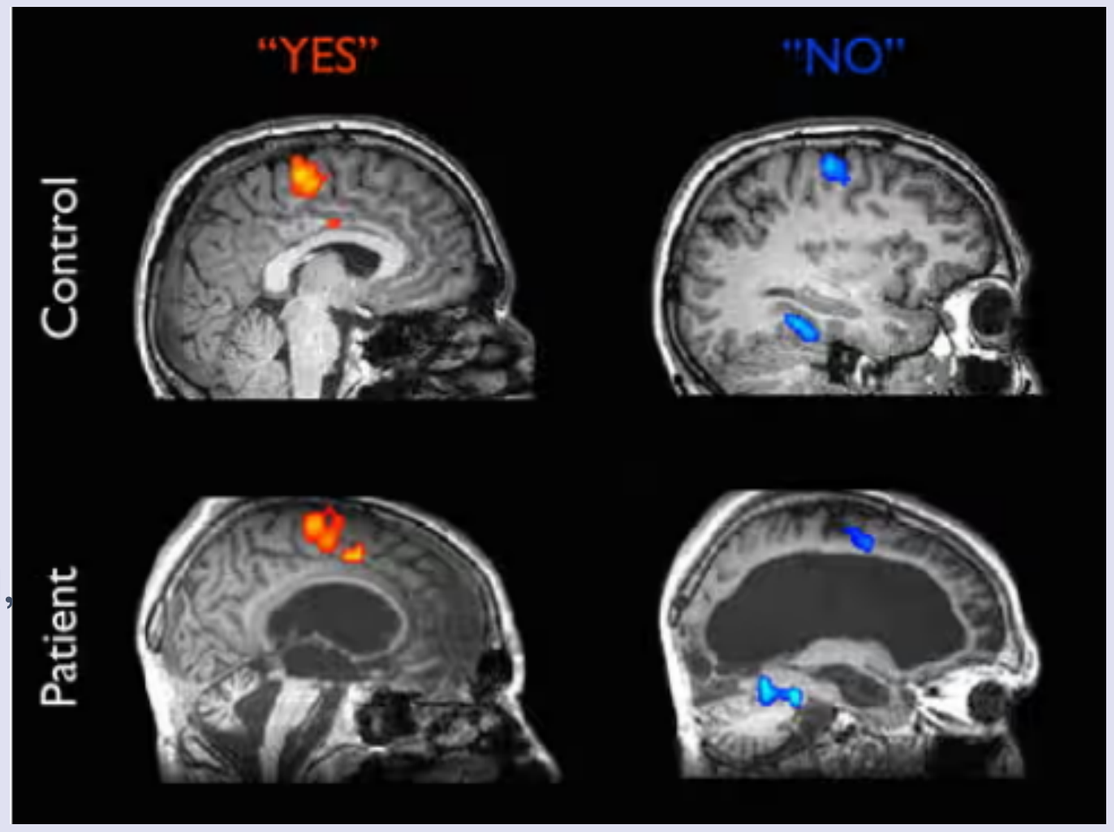
Chinese Version at the back

SMART MAGAZINE AUTHOR: Evelyn Yi EDITOR: Hecate Ye

Consciousness in the Vegetative State

Keywords: : vegetative state; conscious awareness; neuroimaging; fMRI; EEG

Introduction:



Might people in a vegetative state still be conscious? Since a vegetative state is often described as a state of "wakeful unconsciousness," the assumed answer is obviously no. The clinical differentiation between a vegetative state (no awareness) and a minimally conscious state (some awareness) suggests that those in a vegetative state should have no consciousness at all, otherwise they would be categorized as being in a minimally conscious state. However, since the diagnosis of the vegetative state is according to specific clinical criteria based on observable behaviors, there remains a possibility that patients who meet these guidelines might reserve consciousness that evades detection. In fact, in recent studies using advanced functional neuroimaging techniques, researchers discovered that a subset of patients diagnosed with a vegetative state do retain covert awareness.

What is the Vegetative State?

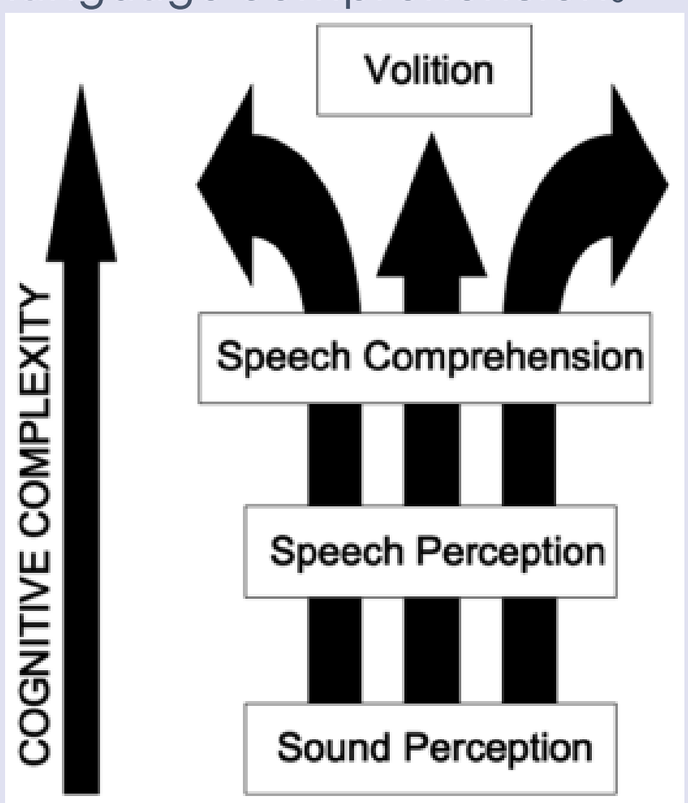
Unlike coma, the vegetative state (VS) is defined by the cyclic state of circadian sleeping and waking with an absence of volitional behavior and conscious awareness. Patients in a chronic vegetative state may exhibit complex reflexive behaviors such as eye movements, yawning, and involuntary responses to noxious stimuli (e.g., withdrawing a limb when experiencing pain) but lack consistent, purposeful responses indicating awareness of self and surroundings. A diagnosis is established once repeated examinations yield no evidence of persistent, volitional responses to visual, auditory, tactile, or noxious stimuli and no evidence of language comprehension or expressive capabilities.

A vegetative state is typically caused by severe brain damage, in which the cerebrum– the part of the brain responsible for higher cognitive functions like thinking, reasoning, voluntary behaviors, and information processing– becomes dysfunctional. Despite the loss of cerebral functions, the hypothalamus and brainstem remain operational, allowing autonomic, survival functions such as the regulation of breathing, heart rate, sleep-wake cycles, and body temperature. In contrast, coma often involves impairment in both the cerebrum and brainstem, limiting the patient's ability to perform autonomic functions without medical intervention.

Measures of Cognition in Vegetative State Patients

Functional neuroimaging, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), can be used to detect covert cognitive functions overlooked by standard clinical assessments. Studies using these neuroimaging techniques were able to confirm certain residual perceptual functions. For instance, researchers developed a series of hierarchical assessments progressing from the simplest form of auditory information processing to high-order cognitive functions in order to ascertain levels of cognition. At the most basic level, the paradigms assess sound perception by comparing responses to all auditory stimuli (speech + white noise) to silence. After sound perception is established, it evaluates speech perception by comparing speech stimuli to signal-correlated noise. The highest cognitive level measures speech comprehension, indicated by comparing ambiguous and unambiguous sentences (e.g., "the creak/creek came from a beam in the ceiling/sealing" is compared to "her secrets were written in her diary") (Owen et al.).

Utilizing this approach, a study of a group of seven vegetative patients found that three of the patients exhibited speech-processing functions, two of which displayed significant responses to the semantic ambiguous comparisons, suggesting higher-order processing of the semantic aspects of language comprehension。



It is important to note, however, that the presence of higher cognitive functioning is the exception rather than the rule in vegetative patients. Larger cohort studies, for instance, illustrated that most vegetative patients only retain the most basic level of sensory processing while higher-level processing areas critical for perception and conscious experience, such as the secondary somatosensory cortex, insular cortex, posterior parietal cortex, or anterior cingulate cortex, remain inactive. Additionally, these brain responses might still be automatic neural responses without warranting conscious awareness. Hence, whether evidence of linguistic processing in these vegetative state patients sufficiently suggests conscious awareness is unclear without knowing how the brain responds to similar stimuli in normal individuals.

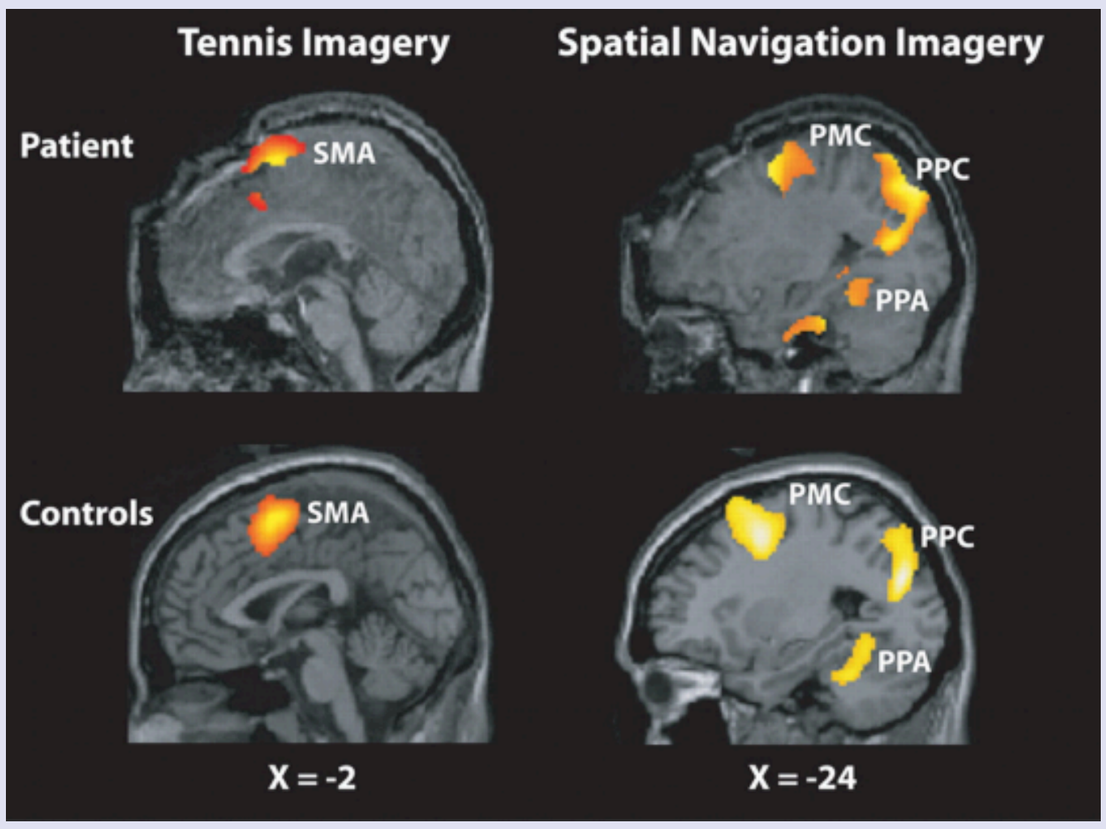
Measures of Cognition in Healthy Individuals

To investigate the relationship between consciousness and higher linguistic processing in healthy subjects, Davis and colleagues studied a group of healthy individuals under different levels of sedation (awake, lightly sedated, and deeply sedated). The volunteers were scanned while listening to: 1) Sentences with ambiguous words. 2) Sentences without ambiguous words. 3) Structured noises that correlated with the sentences. The study found that brain activities related to speech perception were present in volunteers at all three levels of sedation, indicating its imperviousness to sedation. However, on the other hand, additional inferior frontal and posterior temporal responses, linked to language comprehenssion, were absent in even light sedation. Since semantic processing seems to be observed only in volunteers who are awake, it thus can be inferred that vegetative state patients who display similar brain activation associated with semantic processing are consciously aware.

Conveying Consciousness Through fMRI

Still, the most robust way of affirming one's consciousness is tied to their ability to communicate awareness through spoken or recognizable behavioral signs (e.g., blinking an eye to indicate "yes" or "no"). As verbal and behavioral responses in vegetative state individuals are either not possible or inconsistent, researchers devised ways to elicit nonverbal responses via the expression of brain signals.

In neuroscientist Dr. Adrian Owen's study, a patient who sustained an injury in a traffic accident demonstrated behavior consistent with a vegetative state, such as spontaneous eye-opening, sleep/wake cycles, inconsistent reflexive behaviors, and no voluntary motor responses. The patient was instructed to perform two mental tasks: "Imagine playing tennis" or "Imagine visiting the rooms in your home." These tasks were selected because they involve the activation of distinct brain regions. For example, imagining tennis activates the supplementary motor area, while visualizing movement through a house activates areas such as the parahippocampal cortex. Because they are easily distinguishable from one another, these tasks are identified as "neural markers" to ascertain the subject's ability to "understand instructions, to remember those instructions (from the prescan instruction period), and to carry out specific and highly constrained mental tasks in response to those instructions", representing direct, voluntary responses to external stimuli (Owen et al.).



Going a step further, in later studies, Dr. Owen successfully established a two-way communication between doctor and patient by designating “imagine visiting your home” to mean "yes," and “playing tennis” to mean "no”. Communicating with Scott Routley, a patient diagnosed with a vegetative state ten years ago and previously evinced no sign of awareness of his surroundings, Dr. Owen managed to obtain conscious responses. Owen started by asking simple questions such as "Is the sky blue?" and "Is the sky yellow?", to demonstrate Routley’s comprehension of the question and ability to respond. Then, Owen proceeded to ask whether Routley was in pain, to which Routley responded by imagining playing tennis, indicating he was not in pain.

Alternative Approach

An alternative approach to investigating covert consciousness in vegetative patients is through electroencephalography (EEG) to detect their ability to follow commands. A study in 2010 aimed to explore whether some patients, despite appearing entirely unresponsive, could exhibit signs of awareness through brain activity. Patients engaged in EEG tasks consisting of two types of motor imagery: imagining squeezing their right hand into a fist and wiggling their toes. Each task began with auditory instructions, such as: “Every time you hear a beep, try to imagine that you are squeezing your right hand into a fist and then relaxing it/wiggling all of the toes on both your feet, and then relaxing them. Concentrate on the way your muscles would feel if you were really performing this movement.” (Cruse et al.). The instructions are followed by a series of auditory cues that signaled when to start imagining the movements. Healthy controls engaged in the same tasks but were instructed to mind-wander instead of actively following commands, providing a baseline against which the patient’s EEG activities were assessed. As a result, 3 out of the 16 patients (19%) were able to follow commands to a statistically significant degree. The study's findings demonstrated that a notable portion of the tested patients diagnosed as being in a vegetative state exhibited covert awareness by successfully modulating their EEG responses to commands, despite showing no overt signs of awareness.

Conclusion

While most patients in a vegetative state lack any signs of conscious awareness, recent studies nevertheless underscore the necessity of going beyond traditional clinical evaluations when determining a patient's true state of consciousness. The implications of this discovery are significant, highlighting the need for advanced diagnostic techniques that can detect subtle signs of awareness in patients previously deemed vegetative. By refining our approach to assess consciousness, we can better understand the experiences of these patients and ensure they receive appropriate care and support.

References

Coleman, M. R., Rodd, J. M., Davis, M. H., Johnsrude, I. S., Menon, D. K., Pickard, J. D., & Owen, A. M. (2007). Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. Brain : a journal of neurology, 130(Pt 10), 2494–2507. https://doi.org/10.1093/brain/awm170 Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T. A., Fernández-Espejo, D., Pickard, J. D., Laureys, S., & Owen, A. M. (2011). Bedside detection of awareness in the vegetative state: A cohort study. The Lancet, 378(9800), 2088–2094. https://doi.org/10.1016/S0140-6736(11)61224-5 Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. Science (New York, N.Y.), 313(5792), 1402. https://doi.org/10.1126/science.1130197 Shea, N., & Bayne, T. (2010). The Vegetative State and the Science of Consciousness. The British journal for the philosophy of science, 61(3), 459–484. https://doi.org/10.1093/bjps/axp04

SMART MAGAZINE AUTHOR: Olivia Qian EDITOR: Amanda

Advances in the Study of Bird Language

Keywords: Birds, Language, AI, Earth Species Project (ESP)

Abstract:

This article explores the connections between bird songs and behaviors revealed by millions of bird song data collected by scientists.

Background Information:

ESP is a non-profit organization dedicated to "decoding non-human communication using artificial intelligence." Current research subjects at ESP include the zebra finch, crows, and beluga whales.

Bird songs are divided into songs and calls, with varying lengths and onomatopoeic terms such as “tseets”, “chirrups,” “ rreeyoos,” “ seeew-soooos,” etc.

Kleindorfer, during her undergraduate studies, was taught the traditional view that only male songbirds sing while females do not. However, later in her career, she discovered that the songs of female songbirds are as complex as those of males, a finding that overturned her early education. Since then, she has dedicated her research to overlooked or lesser-known bird calls.

Scientists have collected millions of bird call and behavior relationship data, using AI algorithms to study the patterns in the data. They have found that bird language is more complex than previously thought by humans, capable of learning, imitating, understanding grammar, and possessing thinking abilities.

I. The Complexity of Bird Language

Birds sing to attract mates or defend territories, but they also communicate about predators, the location of food, and more. The greylag goose has at least ten different calls, while the tit has a vocabulary of over two hundred types.

II. Birds Can Learn Language

The Superb Fairy Wren, a monogamous bird species that collectively raises young, was studied by Kleindorfer's team, who installed cameras and microphones in their nests. They found that female birds emit a lullaby-like call while brooding, which might attract predators. Further comparison of the hatching calls with the begging calls of the chicks revealed that each begging call matches an element in the mother's brooding call, indicating that chicks begin to learn their mother's language while still in the egg, overturning traditional theories of songbird learning.

Kleindorfer's team also found that each bird family has its unique "dialect" (), and chicks learn these unique calls from their parents. Chicks learn the unique call units of each parent and avoid learning the shared call units, which s them maintain family connections while developincharacteristics.

III. Birds Possess Abstract Thinking Abilities

Scholar Toshitaka Suzuki's research indicates that birds are not just reacting to specific sounds; they seem able to form abstract concepts.

Suzuki designed an experiment that played different calls with actions to test the birds' reactions. His experiment was inspired by ability to recognize specific shapes from vague images, such as imagining shapes in clouds. In the experiment, only when Suzuki played the snake's call and moved a stick like a snake did the birds react as if facing a real threat, indicating they might have a basic concept of a snake. Suzuki's finding emphasizes the birds' potential ability to form mental images.

IV. Birds Understand Grammar

In a 2023 study, Suzuki found that tits are sensitive to the order of calls, such as having different

different reactions to ABCD and DABC calls, even if they contain the same elements. Similar results were obtained in studies on southern pied babblers and chestnut-crowned babblers, suggesting that bird language may have some grammatical rules.

V. Birds Use Symbolic Gestures

Suzuki observed that female tits make a gesture like "after you" with their wings when entering the nest, which seems to be a sophisticated syntax. In Suzuki's view, the wing-flapping action is not just a simple indication but a symbolic gesture. This non-vocal form of communication suggests that birds may also use symbolic gestures to communicate.

VI. Birds Mimic and Deceive

In an unremarkable grove, Maddie Cusimano noticed a kingfisher diving to catch fish while a young eagle perched on a bare tree. In this area, a call resembling that of a red-tailed hawk repeatedly sounded, but soon they realized it was a jay imitating the hawk's call. Researchers say they sometimes do this, possibly to scare away other predators, but the exact reason for vocal mimicry is still unknown.

Comparison of Bird Language and Human Language:

Although bird language shows complexity and diversity, it is far from comparable to human language:

1. Limited Recursion: Linguist Chomsky believes recursion is the core characteristic of human language, allowing us to express complex meanings. Bird language has not shown this ability for infinite recursion; their call combinations are relatively simple, and the meanings they are more limited.

2. Complexity of Cultural Inheritance: The inheritance of bird language is far less complex than human language. The cultural inheritance of human language relies on social structures, education systems, and written records, while the cultural inheritance of birds mainly depends on imitation and learning.

3. Lack of Metalinguistic Ability: Humans can use language to talk about language itself. We can analyze structure, meaning, and function and define and explain language using language.

Related Research:

- Advances in Neuroscience: Scientists have begun to use advanced technology to study how bird brains process and produce .
- Learning and Genetics of Song: Scientists have found that bird song has genetic and learned components, challenging traditional views of animal learning abilities.
- Social Function of Song: Bird not only for attracting mates; they also use it to mark territories and warn companions.

Specific Subject

Interdisciplinary: The article emphasizes the importance of interdisciplinary research in decoding bird , including cooperation in neuroscience, behavioral science, artificial intelligence, and more.

Conclusion:

This article reveals the complexity of bird language and compares it with human language, pointing out the differences between the two. Bird life is not devoid of emotion; much thought and language are hidden deep and are difficult for humans to understand. This research not only redefines our view of bird intelligence but also reminds us to respect and explore with curiosity the creatures we share the Earth with. We should listen to the voices of birds and rethink this vast biological world.

References:

https://www.newyorker.com/magazine/2024/10/21/how-scientists-started-to-decode-birdsong

SMART MAGAZINE AUTHOR: Chris TRANSLATOR: Lunette EDITOR: Hecate

Alzheimer's Disease: Understanding Dementia in the Elderly

Introduction:

Alzheimer's Disease (AD) is characterized by cognitive decline, initially manifesting as memory loss, particularly the forgetting of recent conversations and time, along with a decrease in orientation and calculation abilities. Patients may feel confused in familiar environments, and their perception of time becomes distorted. As the disease progresses, language abilities are often impaired. Patients may struggle to find appropriate words, experience speech interruptions, repetition, or difficulty with naming, all of which severely affect daily communication. Spatial cognition is also a challenge; patients may get lost in familiar places or encounter difficulties performing tasks that require spatial understanding, such as assembling furniture or interpreting maps, thus increasing safety risks. Emotional and behavioral abnormalities are common, with patients experiencing unexplained mood swings, anxiety, depression, and even hallucinations or delusions, which negatively impact their mental state and behavior. As the disease worsens, patients may lose the ability to perform basic self-care tasks, such as dressing, eating, and toileting, significantly reducing their quality of life and placing a heavy burden on family members and caregivers. This condition primarily affects individuals over the age of 60.

Abstract

A lzheimer's Disease (AD) is a progressive neurodegenerative disorder primarily marked by the decline of learning and memory functions. The disease is most common in the elderly, although there is a rising trend in younger onset. AD has a slow onset and insidious progression, leading to the gradual loss of the ability to live independently and significantly threatening the health and life of affected individuals. This article will discuss the pathology of Alzheimer's Disease, treatment methods, and the research progress on multi-target drug development for AD.

First Aspect – Pathology of Alzheimer's Disease

Animal and computational models of Alzheimer's Disease (AD) indicate that early amyloid-β (Aβ) deposition promotes neuronal hyperactivity, while subsequent tau deposition has an inhibitory effect as behavioral deficits manifest.

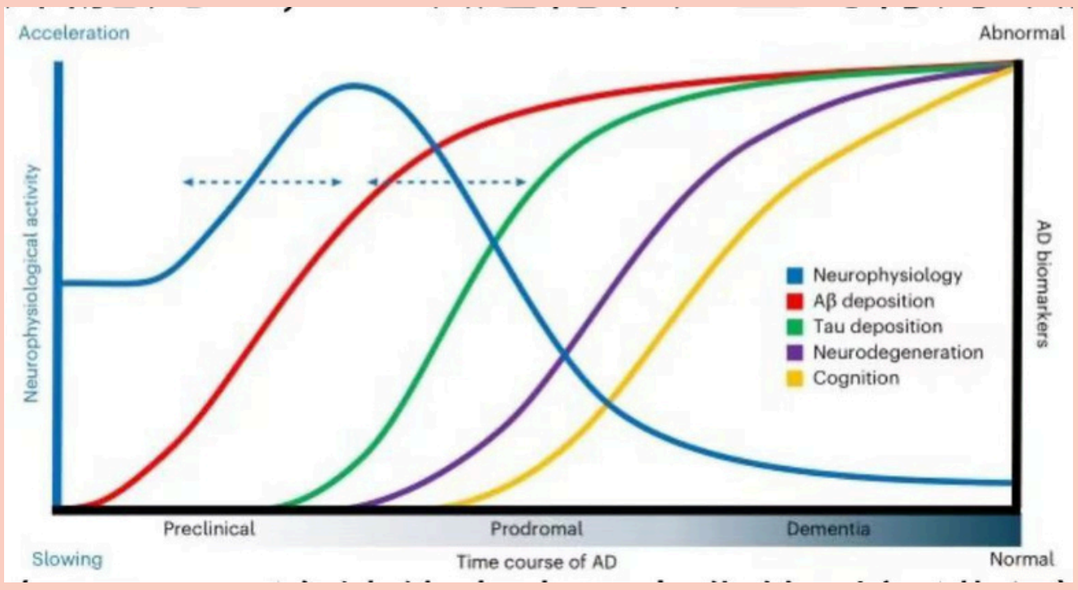
Aβ Plaque Deposition and Tau Accumulation

The key pathological features of AD are the accumulation of β-amyloid (Aβ) plaques and hyperphosphorylated tau protein tangles in the brain. Aβ plaque deposition can begin up to 20 years before symptoms appear, with recent accumulation occurring in high-metabolism cortical regions such as the precuneus, medial orbitofrontal cortex, and posterior cingulate cortex, gradually spreading to the entire neocortex, brainstem, and subcortical nuclei. Tau deposition initially accumulates in the entorhinal cortex, then spreads to limbic areas and eventually to the neocortex.

A potential mechanism underlying these harmful effects is that the combined accumulation of Aβ and tau proteins alters neural physiological signals, triggering a cascade of pathological processes that accelerate disease progression. Animal models suggest that Aβ induces neuronal hyperactivity, thereby exacerbating Aβ pathology itself. This positive feedback loop promotes tau pathology accumulation and propagation, leading to a shift in neuronal activity toward a relatively low-activity state. At this stage, neuronal activity significantly diminishes, ultimately resulting in cell death, tissue degradation, and severe behavioral changes.

Early Aβ and tau deposition may cause causal effects by disrupting the excitatory /inhibitory balance of local neuronal networks, which in turn alters the macroscopic neural physiological spectrum of the entire brain. In the later stages of the disease, the accumulation of Aβ and tau proteins leads to a shift in neuronal activity from high to low, manifesting as a U-shaped curve in the α-band activity across the AD continuum.

(Figure 1: Temporal progression of pathological changes in the AD continuum)



Studies on asymptomatic elderly individuals with a sporadic family history of AD using millisecond-scale MEG source imaging and whole-brain quantification of Aβ and tau protein with PET imaging show that early Aβ deposition is associated with excessive neural activity in macroscopic brain physiology, represented by increased α-band activity and decreased δ-band activity. In individuals with early temporal lobe tau pathology, these effects transition from accelerated oscillations to slower rhythms, marked by a decrease in α-band and an increase in δ-band activity. This transition in neural dynamics correlates with longitudinal cognitive decline.

Neurophysiological changes in brain dynamics widely affect the cortex, extending beyond the middle temporal lobe, and may be an early sign of the widespread slowing observed in later AD stages. This change in neural dynamics is fundamentally driven by rhythmic brain activity rather than by broad-band arrhythmic background activity.

Cholinergic Neuron Selective Degeneration

Cholinergic neurons secrete nerve growth factor (NGF), which has trophic effects on maintaining the basal forebrain cholinergic system. However, Aβ pathological deposits disrupt NGF metabolism, leading to decreased production of mature NGF, accumulation of NGF precursors, and reduced expression of the TrkA receptor (NGF receptor). This leads to synaptic atrophy of basal forebrain neurons, cholinergic system dysfunction, and exacerbation of Aβ and P-Tau pathology. In the early stages of AD, cholinergic synapses in the cortex and hippocampus decrease, leading to progressive loss of memory, particularly episodic memory.

Neuroinflammation

Microglia, the resident macrophages of the central nervous system, participate in neuroinflammation. When Aβ accumulates beyond a threshold, microglial cells' physiological functions of surveillance and remodeling are weakened, leading to chronic inflammation and a positive feedback loop in Aβ processing. This causes continuous accumulation of Aβ and neuronal debris. Activated M1 microglia produce pro-inflammatory cytokines and chemokines, establishing a persistent and unresolved inflammatory state.

Second Aspect – Treatment of Alzheimer's Disease

In the early stages of Alzheimer's Disease (AD), pericytes constrict capillaries, increasing hydraulic resistance and capturing immune cells, thereby reducing cerebral blood flow (CBF). Currently, no treatments exist to alleviate the pericyte-mediated constriction in AD. In the disease progression, early use of nimodipine to block Cav channels improves CBF, reduces the stasis of white blood cells in pericytes, and alleviates brain hypoxia. Cav channel blockade also significantly reduces Aβ-induced pericyte contraction in human cortical tissues. Thus, reducing pericytes in early AD may provide a therapeutic strategy to enhance brain energy supply and cognitive function.

Inhibition of Pericyte Contraction and CBF Improvement in AD Models

Most AD therapies aim to remove Aβ plaques or prevent tau protein hyperphosphorylation, but they fail to halt cognitive decline. One target of interest is cerebral blood flow (CBF), which is reduced by

approximately 45% in regions of the brain affected by AD, enough to cause attention loss, myelin breakdown, spatial memory deficits, and synapse loss. The reduction in CBF is associated with increased heterogeneity of capillary transit times, exacerbating tissue hypoxia. Early reductions in CBF in AD models suggest that changes in blood flow have a causal impact on early cognitive changes, occurring faster than Aβ or tau deposition and correlating with cognitive decline.

In human AD, this reduction in CBF is related to the contraction of pericytes, potentially reflecting Aβ-induced production of reactive oxygen species (ROS), which releases the vasoconstrictor endothelin-1 (ET-1).

Pericyte Contraction Mechanism

Pericyte contraction is induced by an increase in intracellular calcium levels or activation of the Rho kinase pathway. Pericyte contraction reduces CBF through three mechanisms: firstly, by narrowing capillary diameter, which increases resistance according to Poiseuille's law; secondly, by promoting interactions between blood cells and the vessel wall, increasing blood viscosity; and thirdly, by trapping blood cells in the narrowed capillaries, especially white blood cells, which are larger and less deformable than red blood cells.

Drugs that reduce pericyte contraction in AD may increase CBF by expanding capillary diameter, lowering blood viscosity, and preventing capillary blockages. These drugs could preserve normal neuronal function for longer and delay irreversible neuronal damage. In AD mouse models, nimodipine has been shown to reduce pericyte contraction, relax the capillary bed, expand capillaries, and reduce capillary obstruction caused by neutrophils and other cells. This results in improved CBF and reduced tissue hypoxia.

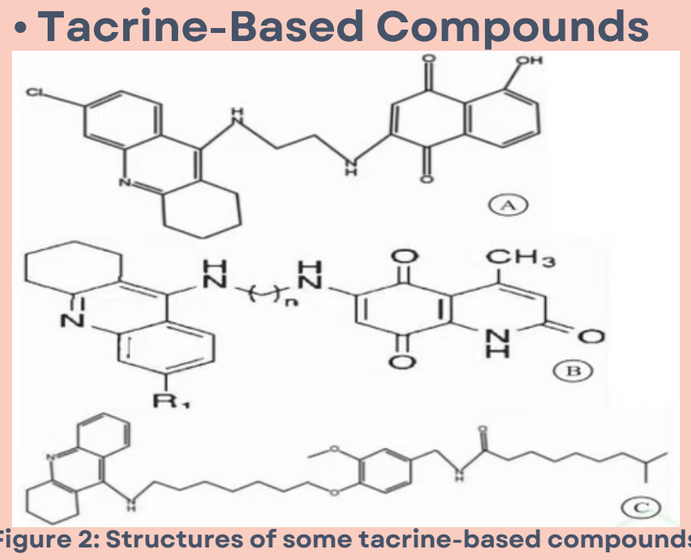
Third Aspect – Research Progress on Multi-Target Drugs for Alzheimer's Disease

Currently, the only approved drugs for the treatment of AD are cholinesterase (ChE) inhibitors (such as donepezil and galantamine) and N-methyl-D-aspartate (NMDA) receptor antagonists (such as memantine). However, clinical applications have shown that these drugs can alleviate symptoms but fail to effectively halt disease progression and may cause serious side effects such as hallucinations, dizziness, and liver toxicity, leading to poor long-term outcomes. In recent years, multi-target drugs have become an important approach in AD drug design due to their ability to target multiple pathological processes and disease pathways, balancing various pathological factors while minimizing side effects.

Multi-Target Drugs for Alzheimer's Disease

Multi-target drugs are typically identified through high-throughput screening of compound libraries or designed based on structure-activity relationships, pharmacophore modeling, protein structures, and endogenous ligands. These drugs target different disease mechanisms with a single molecule, offering advantages over single-target drugs and fixed-dose combination therapies.

- **Tacrine-Based Compounds**



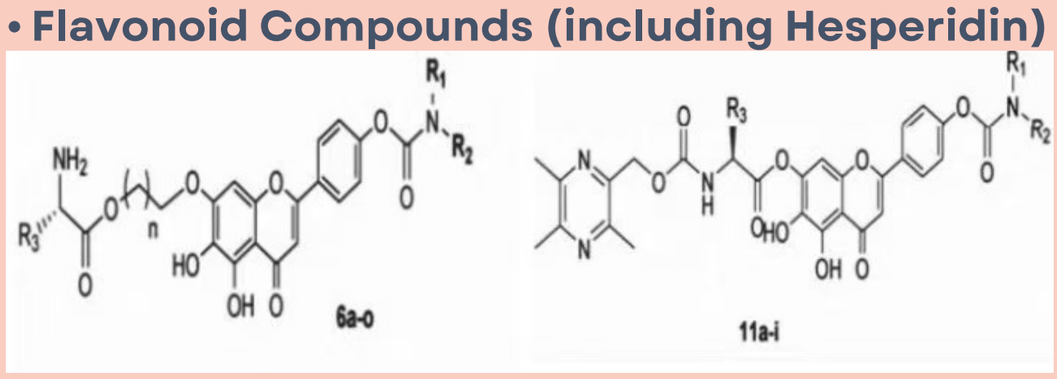
Note:
A. 5-Hydroxy-1,4-naphthoquinone-tacrine
B. Quinoline-2,5,8(1H)-quinolin-3-one-tacrine
C. Compound 5s

(Figure 2: Structures of some tacrine-based compounds)

- **Quinoline-Based Compounds (Iron Chelators)**

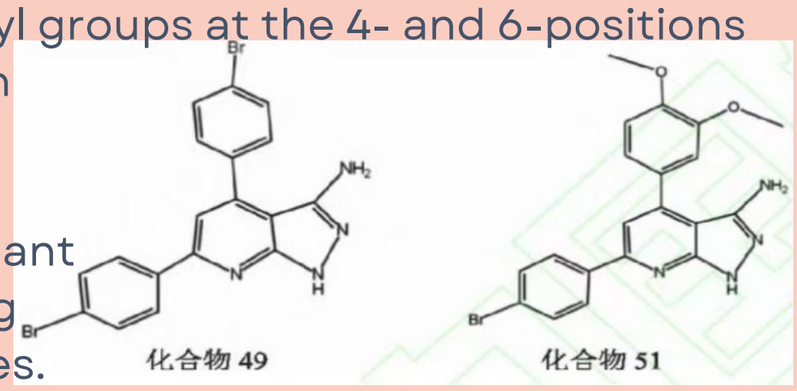
Iron accumulation and precipitation, along with iron-dependent oxidative stress, contribute to various neurodegenerative diseases. Metal chelators have the potential to prevent the generation of reactive oxygen species (ROS), oxidative stress, and Aβ peptide aggregation.

- **Flavonoid Compounds (including Hesperidin)**



- **Pyrazole-Pyridine Scaffold Compounds**

Researchers have synthesized a series of multi-target compounds based on pyrazole-pyridine scaffolds, modifying the phenyl groups at the 4- and 6-positions for active evaluation and toxicity testing. Compounds 49 and 51 exhibited significant activity in improving AD-related outcomes.

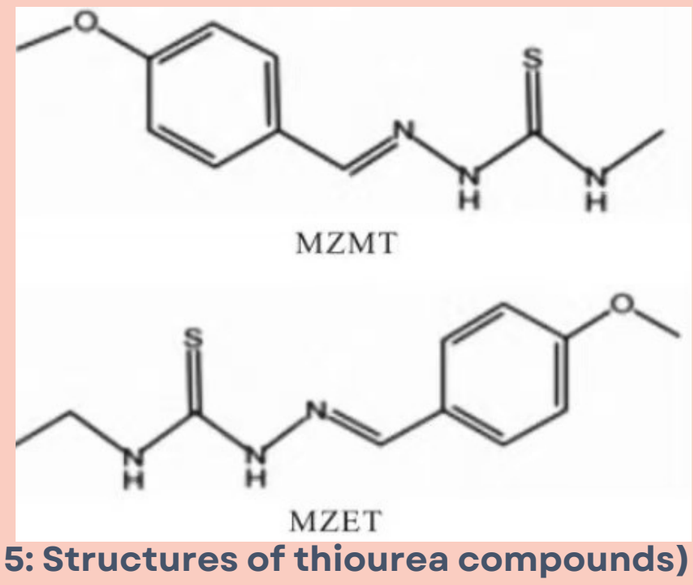


(Figure 4: Structures of compounds 49 and 51)

These compounds inhibit Aβ aggregation, prevent Aβ-induced neurotoxicity, and suppress tau protein hyperphosphorylation and neurofibrillary tangle formation by inhibiting GSK-3β. Furthermore, they have metal chelating properties, preventing oxidative damage in the AD brain, and possess good blood-brain barrier penetration, suggesting their potential as oral anti-AD drugs.

- **Thiourea Compounds**

Thiourea derivatives, due to their known pharmacological activities against Alzheimer's Disease (AD) and the metal chelating properties of thiourea-like analogs, serve as fundamental molecules in the design of multi-target drugs for AD. Some thiourea compounds have the ability to inhibit NMDA receptors, exhibit antioxidant properties, provide neuroprotection by counteracting reactive oxygen species (ROS), and promote the clearance of amyloid-β (Aβ) by enhancing autophagic activity.



(Figure 5: Structures of thiourea compounds)

- **Thiazolidinedione (TZD) Compounds**

Recent studies have shown that TZD compounds exhibit neuroprotective effects by inhibiting neural damage and atrophy, as well as suppressing inflammation. They possess high target specificity and act as PPARγ agonists. By antagonizing inflammation-related transcription factors and activating T cells, TZDs inhibit neuroinflammation. Clinical monitoring has also shown that TZDs regulate multiple AD-related pathological pathways, effectively suppress chronic inflammation, and protect neurons from damage.

- **Quinoline-O-carbamate Compounds**

Quinoline derivatives display broad biological activity, with some shown to possess cholinesterase inhibitory, antioxidant, and anti-inflammatory neuroprotective effects, and are currently undergoing clinical trials.

- **Carotenoid Compounds**

Carotenoid compounds, due to their conjugated polyene structure, exhibit unique pharmacological activities. As lipophilic molecules, they demonstrate strong antioxidant and anti-inflammatory properties, protecting the brain from oxidative stress, neuroinflammation, and mitochondrial

References

【1】 Jonathan Gallego-Rudolf，Alex I. Wiesman, Alexa Pichet Binette.2024,.Synergistic association of Aβ and tau pathology with cortical neurophysiology and cognitive decline in asymptomatic older adults.nature neuroscience.https://doi.org/10.1038/s41593-024-01763-8

【2】 Nils Korte, Anna Barkaway, Jack Wells.2024. Inhibiting Ca2+ channels in Alzheimer's disease model mice relaxes pericytes,improves cerebral blood flow and reduces immune cell stalling and hypoxia. https://doi.org/10.1038/s41593-024-01753-w

【3】 高晓娟.2024.阿尔兹海默症:认识老年痴呆症.山西科技报/2024年/5月/30日/第A03版

【4】 麻煜程,李汶阳,夏雨田.2024.阿尔兹海默病多靶点药物研究发展.https://link.cnki.net/urlid/51.1654.R.20240927.1743.002

【5】 王宇宇,朱丽,陈长梅.2024.药食同源物质抗阿尔兹海默症的作用及其机制.临床合理用药2024年9月10日第17卷25期

SMART MAGAZINE AUTHOR:Derek TRANSLATOR: Zeke EDITOR: Zeke

Indocyanine Green (ICG): A Versatile Near-Infrared Photosensitizer in Medicine

Indocyanine Green (ICG), a near-infrared (NIR) photosensitizer known for its excellent biocompatibility and biodegradability, has found widespread application as a fluorescent dye in medical fields. Its notable roles in photodynamic therapy (PDT) and photothermal therapy (PTT) have garnered significant attention. Both PDT and PTT are emerging tumor treatment strategies that have increasingly intrigued the scientific community. In these therapies, ICG demonstrates unique potential and mechanisms of action for tumor management.

When exposed to NIR light, ICG serves as a PDT fluorophore, producing reactive oxygen species (ROS) upon excitation to specifically damage tumor tissues. Simultaneously, ICG functions as a PTT absorber, converting absorbed light into thermal energy to induce hyperthermic effects. This dual action underscores its promising applications in cancer therapy.

Compared to other dyes, ICG boasts exceptional tissue penetration and lower photobleaching in the NIR spectrum, excelling in optical imaging-guided cancer and antimicrobial treatments. However, its clinical use is limited by challenges such as water instability, photostability, and multifunctionality. To address these limitations, researchers have focused on designing ICG-based composite nanomaterials, especially for oncology applications.

As a cyanine compound, ICG exhibits strong light absorption and fluorescence properties in the NIR range, primarily for cancer diagnosis and therapy. Intraoperative imaging with ICG enhances the precise identification of various solid and metastatic tumors. Additionally, ICG can induce cancer cell death through ROS generation or thermal effects. However, its water instability, photobleaching, photodegradation, and thermal degradation restrict its broader clinical adoption.

To overcome these hurdles, researchers have explored numerous formulations, including encapsulating ICG in inorganic and polymeric nanoparticles (NPs), liposomes, and hybrid cell membranes, to enhance therapeutic efficacy. Constructing ICG-containing delivery systems significantly improves stability, tumor targeting, and therapeutic outcomes. Over the years, diverse approaches have been employed to design ICG composite structures, aiming to enhance its biocompatibility and multifunctionality.

Since ICG's PDT, PTT, and imaging functionalities are all NIR light-activated, efficiently utilizing energy and optimizing these effects remain research priorities. Furthermore, integrating ICG-based nanoparticles into therapeutic platforms has brought new hope to cancer patients. With ongoing research, ICG and its derivatives are poised for even broader applications in oncology.

Amphiphilic Properties and Concentration-Dependent Optical Characteristics of ICG

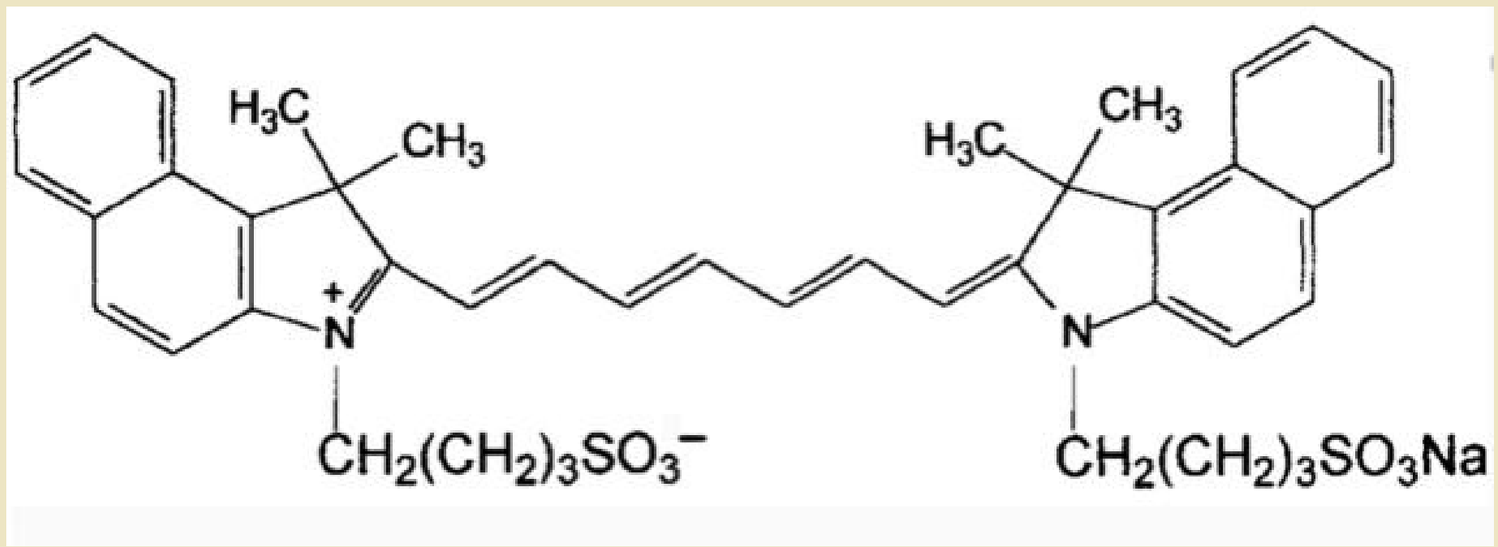
ICG is a unique amphiphilic molecule, exhibiting both hydrophilic and lipophilic properties. Its structure consists of two primary polycyclic components (benzindotricycin) that are inherently lipophilic and connected by a carbon chain. Each polycyclic unit carries a sulfonate group, conferring water solubility to the molecule. This amphiphilic structure enables ICG to interact strongly with hydrophilic and lipophilic substances such as phospholipids, significantly enhancing its fluorescence intensity in solution. These interactions further influence the fluorescence quantum yield of ICG.

At concentrations below 5 μM, ICG predominantly exists as monomers in solution. However, as the concentration increases–particularly beyond 100 μM–ICG molecules begin to aggregate. Monomeric ICG exhibits an absorption peak at approximately 785 nm, while aggregates show a peak near 690 nm. Notably, aggregated ICG (IJA) appears visually as deep green, contrasting with the pale green of monomeric ICG. Compared to monomers, IJA exhibits a redshift of approximately 100 nm in its spectral properties.

In various media, both IJA and ICG display a characteristic fluorescence peak at 892 nm. However, they differ in stability. IJA demonstrates greater water stability and exhibits minimal spectral fluctuations in response to changes in salt concentration compared to ICG. Under physiological conditions, intravenously administered ICG molecules tend to bind with plasma proteins or lipoproteins, forming stable aggregates. This aggregation causes a redshift of the primary absorption peak to approximately 805 nm or 810 nm, resulting in relatively stable spectral features.
These findings indicate that ICG molecules exhibit distinct optical and stability characteristics in aqueous solutions and when conjugated with proteins or lipids. Moreover, the fluorescence intensity of ICG varies significantly with concentration, providing a critical foundation for studying its concentration-dependent biological applications.

Clinical Applications of Indocyanine Green in Tumor Therapy

In photodynamic therapy (PDT), indocyanine green (ICG) generates reactive oxygen species (ROS) under near-infrared (NIR) light exposure, effectively inducing direct cytotoxicity in tumor cells.



Multiple clinical studies have demonstrated the efficacy of ICG-mediated PDT in improving survival rates for patients with colorectal cancer, breast cancer, lung cancer, and other malignancies.Clinical Applications of Indocyanine Green in Tumor Therapy
In photodynamic therapy (PDT), indocyanine green (ICG) generates reactive oxygen species (ROS) under near-infrared (NIR) light exposure, effectively inducing direct cytotoxicity in tumor cells. Multiple clinical studies have demonstrated the efficacy of ICG-mediated PDT in improving survival rates for patients with colorectal cancer, breast cancer, lung cancer, and other malignancies.
Additionally, ICG serves as a contrast agent in photothermal therapy (PTT), where it absorbs light energy and converts it into heat, producing localized thermal effects on tumor tissues. In treating malignant tumors such as hepatocellular carcinoma and pancreatic cancer, ICG-mediated PTT has shown high rates of local control and promising clinical outcomes.
To further enhance ICG's phototoxicity, researchers have investigated its combination with other photosensitizing agents. Zinc phthalocyanine (ZNPC), recognized for its efficient ROS production, has emerged as an ideal candidate for combination therapy with ICG. Chen et al. developed a carrier-free nanoprobe, ZNPC-ICG, using an ultrasound-assisted antisolvent precipitation method. They also created a biomimetic nanoprobe, ZNPC-ICG@RBC, by coating the nanostructure with red blood cell membranes. This system achieved optimal combined PDT and PTT effects with a single NIR laser exposure, significantly improving the physiological and optical stability of both ICG and ZNPC.

Despite these advances, rapid hepatic clearance of ICG remains a clinical limitation. To address this, Du et al. developed ICG-PEG45, the first NIR fluorophore cleared via renal tubular secretion. ICG-PEG45 selectively accumulates in renal tumors with low P-glycoprotein (P-gP) expression, enabling highly specific fluorescence detection. This approach not only offers a novel method for tumor diagnosis and therapy but also holds potential for integration with imaging modalities such as computed tomography (CT) to achieve comprehensive theranostics.
In summary, ICG exhibits immense potential in tumor therapy. However, further large-scale clinical trials and practical validation are necessary to ensure its safety and efficacy. With continued research, ICG is expected to play an increasingly vital role in oncology.

Safety Assessment of Indocyanine Green

As a photosensitizer commonly used in PDT and PTT, the safety of ICG is a key consideration. Its safety evaluation involves in vivo and in vitro toxicological assessments, long-term usage safety, and potential adverse effects on humans.

Numerous studies indicate that ICG is relatively safe when administered at appropriate doses. In vivo toxicological evaluations reveal that ICG only induces cellular damage under suitable light conditions, and standard in vitro doses generally do not harm normal cells. Moreover, long-term usage assessments suggest no significant toxicity to organs or systems.

However, adverse effects may occur under specific conditions. Overdosing or inappropriate light exposure can lead to skin burns, phototoxicity, and other side effects. Therefore, strict control of dosage and optimal light conditions are critical in clinical applications to minimize potential risks.

In conclusion, the safety of ICG in PDT and PTT depends on factors such as dosage and light exposure. While its use is relatively safe under proper conditions, clinical practices must emphasize monitoring and management to ensure safe and effective application.

Managing Side Effects of Indocyanine Green Therapy

Although ICG is widely applied as a photosensitizer in PDT and PTT, some side effects may arise during treatment, including skin burns, pain, pigmentation, and edema. These adverse effects can cause discomfort to patients and potentially impact treatment outcomes.

Several strategies have been proposed to mitigate these side effects. Medical staff should adhere strictly to treatment protocols, ensuring the correct use of ICG and patient safety. Pre-treatment assessments of patients' skin conditions and protective measures for vulnerable areas are essential. For specific side effects, targeted interventions such as cold compresses and topical medications can help manage skin burns.

In summary, while ICG is an important photosensitizer, potential side effects during treatment can be minimized through rigorous protocols, patient assessments, and appropriate management strategies, thereby ensuring patient safety and therapeutic efficacy.

Conclusion

ICG demonstrates broad application prospects in PDT and PTT. Literature reviews indicate that ICG generates ROS to induce oxidative stress and selectively kill tumor cells in PDT, while sparing surrounding healthy tissues, offering a favorable safety profile. In PTT, ICG effectively absorbs light energy and converts it into heat to elevate tumor tissue temperature, leading to tumor destruction. Thus, ICG holds significant therapeutic value in these cancer treatment modalities.

However, challenges remain in its clinical application. Issues such as drug delivery systems, biodistribution, and controlled release of ICG require further investigation. Additionally, the efficacy and safety of ICG for different tumor types need more robust clinical trials and validation. Future research should integrate advanced technologies and conduct in-depth studies on ICG's applications in PDT and PTT to provide more reliable evidence and support for clinical use.

Reference

[1] Yu B , Liu Q , Sun J ,et al.Phototherapy-based multifunctional nanoplatform for synergistic therapy against drug resistance bacteria: Progress, advances and challenges[J].Chemical Engineering Journal, 2024, 487.DOI:10.1016/j.cej.2024.150705.
[2] Wan Z , Mao H , Guo M ,et al.Highly Efficient Hierarchical Micelles Integrating Photothermal Therapy and Singlet Oxygen-Synergized Chemotherapy for Cancer Eradication[D].IVYSPRING INT PUBL,2014.
[3] H Lin,Z Lin,K Zheng,et al.Near-Infrared- II Nanomaterials for Fluorescence Imaging and Photodynamic Therapy[D].Advanced Optical Materials,2021
[7] G He,C Mei,C Chen,et al.Application and progress of nanozymes in antitumor therapy[D].International Journal of Biological Macromolecules,2024
[8] A S H , A C D B , A J W ,et al.Assemblies of indocyanine green and chemotherapeutic drug to cure established tumors by synergistic chemo-photo therapy - ScienceDirect[J].Journal of Controlled Release, 2020, 324:250-259.DOI:10.1016/j.jconrel.2020.05.018.
[9] TW Wong,SZ Liao,WC Ko,et al.Indocyanine Green-Mediated Photodynamic Therapy Reduces Methicillin-Resistant Staphylococcus aureus Drug Resistance[D].Journal of Clinical Medicine,2019
[10] Guan Wenchao,Gao Hongxia,Liu Yaqiong,et al.Application of magnetism in tissue regeneration: Recent progress and future prospects[D].,2024
[11] X Huang,J Wu,M He,et al.Combined Cancer Chemo-Photodynamic and Photothermal Therapy Based on ICG/PDA/TPZ-Loaded Nanoparticles.[D].Molecular Pharmaceutics,2019
[12] Q Zhang,X Wang,G Kuang,et al.Pt(IV) prodrug initiated microparticles from microfluidics for tumor chemo-, photothermal and photodynamic combination therapy[D].,2023
[13] C Huang,Z Zhang,Q Guo,et al.A Dual-Model Imaging Theragnostic System Based on Mesoporous Silica Nanoparticles for Enhanced Cancer Phototherapy[D].Advanced Healthcare Materials,2019
[14] Y Wang,NN Jin,J Zhang.Research progress of fullerene derivatives in photodynamic therapy[D].Applied Chemical Industry,2019
[15] FU Rong,C Yang,HU Yanyan,et al.Progress in preparation and application of core-shell structure nanocomposites with magnetism and fluorescence[D].Chemical Industry & Engineering Progress,2019
[16] Jingke Zhang,Hengxue Xiang,Zhiwei Cao,et al.Research Progress of Lignin-Derived Materials in Lithium/Sodium Ion Batteries[D].,2024
[17] Siqi Zheng,Min Bai.Application Progress of Ultrasound Elastography in the Evaluation of Diabetic Peripheral Neuropathy[D].,2024
[18] Y Chen,X Zhou,Y Li.Application and Progress of Microstructure and Mechanical properties Control Methods for Ultra-High Strength Steel in Rolling Process[D].Journal of Physics Conference,2020
[19] Yuhua Zhang,Lijie An,Jinli Shi,et al.Letter to the Editor Re: Research Progress of Music Therapy in Reducing Patient Pain Response and Its Intervention Effect Evaluation[D].,2024
[20] Xing-lu,PAN,Feng-shou,et al.Progress of the discovery, application, and control technologies of chemical pesticides in China - ScienceDirect[D].Journal of Integrative Agriculture,2019
[21] Jing Huang,Jinglan Yan,Taiyi Wang,et al.Research progress on central autonomic nervous mechanism of acupuncture at Neiguan point in the treatment of atrial fibrillation[D].,2023
[22] DR Sanchez-Ramirez,R Dominguez-Rios,J Juarez,et al.Biodegradable photoresponsive nanoparticles for chemo-, photothermal- and photodynamic therapy of ovarian cancer[D].Materials Science & Engineering C Materials for Biological Applications,2020
[23] Chen Jiang,Tianlong Ji,Qiao Qiao.Application and progress of artificial intelligence in radiation therapy dose prediction[D].,2024

SMART MAGAZINE AUTHOR:Molly Meng TRANSLATOR: Rick EDITOR: Amanda

The Physiological Mechanism of AgRP Neurons in Promoting Food Intake

Keywords: AgRP protein, food intake, temperature, paraventricular nucleus

Abstract

This article discusses how the expression of agouti-related protein (AgRP) in the hypothalamus effectively increases food intake, while neurons expressing calcitonin gene-related peptide (CGRP) in the paraventricular nucleus (PBN) effectively suppress appetite. The experiment demonstrated that by restricting food intake and using light stimulation, activation of AgRP neurons could be induced, overcoming the appetite-suppressing effects of amylin, cholecystokinin (CCK), and LiCl. This validated the hypothesis that AgRP neurons can overcome the appetite suppression caused by anorectic compounds and reduce the activity of PBN CGRP neurons.

Research Methods and Design

The researchers explored the mechanism of action of AgRP from three aspects: the effectiveness of overcoming the appetite-suppressing effects of amylin, CCK, and LiCl when AgRP neurons promote appetite; the effectiveness of inhibiting the activation of PBN CGRP neurons that leads to appetite suppression; and the effectiveness of inducing food intake under various appetite-suppressing conditions by targeting the projections of PBN CGRP neurons.

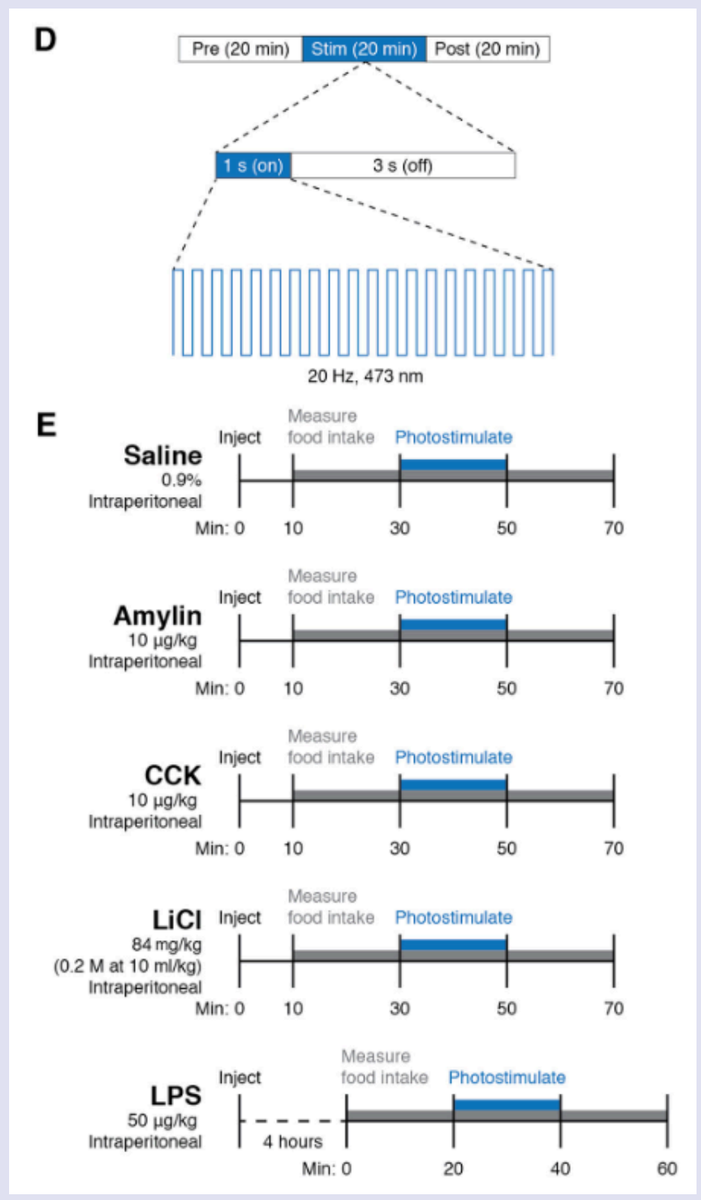
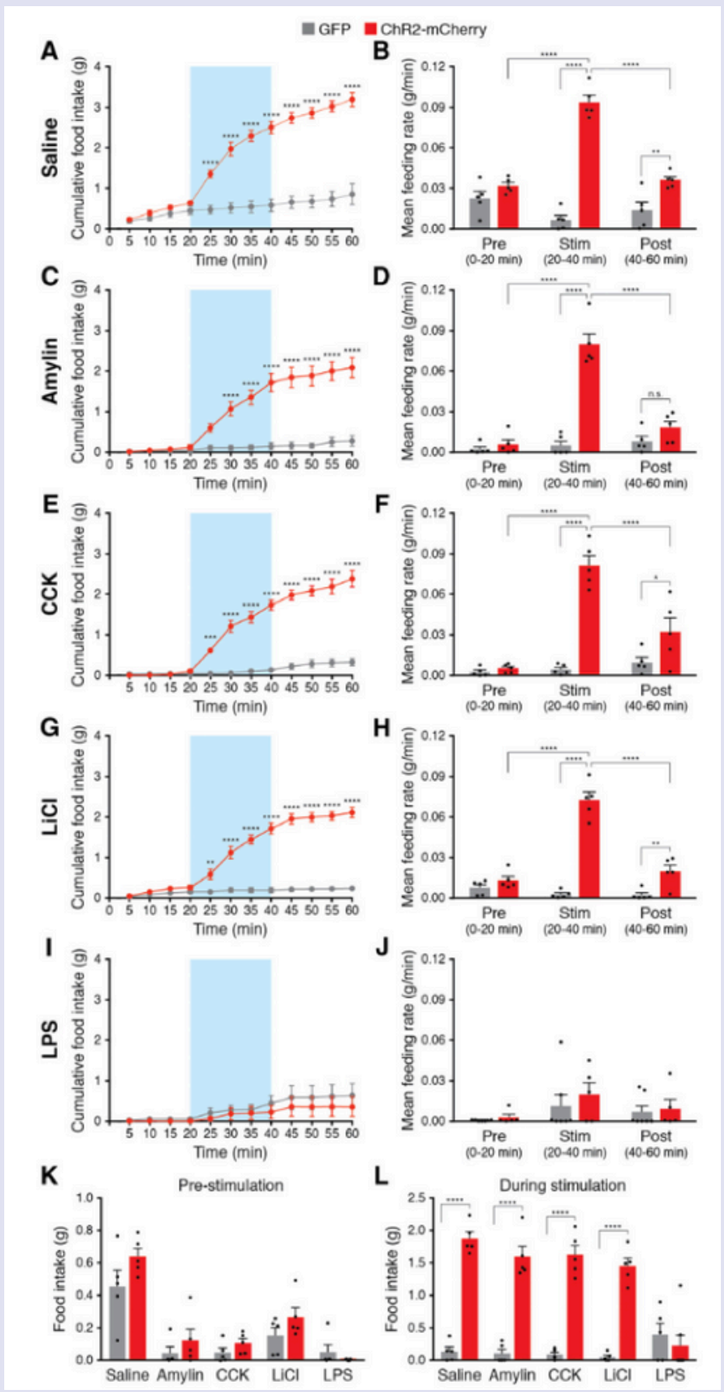


Figure 1
Experimental Procedure for Light Stimulation (D) and Injection of Appetite Inhibitors (E)

To suppress appetite, the researchers injected mice intraperitoneally with amylin (10 µg/kg), CCK (10 µg/kg), LiCl (0.20 M; 84 mg/kg), or LPS (50 µg/kg), with all doses previously used in studies to minimize food intake. In comparison, it was observed that light activation of AgRP neurons eliminated the appetite-suppressing effects of amylin, CCK, and LiCl, leading to an increase in food intake to levels similar to those of animals stimulated with saline injection.

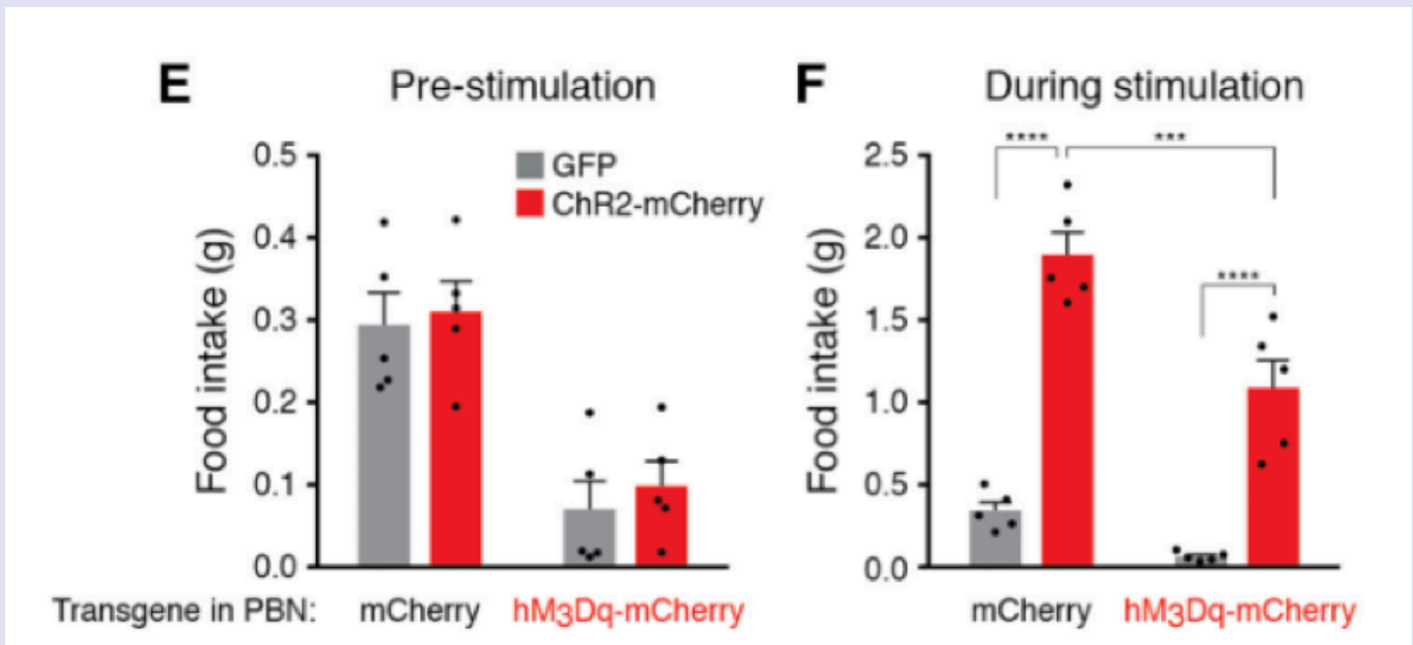
As AgRP neurons are highly effective in inhibiting appetite-suppressing compounds that activate the anorexigenic paraventricular nucleus (PBN) CGRP neurons, such as amylin, CCK, and LiCl, the researchers sought to explore whether AgRP could overcome appetite suppression caused by direct activation of PBN CGRP neurons. The researchers used the engineered receptor hM3Dq and synthetic ligand clozapine-N-oxide (CNO), then transduced AgRP neurons with ChR2-mCherry or GFP, and PBN CGRP neurons with hM3Dq-mCherry or mCherry. They injected AgRPCre/Cre and CalcaCre/+ hybridized double gene knockout mice (Calca encodes CGRP). The results showed that even with the activation of PBN CGRP neurons, stimulating AgRP neurons effectively increased cumulative food intake, indicating that AgRP neuron stimulation, after the administration of anorectic compounds, effectively reduced the activity of PBN CGRP neurons.

Figure 2
Stimulation of AgRP neurons is sufficient to increase food intake after the administration of non-inflammatory anorectic compounds



Furthermore, after the injection of amylin, CCK, and LiCl, stimulating AgRP projections to the PBN was also able to overcome the appetite-suppressing effects and increase food intake. However, similar to direct stimulation of AgRP neurons, stimulating the AgRP projections to the PBN could not overcome the appetite-suppressing effect of LPS injection, meaning it could not increase food intake following the administration of inflammatory anorectic compounds. Notably, stimulating the AgRP neurons' projections to the PBN increased food intake to levels similar to those of saline-injected animals, but the feeding-promoting effect was lower than that of direct light stimulation of the AgRP neuronal soma.

Figure 3
Total food consumed before and during cross-condition stimulation of AgRP neurons.



Summary

This study suggests that under non-inflammatory appetite suppression conditions, stimulating AgRP neurons is sufficient to increase food intake. AgRP neurons can overcome appetite reduction induced by both indirect and direct stimulation of CGRP neurons in the PBN, but under inflammatory appetite suppression conditions, stimulating AgRP neurons is not sufficient to increase food intake. AgRP neurons are not only actively involved in downstream circuits that trigger foraging behavior but also actively inhibit PBN neurons that have appetite-suppressing effects. Recent studies have also shown that AgRP neurons stimulate food intake through projections to the striatum, lateral hypothalamus, hypothalamic paraventricular nucleus, and thalamic paraventricular nucleus. This research indirectly supports the existence of a connection between AgRP and PBN, but it is not enough to prove that there is a monosynaptic connection between AgRP and PBN. Since the PBN is a heterogeneous region containing many genetically and functionally distinct cell types, further research is needed to explore the connectivity between AgRP and individual PBN neurons. Our findings complement related discoveries, suggesting that projections from AgRP neurons to the PBN can overcome various forms of appetite suppression to increase feeding behavior.

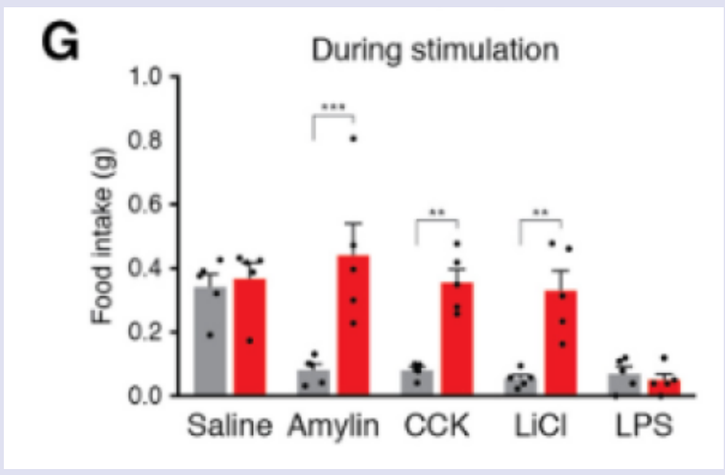


Figure 4
Stimulating the projections of AgRP neurons to the paraventricular nucleus increased food intake following the administration of non-inflammatory anorectic compounds.

Work Cited

Essner, R. A., Smith, A. G., Jamnik, A. A., Ryba, A. R., Trutner, Z. D., & Carter, M. E. (2017). AgRP Neurons Can Increase Food Intake during Conditions of Appetite Suppression and Inhibit Anorexigenic Parabrachial Neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience, 37(36), 8678–8687. https://doi.org/10.1523/JNEUROSCI.0798-17.2017

SMART MAGAZINE AUTHOR: Seraphina TRANSLATOR: Anaya EDITOR: Zeke

Alginate Composite Hydrogels: A New Hope for Bone Tissue Engineering

Keywords: Keywords: alginate; bone tissue engineering; hydrogels

Introduction:

Bone tissue engineering plays an important role in repairing bone tissue and diseases. Recently, the alginate composite hydrogels have attracted attention from the public because of their specific characteristics and potential application. In this review, the basic properties, limitations and improvement strategies of alginate are reviewed, especially the research progress on nanocomposite hydrogels, interpenetrating network composite hydrogels, and three-dimensional bioprinting materials; meanwhile, it discusses the current challenges and future directions.

Alginate---a natural material

Alginate is a kind of natural hydrophilic anionic polysaccharide extracted from the brown algae. Due to their high biocompatibility, degradability, non-toxic, and other abilities, it has a broad application in bone tissue engineering. Under normal conditions, alginates form a three-dimensional reticular hydrogel structure with divalent calcium ions to provide a microenvironment that is similar to the extracellular matrix of cells. Relative researches indicate that a variety of cells, such as mouse preosteoclasts and human adipose stem cells, exhibit excellent survival and proliferation condition in alginate hydrogels.

In bone engineering, alginate can be cross-linked with divalent calcium ions under mild conditions to form hydrogels that have an opening network structure. This hydrogel can provide cells with a microenvironment similar to the extracellular matrix of the human body, promote the exchange of nutrients and metabolites in cells, and provide good conditions for cell survival and growth. Research shows that mouse pre-osteoblasts, human adipose stem cells, and bone marrow stromal cells are all able to survive in alginate hydrogels and form extracellular matrices.

The limitation of alginate hydrogels

There are shortcomings of single alginate hydrogel as a scaffold material for bone tissue engineering. Its mechanical properties are suboptimal as it is prone to disintegration in a physiological environment and lacks cell-specific recognition sites. These defects severely limit its clinical application in bone tissue engineering.

The innovation of alginate composite hydrogels

To overcome the shortcomings of single alginate hydrogel, scientists proposed the alginate composite hydrogels. Appropriately adding one kind or various other materials into the alginate substrate and utilizing the synergy between different materials to be complementary can improve the biological suitability of hydrogels.

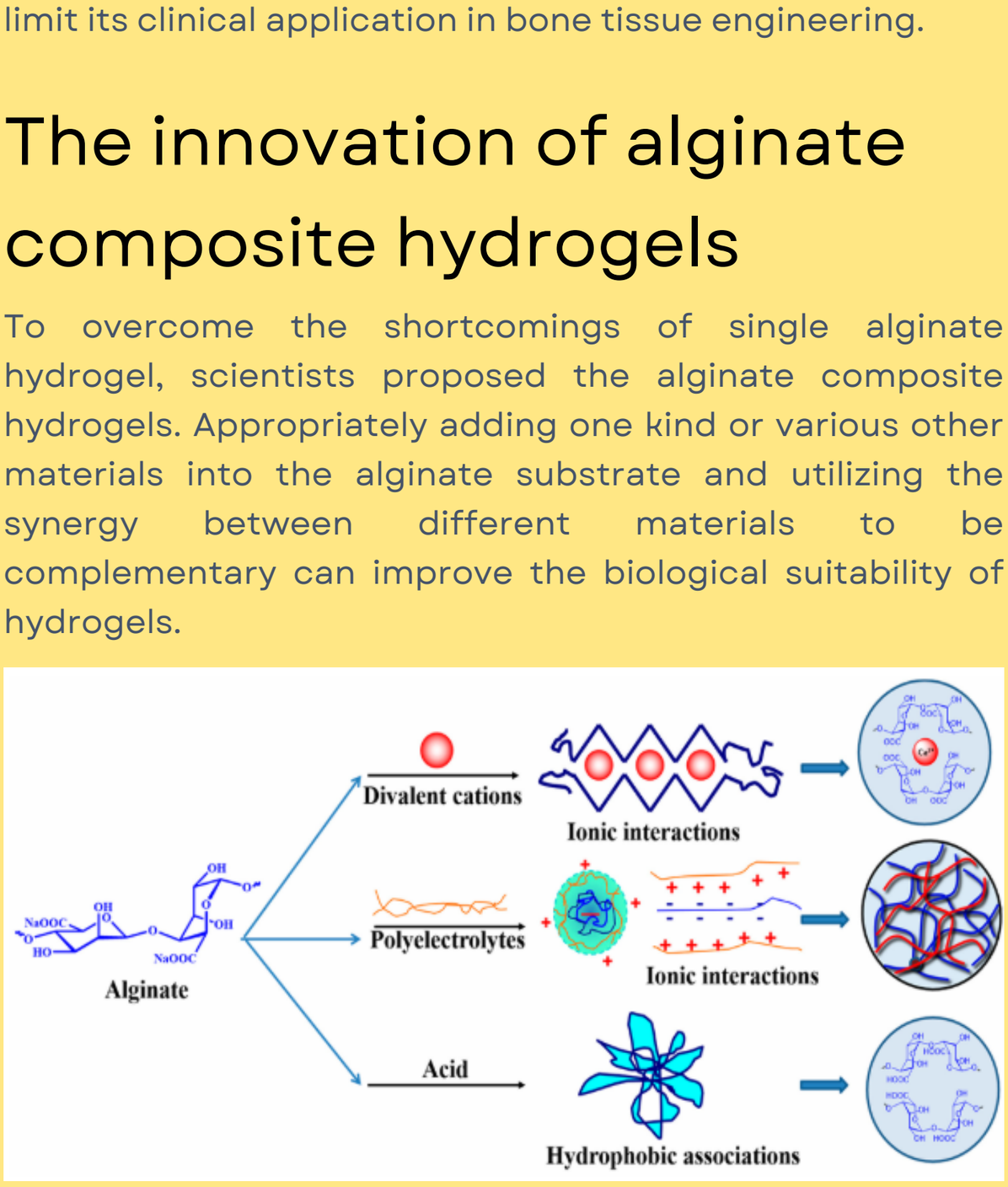


Figure 1. Schematic diagram of physically crosslinked alginate hydrogels.

1) Nanocomposite hydrogels

Nanocomposite hydrogels are a new kind of hydrogel that combines nanoparticles with alginate polymers. Since nanoparticles are small and can evenly distribute on polymer substrates, the hydrogel gains better mechanical properties, elasticity and heat resistance. Normal nanoparticles utilized include hydroxyapatite, cellulose, nano-titanium dioxide, and silica particles, among others. These nanocomposite hydrogels have excellent performance in cartilage regeneration, such as cellulose nanocrystals and polyvinyl alcohol nanocomposite hydrogels in some studies, which have demonstrated good mechanical properties and application potential in tissue engineering and biomedical fields.

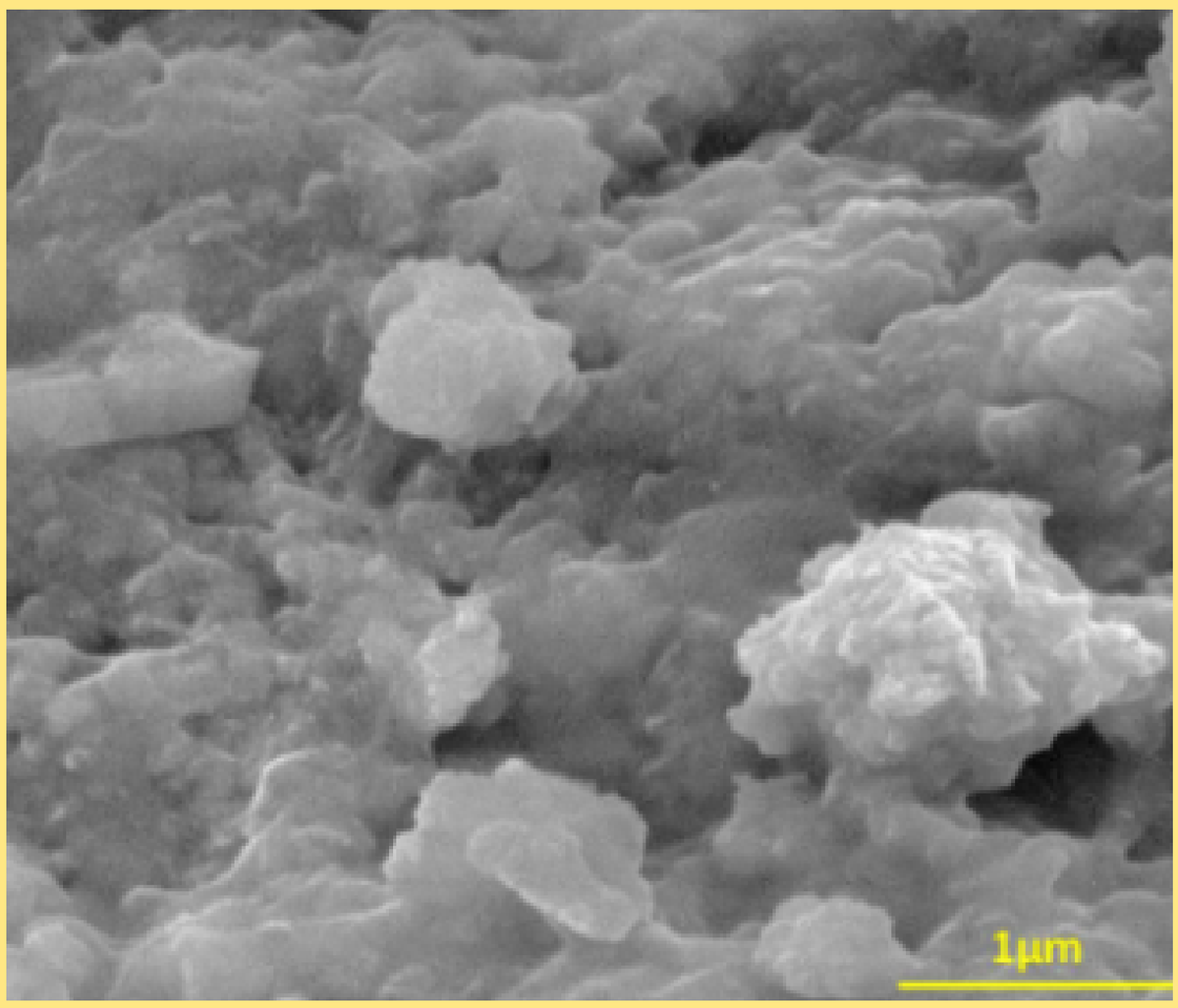


Figure 2. Physico-chemical characterization of as-synthesized nHAp-GO nanocomposite: FESEM image

2)Interpenetrating network composite hydrogel

Interpenetrating network composite hydrogels are formed by interpenetrating and cross-linking entanglements of two or more polymer molecular chains. This structure allows the different polymer networks to not only be independent but also interconnected, retaining every polymer's special characteristic and enhancing the physical feature of composite hydrogels. For example, mixing alginate with natural synthetic polymers can solve the problem that pure alginate hydrogels have low biological activity and poor mechanical properties. Some studies have used alginate and methacrylated gelatin to prepare interpenetrating network composite hydrogels, which can also adsorb osteo-inducing drugs to regulate the osteogenic differentiation of stem cells through further modification.

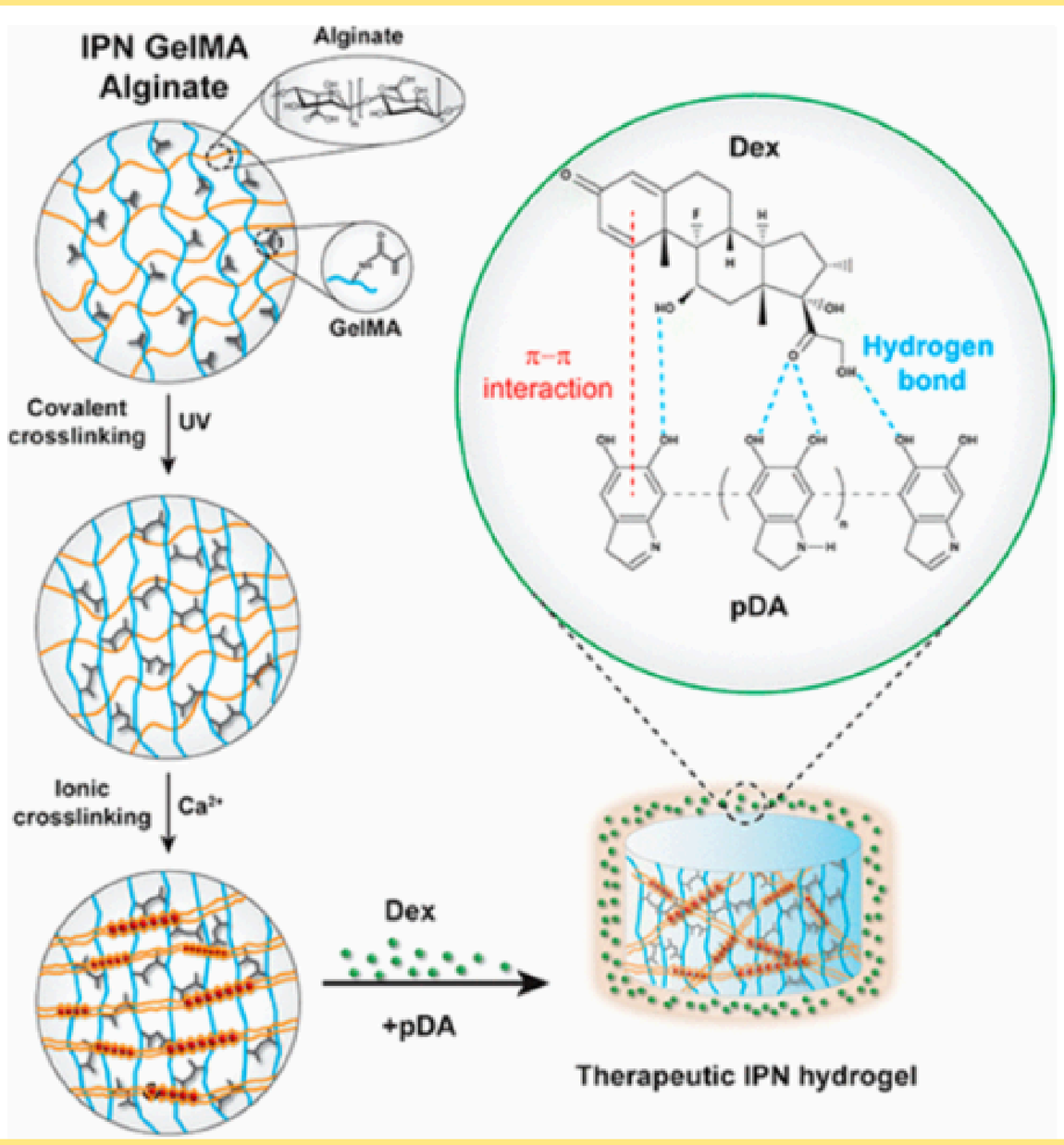


Figure 3. Mechanism diagram of an alginate/methacrylated gelatin IPN composite hydrogel

3) Alginate composite hydrogel for three-dimensional bioprinting

With the development of technology, three-dimensional bioprinting brings new opportunities for bone tissue engineering. Alginate-based bio-inks have shown great potential in this area. By injecting specific cells into alginate-based hydrogel inks, 3D bioprinting technology can be used to create tissue-engineered scaffolds that are tunable to degradable and non-toxic. These scaffolds are able to mimic the microenvironment of native tissues, providing excellent conditions for cell growth and differentiation. For example, some studies have significantly improved the mechanical properties of hydrogels and the proliferation of cells by adding bioactive glass nanoparticles or binding to collagen.

Challenges and Future Directions

Although alginate composite hydrogels have achieved significant improvement in bone tissue engineering, they still face some challenges. For instance, in terms of preparation methods, the commonly used Ca^{2+} exogenous crosslinking method has problems such as uneven crosslinking and scaffold deformation, and the influence of alginate crosslinking structure on scaffold degradation and surface activity has not been studied deeply enough. In addition, the effects of the controlled release of composite hydrogels on the differentiation and proliferation of certain active biological growth factors need to be further explored.

With the development of technology, scientists have been investigating alginate composite hydrogels more deeply. In the future, it is expected that by further optimizing the preparation method and in-depth study of the relationship between its structure and properties, we can develop more ideal alginate composite hydrogel materials, which will provide stronger support for the development of bone tissue engineering and bring more hope to patients with bone injury.

Inference:

1. Fabrication and Biomedical Application of Alginate Composite Hydrogels in Bone Tissue Engineering A Review.
2. Alginate derivatization A review of chemistry, properties and applications.
3. Fabrication of Graphene Oxide and Nanohydroxyapatite Reinforced Gelatin–Alginate Nanocomposite Scaffold for Bone Tissue Regeneration.
4. Angiogenesis in bone tissue engineering via ceramic scaffolds A review of concepts and recent advancements.
5. Development of porous hydroxyapatite/PVA/gelatinaginate hybrid flexible scaffolds with improved mechanical properties for bone tissue engineering.

SMART MAGAZINE AUTHOR: Ariana TRANSLATOR: Yaqi EDITOR: Yates

What is a Pseudogene?

Discovery

In 1977 , Jacq and colleagues discovered a nucleotide sequence in African clawed frog genome that was not transcribed. This sequence bore a high similarity to the functional gene encoding 5S rRNA but lacked expression activity. As a result, it was defined as a pseudogene.

African Clawed Frog

According to Chinese texts like Genetics Terminology, pseudogenes are defined as sequences similar to functional genes but do not produce functional products, distinguishing them from true (functional) genes. For a long time, pseudogenes were considered evolutionary relics or nonfunctional "fossils" in the genome. To enable quick identification of pseudogenes, scientists have assigned them special notations: ψis commonly used as a prefix (e.g., ψPPM1K).Alternatively, a capital P may be added after the parent gene's name (e.g., HMGA1-P).

Definition

A pseudogene refers to a gene that is similar in sequence to a known functional gene but does not produce functional products. Unlike functional genes, pseudogenes are "silent regions" within the vast genome. Pseudogenes are nonfunctional DNA copies in the genome that closely resemble coding gene sequences. While their sequences are often similar to their corresponding functional genes, they have lost at least part of their functionality–for example, the inability to express the gene and the inability of the encoded protein to perform its function. It is generally believed that pseudogenes originate from genes that were not essential for an organism's survival. Over time, mutations may accumulate, leading to features such as premature stop codons and frameshift mutations.

These changes gradually render the gene nonfunctional, transforming it into a pseudogene. Additionally, copy number variations can also give rise to pseudogenes.

Similarities and Differences Between Genes and Pseudogenes

According to the definition, genes are the basic physical and functional units of an organism, while pseudogenes are defective copies of functional genes that have accumulated mutations during evolution.

What similarities exist between pseudogenes and genes?

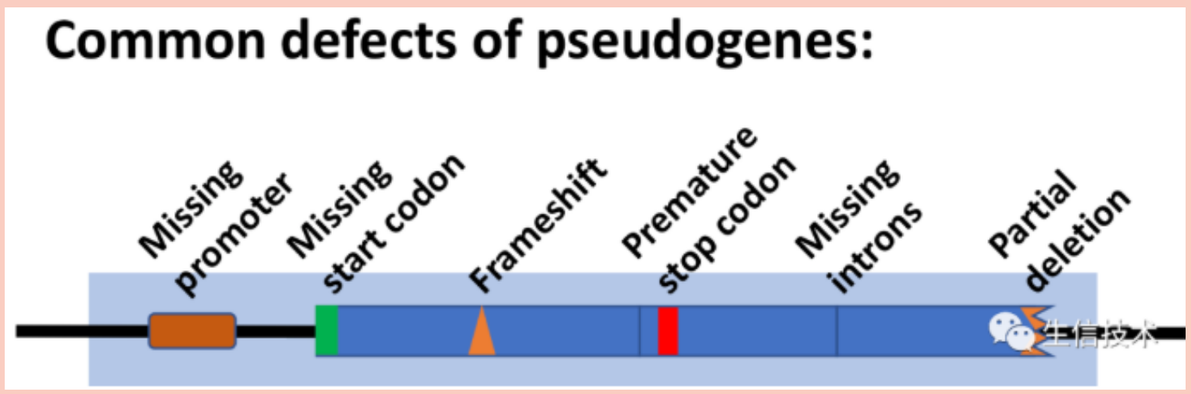
- Both are present in the genome.
- Structurally, they are fragments of DNA.
- They are heritable genetic elements.
- Both undergo mutations.
- Both can act as oncogenes or tumor suppressors.

The main differences between pseudogenes and genes are as follows: pseudogenes are non-functional genetic elements that do not encode proteins, whereas genes are functional genetic elements that encode proteins. Additionally, pseudogenes lack the critical regulatory elements essential for translation and transcription. In contrast, a gene possesses all the key regulatory elements vital for translation and transcription. This constitutes another significant distinction between pseudogenes and genes.

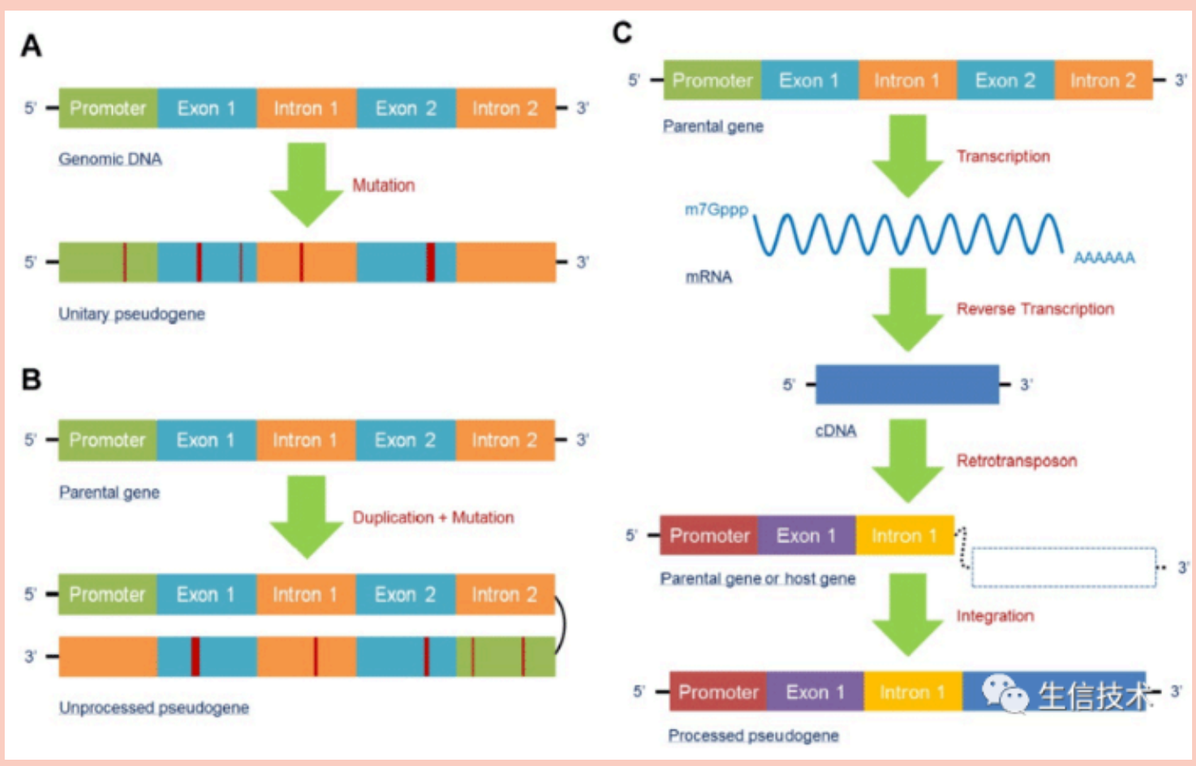
Generation

The most common type of gene duplication involves the creation of a second copy adjacent to the original. Duplicated genes may diverge to form distinct genes, or one copy may become an inactivated pseudogene. Unless the product encoded by the gene is required in high concentrations within the cell, organisms are unlikely to retain two identical copies of a gene. When differences arise between duplicated genes, one of the following two types of events may occur

1) Both genes become necessary for the organism. This can happen if the proteins encoded by the two genes acquire different functions or are expressed at different times or in different cell types.
2) If the above scenario does not occur, one of the genes is likely to become a pseudogene. This happens because, in the absence of purifying selection, it can accumulate deleterious mutations without being eliminated. Consequently, through random genetic drift, the frequency of mutations may increase and become fixed within a species.
Pseudogenes typically lack the regulatory elements crucial for translation and transcription. Various biological processes can lead to the formation of pseudogenes, and there is no specialized mechanism to remove them from the genome. Ultimately, pseudogenes may be deleted from the genome due to accidental replication or DNA repair errors. Otherwise, they will accumulate different mutations over time and no longer be recognized as their original genes. Pseudogenes can be identified through genome sequence analysis.

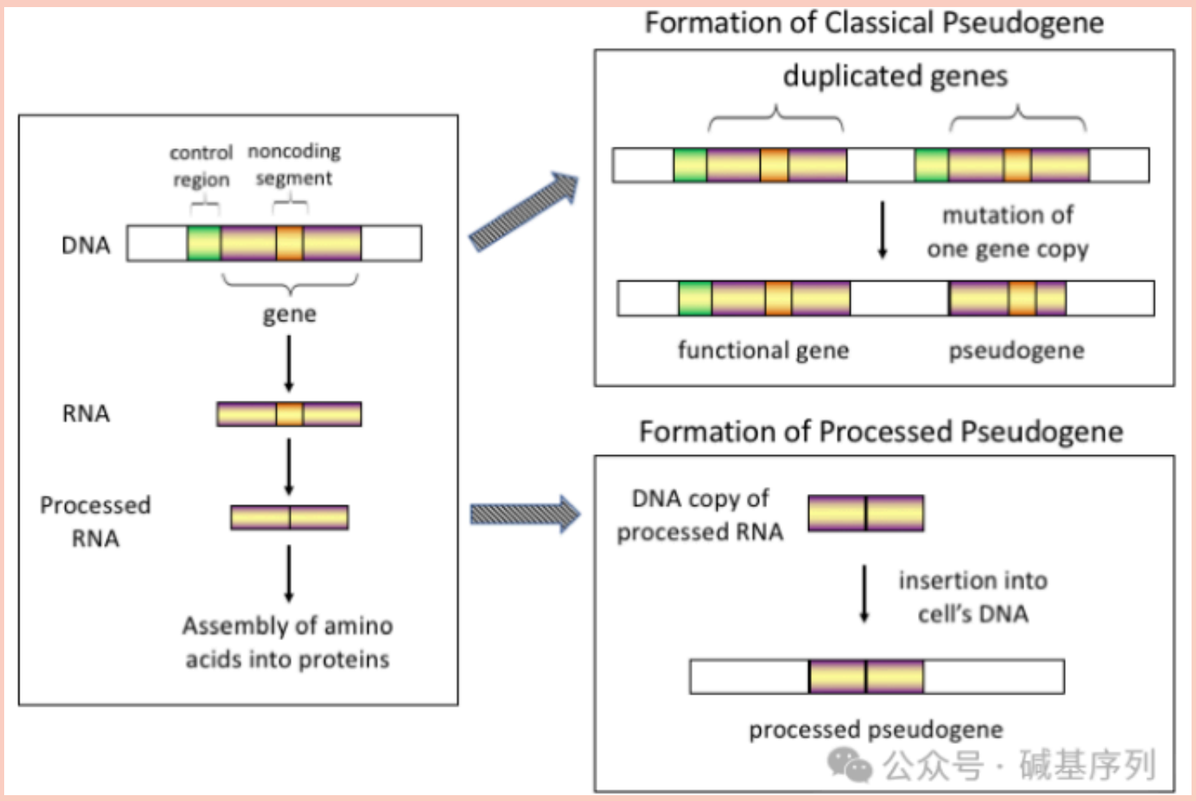


Sometimes, due to promoter elements, pseudogene sequences can be transcribed into RNA at low levels. These promoter elements come from ancestral genes or new mutations. Although most of these pseudogene transcripts have no functional significance, some may produce beneficial regulatory RNAs or new proteins.

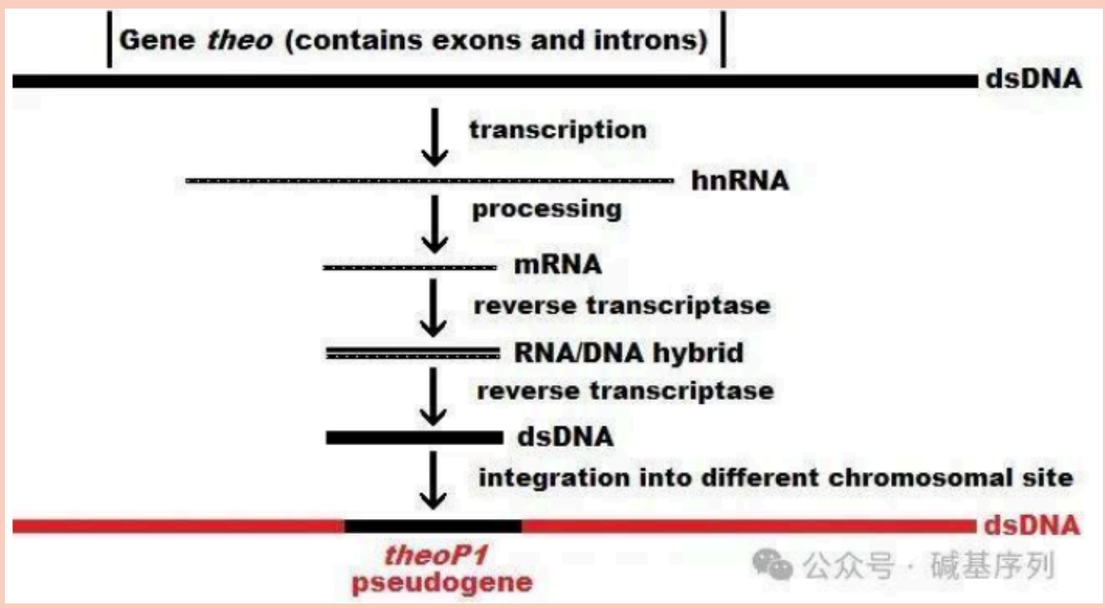


Classification

Pseudogenes are defined as copies of functional genes that have altered or lost certain regions, preventing them from producing the original functional polypeptide products. They can be non-functional, produce mutated functions, or generate RNA products with regulatory functions. For example, some pseudogenes exhibit frameshift mutations or nonsense mutations compared to their functional counterparts, leading to the loss of the gene's protein-coding function. Based on their origin, pseudogenes can be classified into **two categories**.



Processed pseudogenes originate from mature mRNA that is reverse transcribed into cDNA, and then integrated into the host or parental genome via retrotransposons.When active reverse transcriptase is present in the cell, such as during an active retroviral infection or when retrotransposons are active, the transcript may be processed, causing the mRNA to randomly reintegrate into the genome and lose its function, becoming a pseudogene. As a result, processed pseudogenes typically lack the regulatory regions necessary for normal expression. Thus, although initially containing coding sequences for functional polypeptides, once formed, they become inactive. These pseudogenes also lack introns and may contain residual poly(A) tails from mRNA and characteristic direct repeat sequences inserted by reverse transcriptase. Processed pseudogenes can be found far from their functional counterparts or on different chromosomes.



Unprocessed pseudogenes arise from inactivating mutations in one copy of a multigenic or single-copy gene, or from an incomplete duplication of an active gene. The formation of unprocessed pseudogenes is often associated with tandem repeats. If an entire gene is duplicated, including the regulatory regions, two active copies of the gene exist, and one copy may acquire an inactivating mutation that is not subject to negative selection. This results in the formation of a gene family containing unprocessed pseudogenes, as exemplified by the existence of several pseudogenes in the globin gene family. Alternatively, an incomplete duplication of an active gene, resulting in copies lacking regulatory regions and/or coding sequences, leads to the loss of transcriptional and translational capabilities, with no fully functional counterpart in the same genome.

Function

From a molecular evolutionary perspective, genes that lose their function and remain uncorrected or undeleted over long periods of evolution suggest that they may not significantly impact human survival. These genes were once considered genetic "junk" or evolutionary remnants. However, an increasing body of research has shown that pseudogenes are linked to the development and progression of diseases, including cancer and endocrine disorders.

As research deepens, it has become clear that pseudogenes play a crucial role in gene expression, gene regulation, and the generation of genetic diversity. Even in standard reference genomes, some sequences once considered pseudogenes are expressed normally in certain individuals. Studies suggest that pseudogenes may function in several ways: they can competitively bind miRNAs, thereby regulating the expression of functional genes; produce endogenous small interfering RNAs that inhibit the expression of functional genes; encode partial functional proteins; and sometimes, inactive pseudogenes can "reactivate," contributing to the creation of new genes and expanding their functions.

Diagnosis

Pseudogenes are crucial in the diagnosis of certain diseases. Due to the high sequence similarity between pseudogenes and functional genes, they can interfere with diagnostic results and complicate the interpretation of findings. However, pseudogenes also provide new perspectives and approaches for understanding and addressing diseases.

For example, 21-hydroxylase deficiency is the most common form of congenital adrenal hyperplasia (CAH). The CYP21A2 gene encodes the active 21-hydroxylase enzyme, while CYP21A1P is a pseudogene that transcribes a non-functional 21-hydroxylase. When using next-generation sequencing (NGS) to sequence human genes, the high similarity between the true and pseudogene sequences can cause interference, affecting the final determination of genetic variants. To overcome this challenge, alternative methods such as long-PCR, nested PCR, and MLPA (Multiplex Ligation-dependent Probe Amplification) are used for more accurate detection.

Another example is spinal muscular atrophy (SMA), where the disease-causing gene is SMN1, which produces the functional SMN protein.However, there is also a highly homologous gene, SMN2, with over 99.9% sequence similarity to SMN1. The only difference between SMN1 and SMN2 is five nucleotides. While SMN2 can produce a truncated and less stable SMN protein, it only accounts for about 10% of the full-length transcript of SMN1, and is therefore considered a "pseudo-pseudogene."Importantly,the detection of the SMN2 copy number can serve as a reference indicator for treatment, clinical management, and prognosis assessment after patient diagnosis. Generally, the more copies of SMN2 a patient carries, the milder the clinical symptoms will be.

With the development of molecular biology techniques and high-throughput sequencing in recent years, some pseudogenes have been found to transcribe and even translate into complete proteins with important functions, such as the activation of oncogenes, regulation of three-dimensional genome conformation, and participation in individual growth and development processes. Although some functional pseudogenes have been reported, the overall expression and evolutionary regulation of pseudogenes remain unknown. Issues such as the timing of their evolutionary origin, expression activity, and their roles in development and cancer still require further investigation.

For the detection of pseudogenes or highly homologous genes, third-generation sequencing technology stands out.The third-generation single-molecule real-time (SMRT) sequencing technology, which offers long read lengths, can directly obtain full-length gene transcripts. Its exceptionally high accuracy also enables the differentiation of highly similar sequences, providing significant advantages in the screening and diagnosis of genetic diseases related to pseudogenes. The advancement of sequencing technology has uncovered the true nature of pseudogenes and other unknown mysteries, bringing new vitality to disease tackling and scientific research.

Reference

[1] JACQ C, MILLER JR, BROWNLEE GG. A pseudogene structure in5S DNA of Xenopus laevis Cell [J]. Cell, 1977, 12(1) : 109 – 120.

[2] 刘慧，邹枨，林凤.假基因鉴定及其功能分析.生物工程学报，2013，29（5）：551-567.Liu H, Zou C, Lin F. Identification and function analysis of pseudogenes. Chin J Biotech, 2013, 29(5): 551–567.

[3] 刘国庆，白音宝力高，邢永强.假基因研究进展[J].生物化学与生物物理进展，2010（11）：1165-1174.6]

[4] 宋昉等. 脊髓性肌萎缩症遗传学诊断专家共识. 中华医学杂志2020年11月3日第100卷第40期.

SMART MAGAZINE AUTHOR: Ariana EDITOR: Amanda

The Influence of the Y chromosome on Autism spectrum disorder

Introduction

Autism spectrum disorder (ASD) is a human neurodevelopmental disease, characterized by impaired social interaction and communication, and restricted and repetitive behaviors, interests, and activity patterns. In clinical research on autism, it was found that the number of males with autism is far greater than that of females, with a ratio of nearly 4:1. The protective effect of females has always been considered the main explanation for this phenomenon. Therefore, scientists speculate that although the gene for autism may be related to the Y chromosome, genetic and epidemiological investigations on this hypothesis have not yet been able to fully and effectively explain the huge differences in the prevalence and morbidity of ASD between the sexes.

Research Introduction

In a research report, “A genome-first study of sex chromosome aneuploidies provides evidence of Y chromosome dosage effects on autism risk,” published on Nature Communications, some scientists from U.S. Gyi Singer Health System and other institutions found that the Y chromosome is associated with an increased risk of autism in the body, additional Y chromosome leads to nearly double the possibility of occurring individual autism, and this discover maybe provides a new explanation why the autism occurring in the male population is more common.

nature > nature communications > articles > article

Article | Open access | Published: 15 October 2024

A genome-first study of sex chromosome aneuploidies provides evidence of Y chromosome dosage effects on autism risk

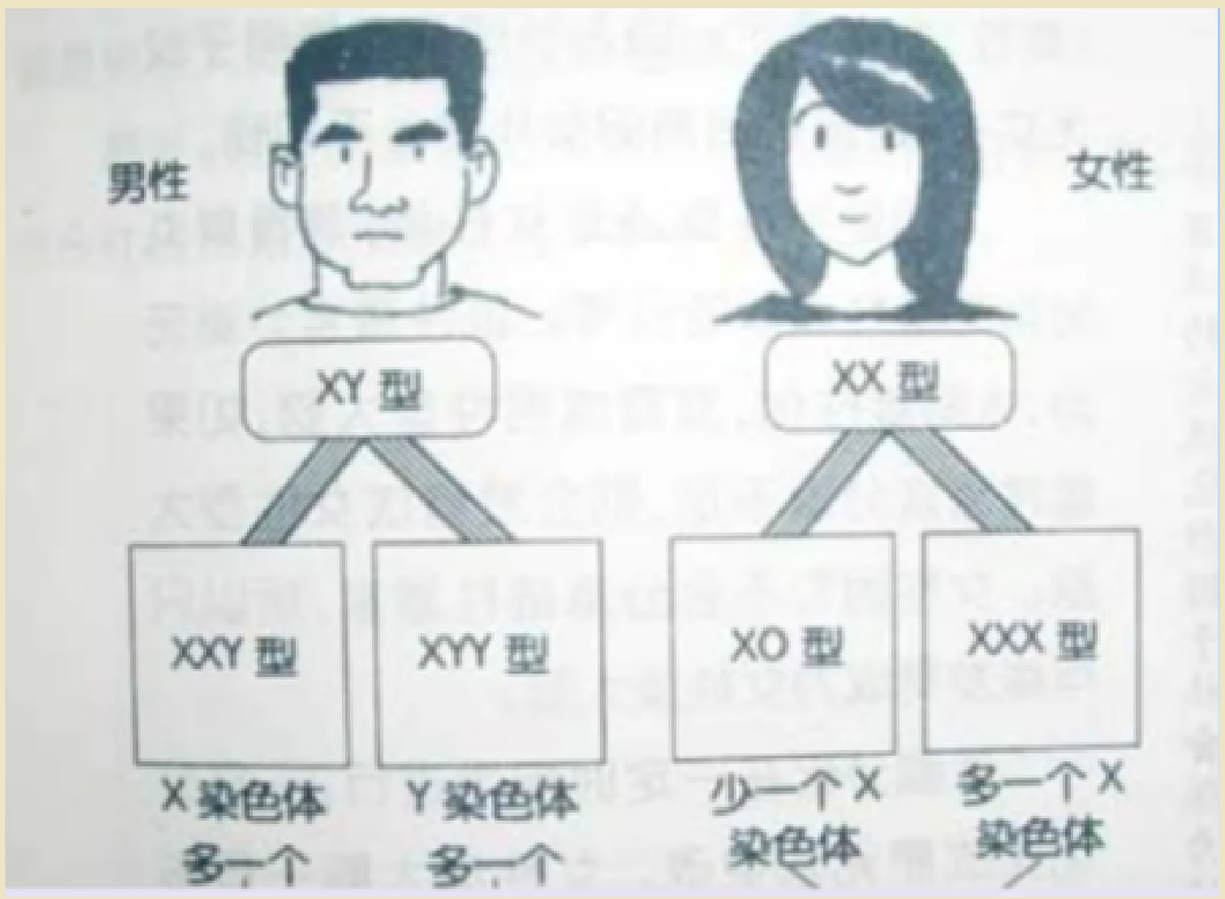
Alexander S. F. Berry, Brenda M. Finucane, Scott M. Myers, Lauren K. Walsh, John M. Seibert, Christa Lese Martin, David H. Ledbetter & Matthew T. Oetjens

Nature Communications **15**, Article number: 8897 (2024) | Cite this article

774 Accesses | **27** Altmetric | Metrics

Methods

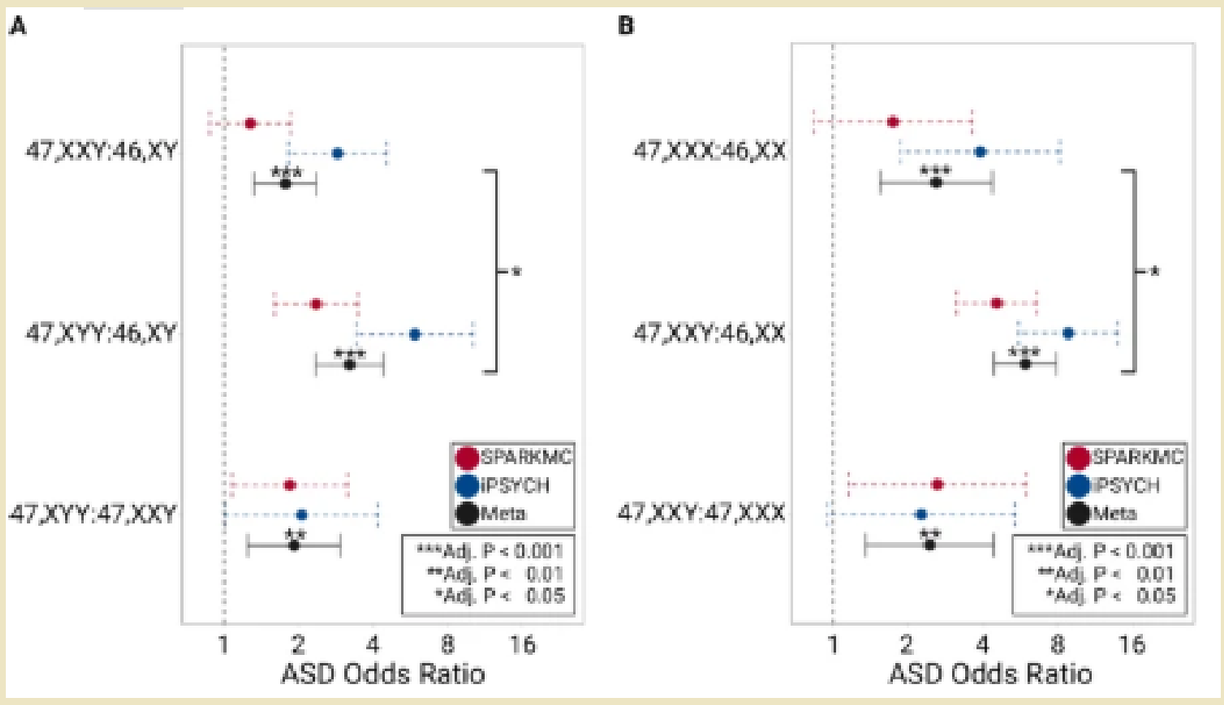
The research team systematically evaluated several key predictions of the ASD liability threshold model, so they found several lines of evidence refuting the female protective effect. Therefore, they called for the need for researchers to develop an alternative conceptual framework to investigate the observed sex differences in ASD. The study of sex chromosome aneuploidy (SCA) provides an innovative strategy to further elucidate the genomic factors (including female protective effects) that lead to the sex ratio skewness observed in ASD.

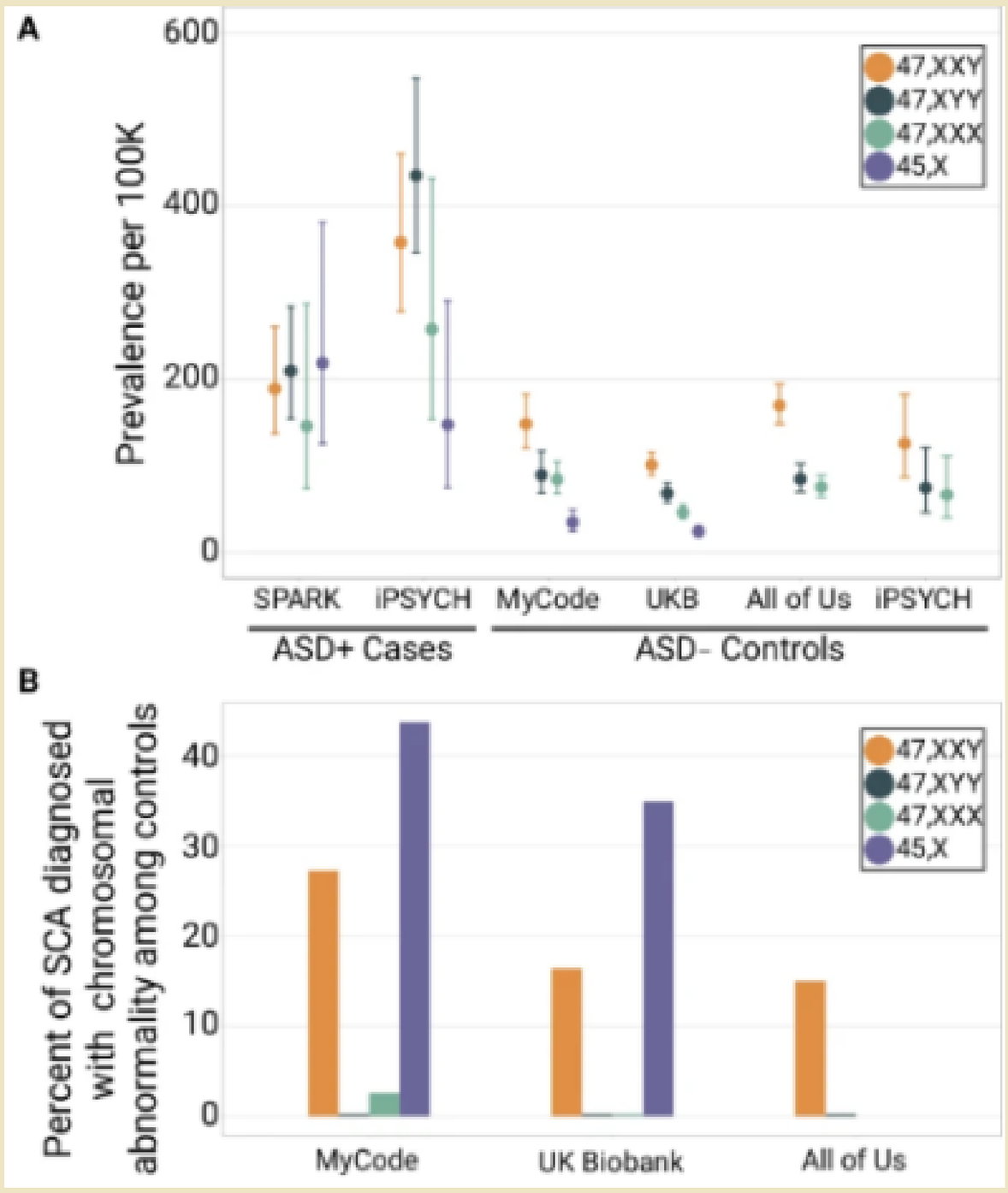


Over the decades, multiple SCA studies have well documented their association with an increased prevalence of neurodevelopmental disorders, including ASD. Although many studies have aimed to characterize the neurodevelopmental effects of specific SCAs, a more comprehensive analysis of the sex chromosome complement, including an examination of SCAs across SCAs, could reveal contrasting relative contributions of X and Y gene dosage. The researchers pooled the reported clinical prevalence of ASD in the four most common SCAs (45X, 47XXX, 47XXY, and 47XYY) and proposed a model to explain the relationship between sex chromosome dosage and ASD risk.

Three central hypothesizes provide information for this model:

1. the ASD risk increases with the addition of a Y chromosome each time, so it is called “the additional Y effect”
2. when adding the X chromosome, the change in the ASD risk is small and no change, so it is called “the additional X effect”
3. X chromosome haploinsufficiency increases ASD risk. Although descriptive and not yet statistically validated, this conceptualization provides a framework for using SCA studies to inform the effects of X and Y gene dosage on sex differences in ASD risk. A recent population study in Denmark, iPSYCH-SCA, examined the association between SCA and risk for neuropsychiatric disorders, including ASD. Although this study broadly identified SCA as an important risk factor for neuropsychiatric disorders, it did not examine the comparative effects of having an extra X chromosome versus an extra Y chromosome on ASD.





Finding

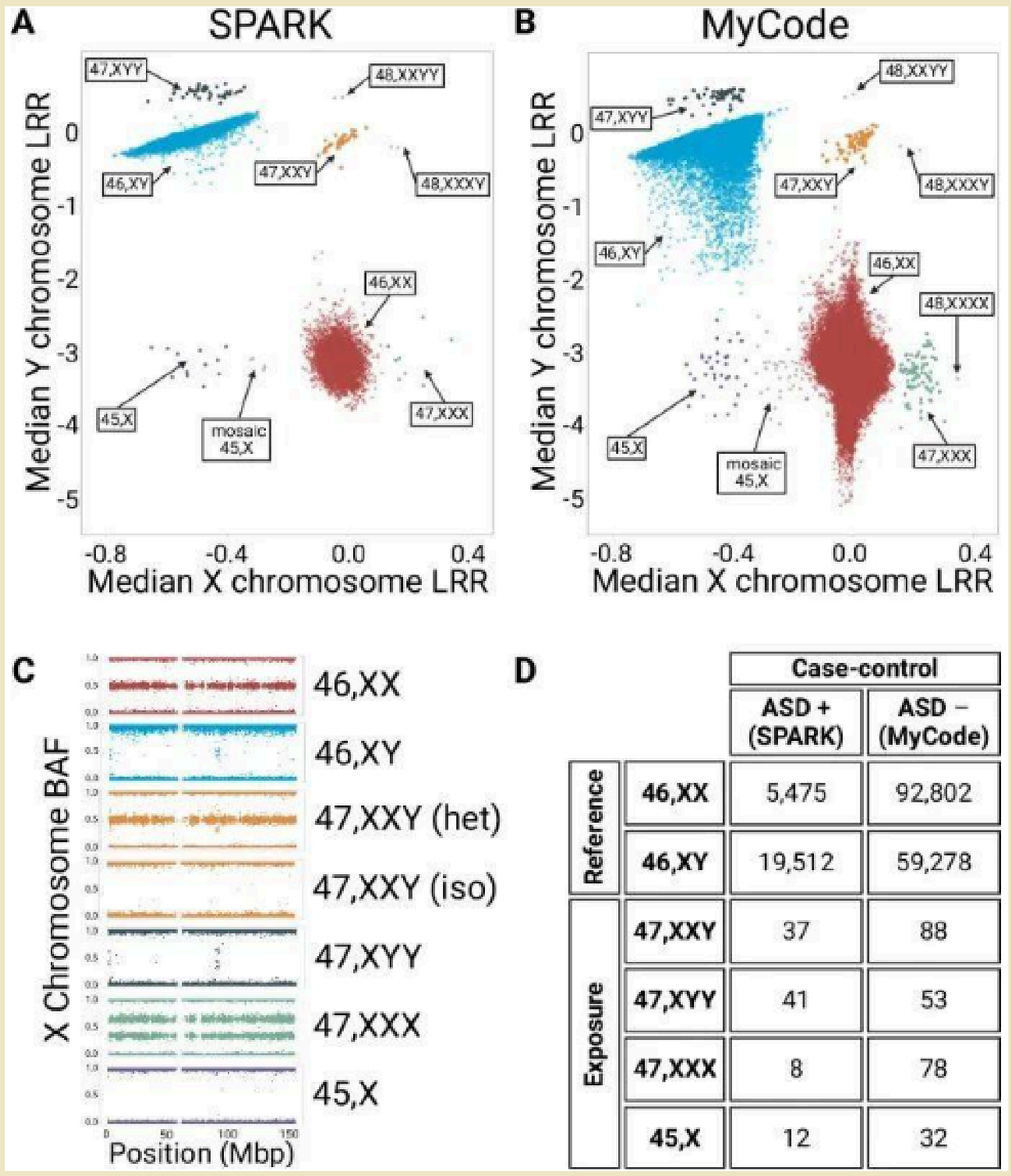
In separate analyses of 47XXY and 47XYY relative to 46XX and 46XY, the researchers modeled the association between the extra Y chromosome and ASD risk to test for the extra Y effect. They found that both 47XYY and 47XXY were significantly associated with an increased risk of ASD, with the effect of 47XYY significantly greater than that of 47XXY; at the same time, both 47XXY and 47 XXX were associated with an increased risk of ASD, with the risk estimate associated with 47XXY significantly greater than that of 47XXX. 47XXX was not increased dramatically in the likelihood of being associated with ASD compared with 46XX and 47XXY. Likewise, they also tested the effect of haploinsufficiency by modeling the association between 45X and ASD risk relative to 46XX and 46XY. 45X was found to have a significantly higher likelihood of being associated with ASD compared with 46XX, but not with 46, XY. Finally, consistent with a larger extra-Y effect between SCA analyses, individuals with 47, XYY had a higher risk than those with 47XXY. Similarly, 47XXY was significantly more likely to be associated with ASD compared with 47XXX.

To sum up, the risk pattern between sex chromosome dosage and ASD was generally consistent with that reported in the iPSYCH study. The rank order of effect sizes in sex-matched comparisons was consistent across studies: 45X had the largest effect on ASD risk, followed by 47XYY, 47XXY, and 47XXX.

The protecting effect of X chromosome

There is a common hypothesis involving sex chromosome differences between males and females in genetics that typical females have two X chromosomes, and typical males have only one X chromosome and only one Y chromosome. One major theory is that the mutual protection between the two X chromosomes helps reduce the risk of autism in women, however, to date, the evidence on the mutual protective effect of the X chromosome is not sufficient. In this research, researchers assessed the effect of the X chromosome and Y chromosome on autism risk by analyzing the diagnosis of ASD in individuals with an abnormal number of X or Y chromosomes in the body in a database. The aim of the research team is to determine whether the Y chromosome increases the incidence of autism and whether the X chromosome has a protective effect on reducing the incidence of autism by studying this congenital chromosomal abnormality.

The study found that the underlying biological mechanisms behind the gender imbalance in autism are far more complex than the existing theories of 'female protection' can explain. Further research is needed to elucidate the biological mechanisms of autism risk associated with excess Y chromosome doses, and whether it is associated with sex differences in autism.



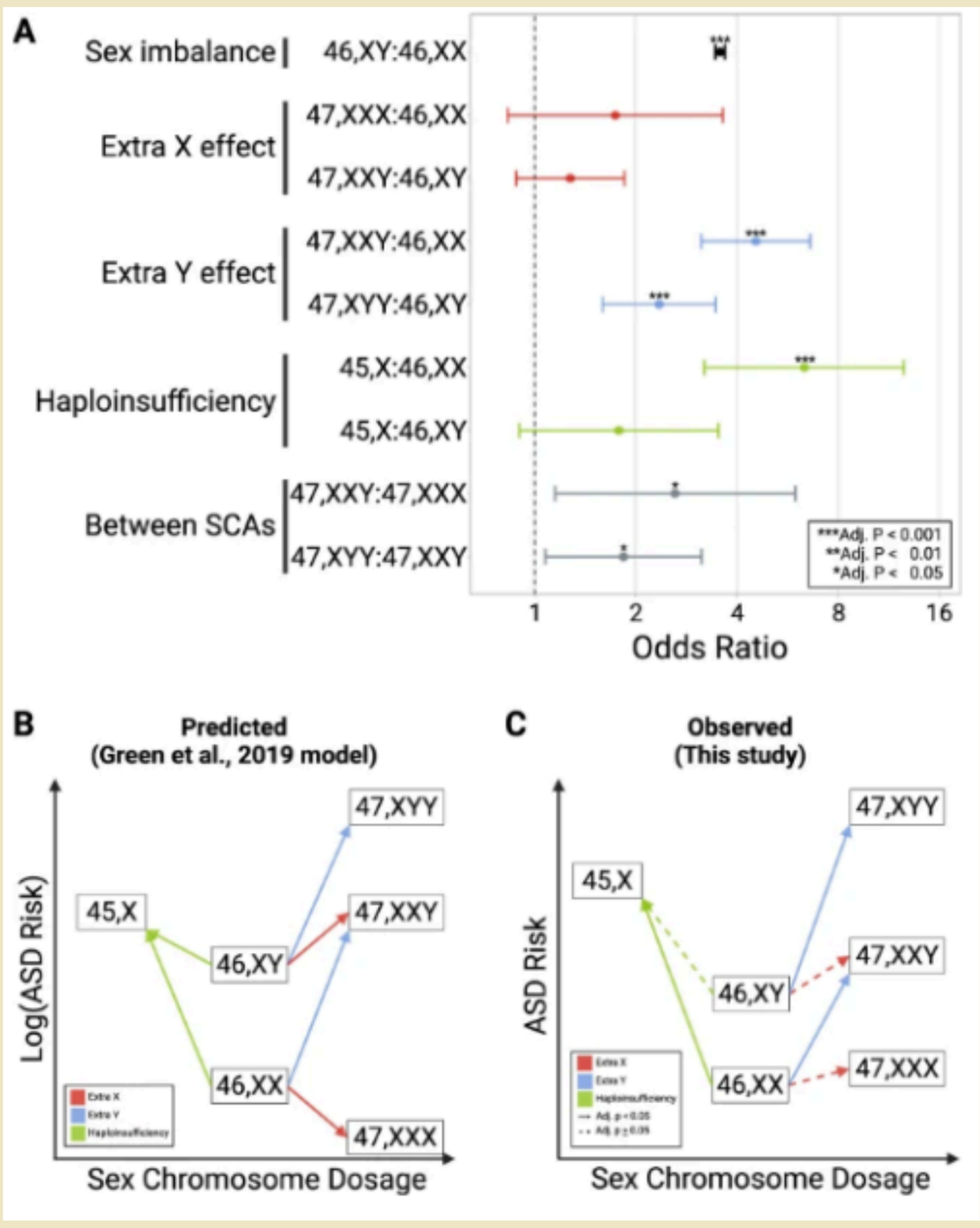
		Case-control	
		ASD + (SPARK)	ASD – (MyCode)
Reference	46,XX	5,475	92,802
	46,XY	19,512	59,278
Exposure	47,XXY	37	88
	47,XYY	41	53
	47,XXX	8	78
	45,X	12	32

The Autism Risk on the Y chromosome

This team analyzed 177,416 participants' genetic data and the ASD diagnosis. They found that the ASD risk for an individual possessing an additional X chromosome had no significant change. Whether it is XXX, XXXX is close to the rate of XX autism in normal women; Similarly, there was no significant difference in the proportion of autism in XXY compared to normal male XY. However. Individuals with extra Y chromosomes are twice as likely to have ASD, i.e., XYY has a significantly higher rate of autism compared to XY. This reveals a risk factor associated with the Y chromosome, rather than a protective factor associated with the X chromosome.

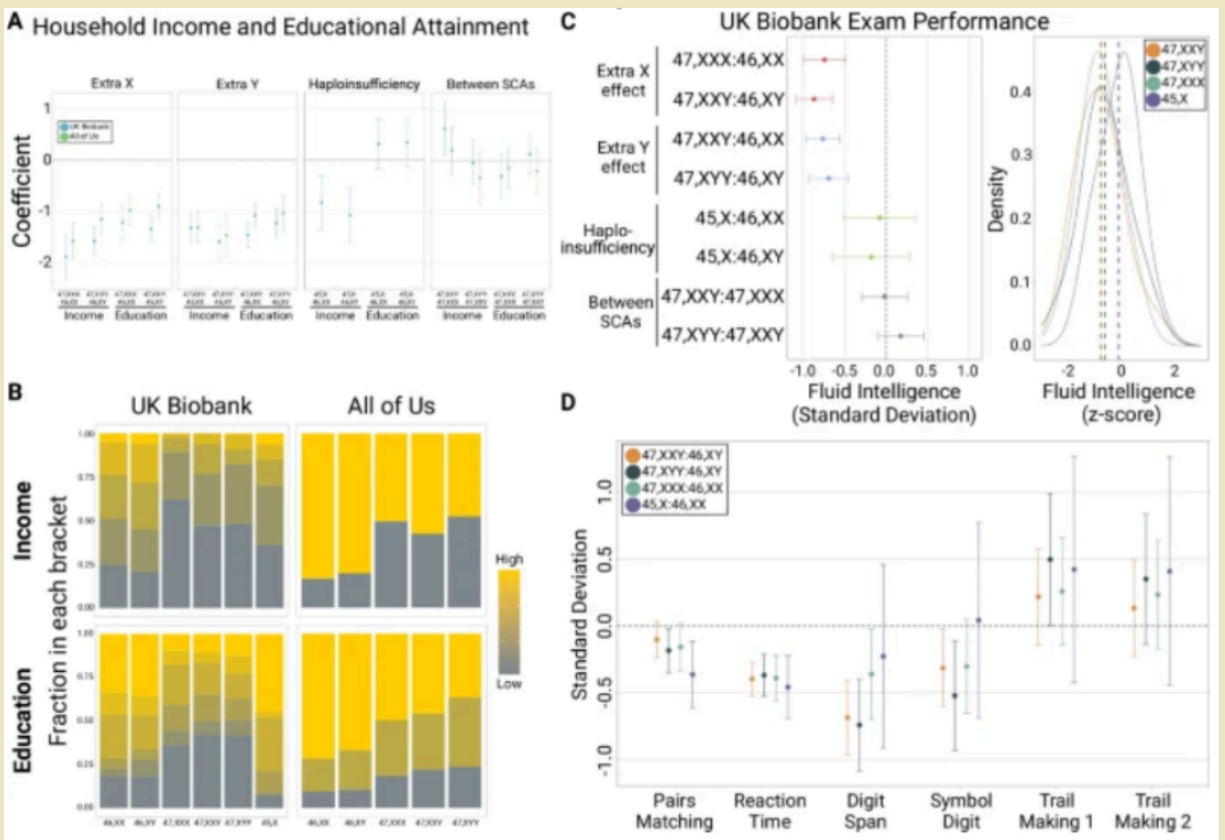
In addition, the Y chromosome's dramatic effect on ASD indicates that one or more dose-sensitive genes on the Y chromosome cause increased susceptibility to ASD in males. The Y chromosome is the smallest chromosome and contains a unique sequence of about 23 Mb called a male-specific region (MSY). Since the differentiation of the X and Y chromosomes about 200 million years ago, the 18 genes on the MSY have maintained a high degree of homology with their X chromosome counterparts in mammalian species. These genes, called gamete homologs, have different expression patterns in adult tissues, including the brain. Like many ASD genes reported in the literature, gamete profiles have strong evidence of purification selection and dose sensitivity, which is thought to underscore their importance for human health and development. The gamete homologs NLGN4Y and USP9Y have been proposed as candidate ASD sites.

The additional Y-linked influence on the risk of autism spectrum disorder (ASD) may result from the impact of the extra Y chromosome on overall gene expression. For instance, a pair of homologous genes, ZFX and ZFY, located on the X and Y chromosomes respectively (both serving as transcription factors), have been found to regulate the expression of hundreds of genes. These genes exhibit abnormal expression in individuals with sex chromosome aneuploidies (SCA). Studies have also revealed that the function of ZFY is highly sensitive to variations in Y chromosome dosage. Interestingly, recent research has identified variations in ZFX as the cause of X-linked intellectual disability (ID) syndrome, highlighting the importance of this gene in neurodevelopment. Although phenotypic consequences of variations in its Y-linked homolog ZFY have not yet been reported, this gene stands as a candidate mediator of the effects associated with an extra Y chromosome.



The Chromosome and the Cognition

Because cognition and ASD have many genetic bases, researchers hypothesized that the related mode between SCA and ASD observed by researchers is similar in cognition behavior and healthy social determine factor measurement, including measurements based on academic and career achievement. However, if this pattern deviates, it suggests that the association between sex chromosome dose and ASD is at least partially independent of the harmful effects on cognition. The study found that the cognitive performance of 47XXY, 47XYY and 47XXX was significantly lower than that of 46XX and 46XY individuals. Effect sizes between supernumerary SCAs did not differ significantly from each other, and differences in additional X or extra Y effects for these measures were not supported. In contrast, there was no significant difference in fluid intelligence test scores or educational attainment between 45X and 46XX or 46XY, although it was observed to have a large impact on ASD risk in the SPARKMC-SCA and iPSYCH-SCA studies. The results showed that the pattern of effects between sex chromosome dose and social determinants of cognitive performance and health was different from that of ASD.



The increased incidence of ASD in males can't be explained simply by cognitive differences between the sexes. Having an extra X or Y chromosome has a similar impact on cognitive performance. This suggests a pattern that aligns with the relationship between gender, ASD, and cognitive ability: The difference in the effect of increased doses of X and Y chromosomes on the risk of ASD can't be accounted for by their relationship with cognitive ability.

Limitations:

1. Different cohorts from cases and controls may have different determination biases.
2. Control participants are defined solely by electronic health records or lack of ASD diagnosis in self or parent reports
3. Unable to test associations between hormonal differences associated with SCA and ASD risk. Hormonal differences are unlikely to explain the association between ASD and Y chromosome dose.
4. The effect of racial or ethnic groups on the genetic ancestor population for determining ASD cohorts is not well described and cannot be explained in statistical modeling.

Prospects

The findings of this study encourage a focus on risk factors for autism on the Y chromosome, rather than limiting research solely to identifying protective factors on the X chromosome. Subsequently, researchers need to further investigate and identify specific risk factors associated with the Y chromosome. This study's analysis also confirms previous research results, which suggest that Turner syndrome, a condition involving the absence of an X or Y chromosome (resulting in 45 chromosomes instead of the usual 46), may be associated with a significantly increased risk of autism. Specifically, individuals with 45,X (Turner syndrome) have a higher incidence of autism than those with the normal XX or XY karyotype. Researchers need to delve deeper to determine whether autism risk factors related to sex chromosome aneuploidy can explain the difference in autism incidence between the sexes.

To sum up, this research provides a study framework for understanding the relation between the dose of X and Y chromosomes on the risk of autism, maybe giving new evidence and a study foundation for future scientists to investigate and observe sharing factors on the genetic group of gender difference. Be cautious, although it is true that the Y chromosome increases a child's risk of autism, as the study concluded, sex selection SHOULD NOT be carried out for fear of having an autistic child.

Reference

[1]Berry, A.S.F., Finucane, B.M., Myers, S.M. et al. A genome-first study of sex chromosome aneuploidies provides evidence of Y chromosome dosage effects on autism risk. Nat Commun 15, 8897 (2024).doi : 10.1038/s41467-024-53211-7

[2]https://www.geisinger.org/about-geisinger/news-and-media/news-releases/2024/10/17/17/42/increased-autism-risk-linked-to-y-chromosome-geisinger-study-finds

1.

SMART MAGAZINE AUTHOR: Zeke EDITOR: Amanda

In Vivo Screening Platform Identifies Senolytic Compounds Targeting p16INK4a Positive Fibroblasts in Pulmonary Fibrosis

Keywords: p16INK4a, senescent cells, senolytic, HSP90 inhibitor

Abstract

Senescent cells play a crucial role in various age-related diseases, characterized by permanent cell cycle arrest and secretion of the "senescence-associated secretory phenotype" (SASP). This study developed a high-throughput in vivo screening platform utilizing a fluorescence-labeled reporter system (INKBRITE) to directly isolate p16INK4a positive fibroblasts from fibrotic tissues and screen for senolytic compounds capable of clearing senescent cells. Through single-cell RNA sequencing and immunohistochemical analysis, it was confirmed that p16INK4a positive fibroblasts possess pro-fibrotic characteristics. In vitro and in vivo experiments demonstrated that overexpression or knockout of p16INK4a exacerbated or alleviated fibrosis, respectively. Screening revealed that the HSP90 inhibitor XL888 significantly reduced p16INK4a positive cells and related pathological remodeling in fibrosis models. Furthermore, XL888's efficacy was validated in idiopathic pulmonary fibrosis (IPF) patient samples. This study provides a precise senolytic screening platform, offering a new approach for treating fibrotic and other age-related diseases.

Research Background

Senescent cells are those that have undergone irreversible cell cycle arrest and lost proliferative capacity but remain alive. These cells typically exhibit enlarged cell size, increased genomic instability, and express specific biomarkers such as p16INK4a and p21. The accumulation of senescent cells is not only a part of the normal aging process but also plays a key role in various age-related diseases, including neurodegenerative disorders, cardiovascular diseases, osteoarthritis, and fibrosis.

Senescent cells secrete a range of cytokines, inflammatory mediators, and proteases through the “senescence-associated secretory phenotype” (SASP), which leads to alterations in the tissue microenvironment, exacerbating chronic inflammation and tissue degeneration. Removing these cells can reduce these negative effects and improve tissue function and overall health.

Senolytics are compounds specifically designed to target and selectively eliminate senescent cells. Their mechanism of action is based on disrupting the anti-apoptotic signaling networks unique to senescent cells, making them more susceptible to apoptosis and subsequent clearance. Although these cells can no longer divide, they remain alive and continue to secrete inflammatory cytokines, factors, and proteases that form the SASP, which negatively impacts the tissue microenvironment and organ function. Therefore, the accumulation of senescent cells in aging tissues and many age-related diseases is considered a crucial pathological mechanism.

In this study, the research team developed a high-throughput screening platform targeting senescent cells in disease tissues, overcoming the limitations of traditional screening strategies. The platform uses a fluorescent reporter system (INKBRITE), which allows for in vivo labeling and isolation of p16INK4a positive cells, combined with in vitro, ex vivo tissue slice (PCLS), and in vivo model validation of compound efficacy. This platform provides a more reliable tool for discovering effective senolytics within disease contexts.

p16INK4a is a key marker of cellular senescence, encoded by the CDKN2A gene. It primarily functions by inhibiting cyclin-dependent kinase 4/6 (CDK4/6), preventing the phosphorylation of the Rb protein, thus inducing permanent cell cycle arrest. In age-related diseases, the upregulation of p16INK4a expression is closely associated with the accumulation of senescent cells. As a target, p16INK4a can be used to identify and clear senescent cells, enabling senolytic compounds to specifically act on p16INK4a positive cells, thereby slowing tissue damage and disease progression.

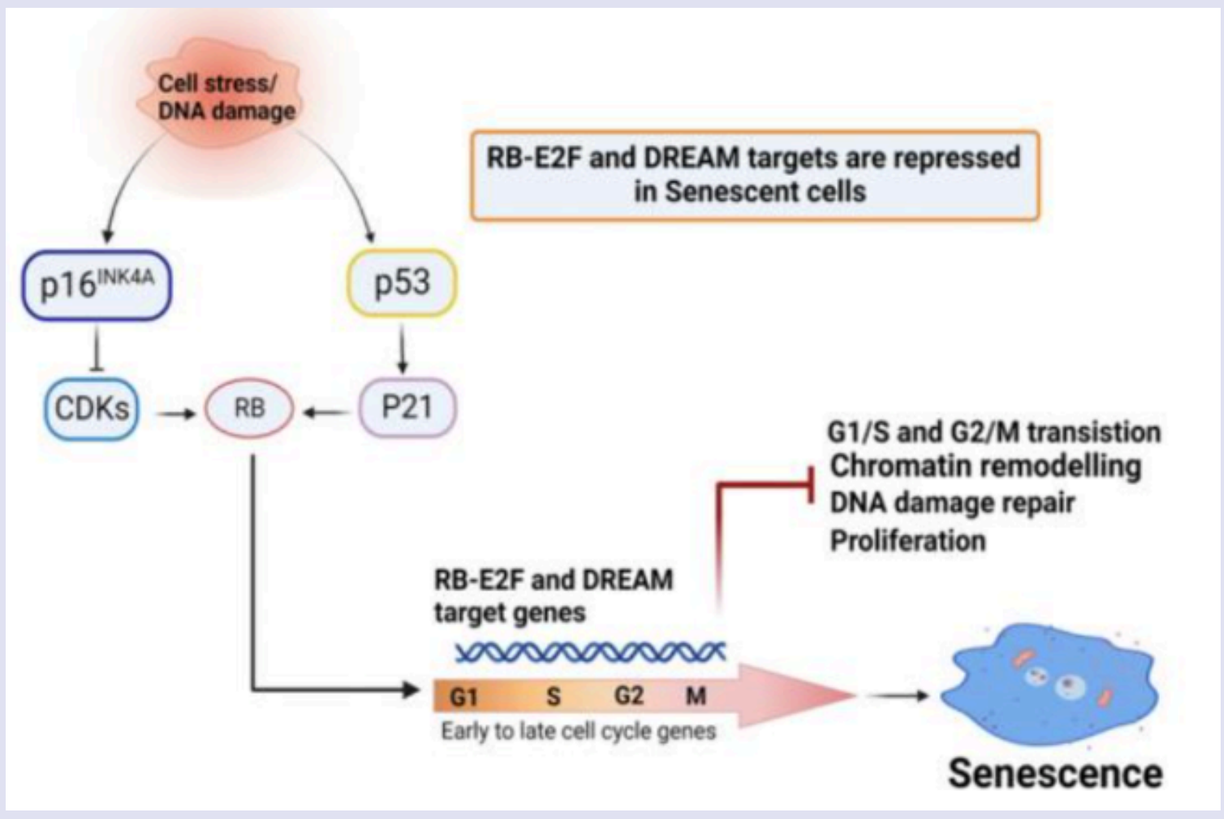


Fig1. Mechanism of p16INK4a

Results

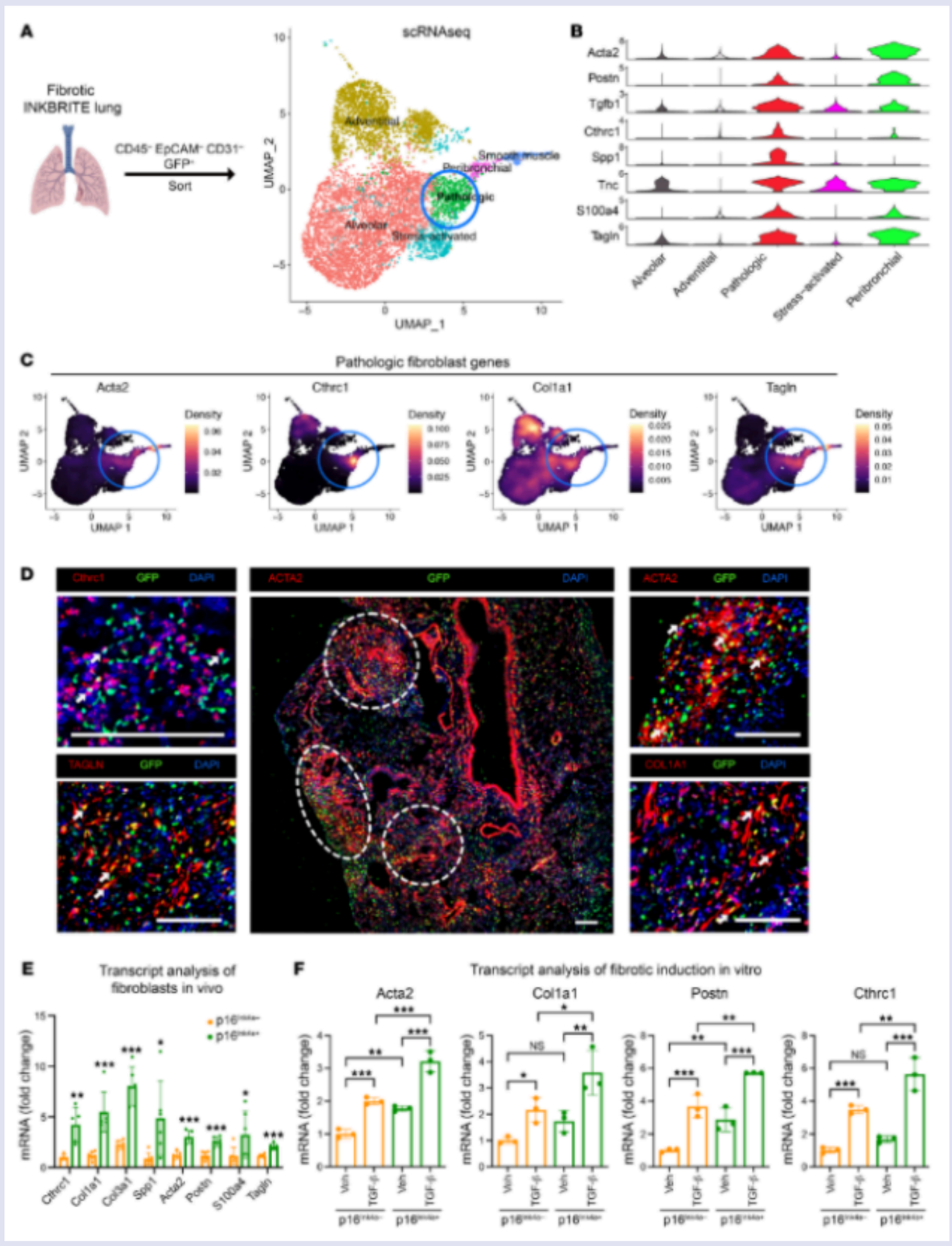


Fig. 2. p16INK4a Fibroblasts Contribute to Pathological Fibroblasts in a Mouse Model of Pulmonary Fibrosis

Through single-cell RNA sequencing (scRNA-Seq) and immunohistochemistry (IHC) experiments, the study extensively characterized the properties of p16INK4a expressing fibroblast subtypes in fibrotic lung tissues. scRNA-Seq analysis isolated GFP-labeled p16INK4a positive fibroblasts from a bleomycin-induced fibrosis mouse model, identifying multiple subpopulations, including well-known stromal subtypes such as basal membrane fibroblasts and peribronchial fibroblasts, as well as emerging fibrotic-specific subtypes, such as profibrotic fibroblasts. Further analysis revealed that profibrotic fibroblasts significantly upregulated several fibrotic genes (e.g., ACTA2, COL1A1, TAGLN, and CTHRC1). Moreover, IHC further validated the presence of these subtypes, showing that p16^INK4a^ positive cells co-localized with fibrotic markers (e.g., ACTA2 and COL1A1) in the fibrotic lesions, particularly in regions of high collagen deposition. These results suggest that p16INK4a positive fibroblasts are not only involved in the fibrotic response but also possess significant pathogenic potential, strongly supporting their role as therapeutic targets.

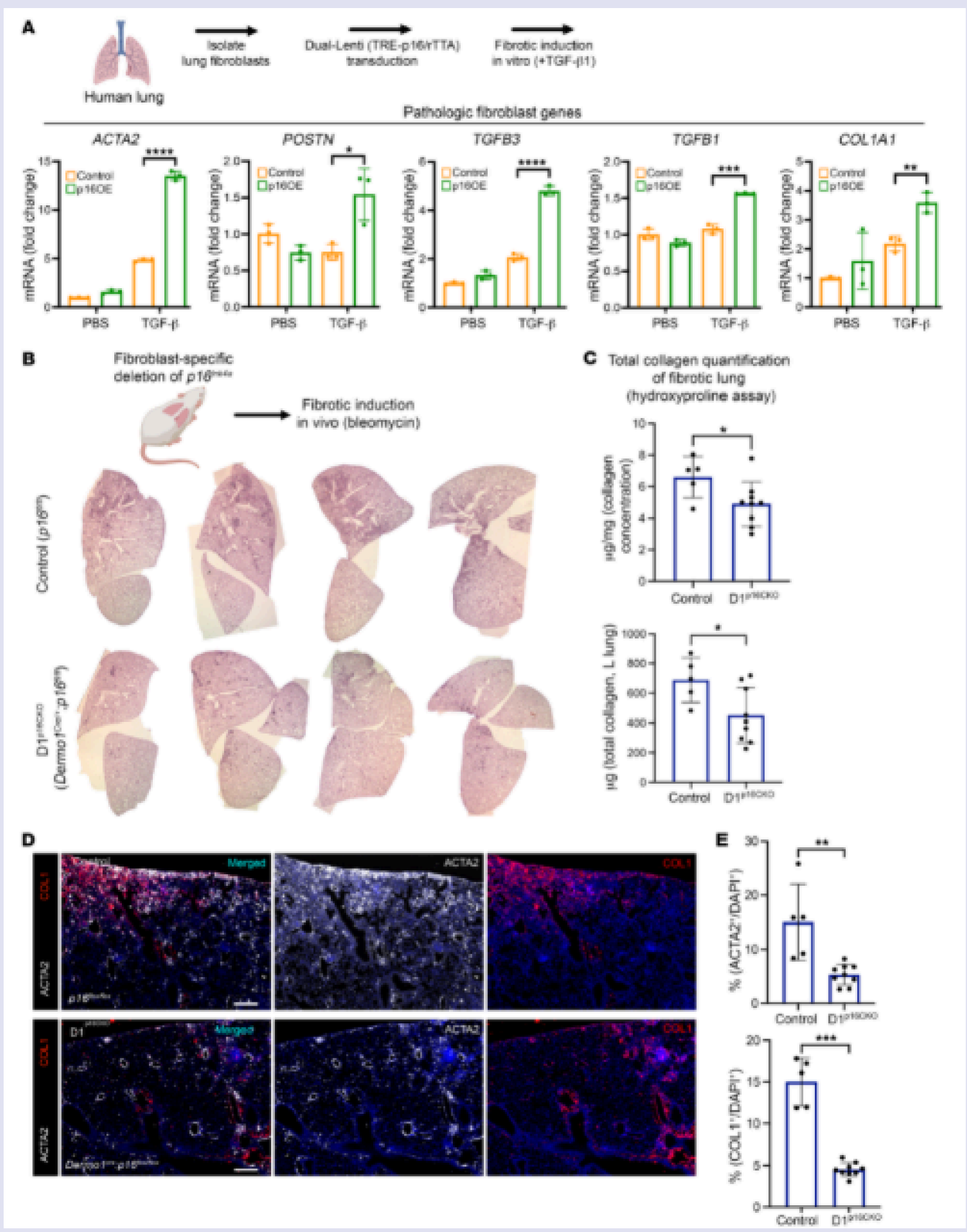


Fig. 3. p16INK4a Expression Stimulates Fibroblasts to Enhance Fibrotic Response

In vitro experiments were conducted to explore the specific effects of p16^INK4a^ expression on fibroblast-driven fibrotic responses. Researchers utilized an inducible p16^INK4a^ overexpression system to study this effect. Specifically, they implemented a binary transgenic system to achieve controlled overexpression of p16INK4a in human lung fibroblasts, simulating a fibrotic environment by adding TGF-β1. The results demonstrated that, compared to the control group, p16INK4a overexperssing fibroblasts

showed a significant upregulation of several profibrotic genes, including COL1A1, ACTA2, and TAGLN, in response to TGF-β1 stimulation. However, in the absence of TGF-β1, there was no significant change in the expression of these profibrotic genes. This indicates that p16INK4a does not directly drive fibrosis but rather enhances fibroblasts' sensitivity to profibrotic signals through a "sensitization" mechanism.

In vivo experiments were performed using fibroblast-specific p16INK4a knockout (D1p16CKO) mice to further validate the role of p16INK4a in the fibrotic response. In uninjured lung tissues, p16INK4a knockout did not induce significant morphological changes. However, in a bleomycin-induced lung fibrosis model, D1p16CKO mice exhibited significantly reduced fibrosis compared to controls. Histological observations showed reduced collagen deposition, which was further confirmed by a decrease in lung collagen content as measured by hydroxyproline quantification. Additionally, immunohistochemistry (IHC) revealed a significant reduction in the number of fibroblasts positive for profibrotic markers such as ACTA2 and COL1A1 in the lungs of D1p16CKO mice. These results strongly support the critical role of p16INK4a in promoting fibrosis and suggest that p16^INK4a^ may drive fibrosis progression by increasing fibroblasts' sensitivity to profibrotic stimuli such as TGF-β1.

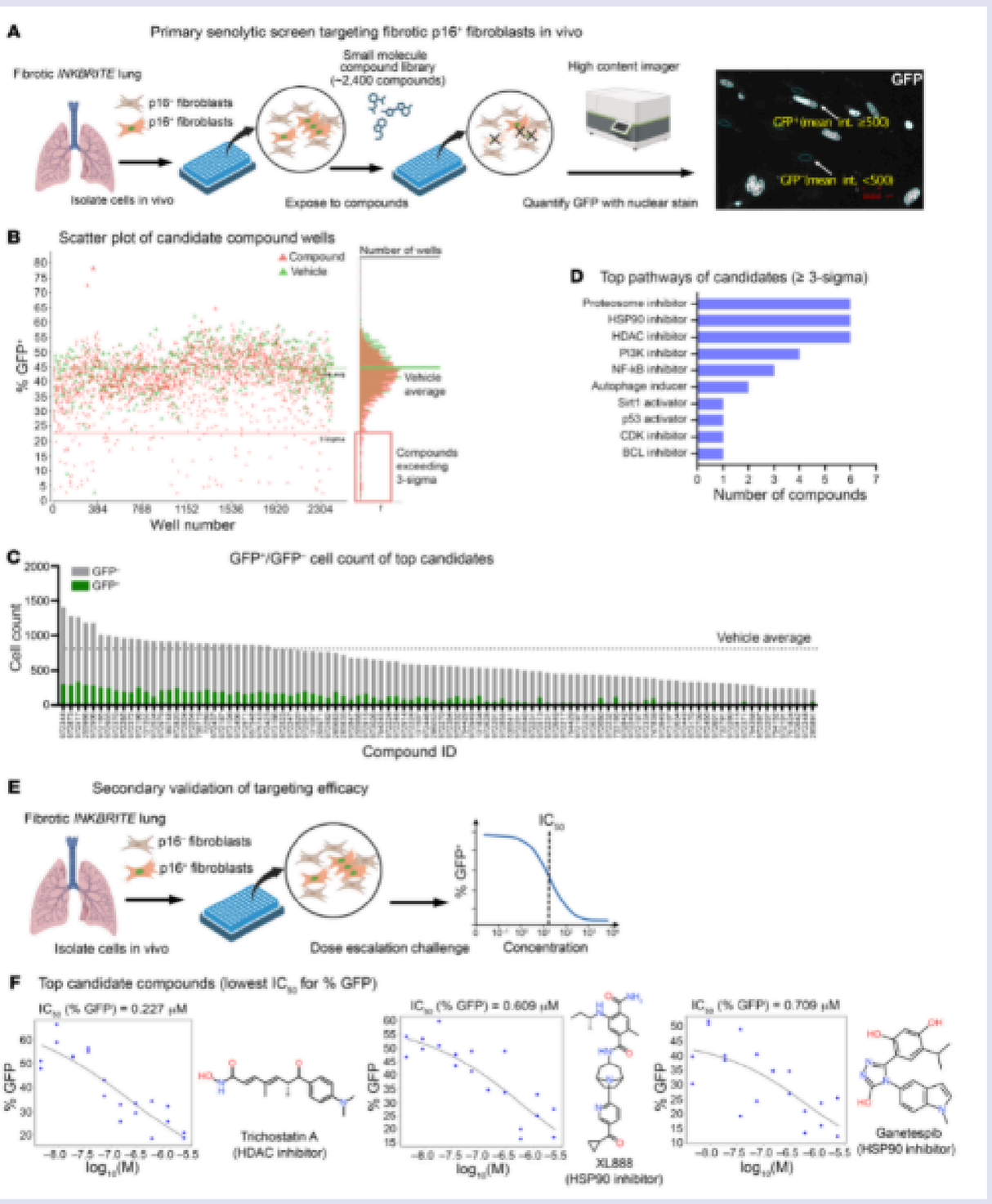


Fig. 4. HTS Targeting p16INK4a Fibroblasts Isolated from Fibrotic INKBRITE Lungs

The research team performed a high-throughput screening (HTS) of 2000 compounds using GFP-labeled p16INK4a + fibroblasts to identify compounds that selectively target p16INK4a + fibroblasts without affecting p16INK4a - cells. Several promising compounds were identified, including HSP90 and HDAC inhibitors, which demonstrated significant potential for targeting p16INK4a + fibroblasts.

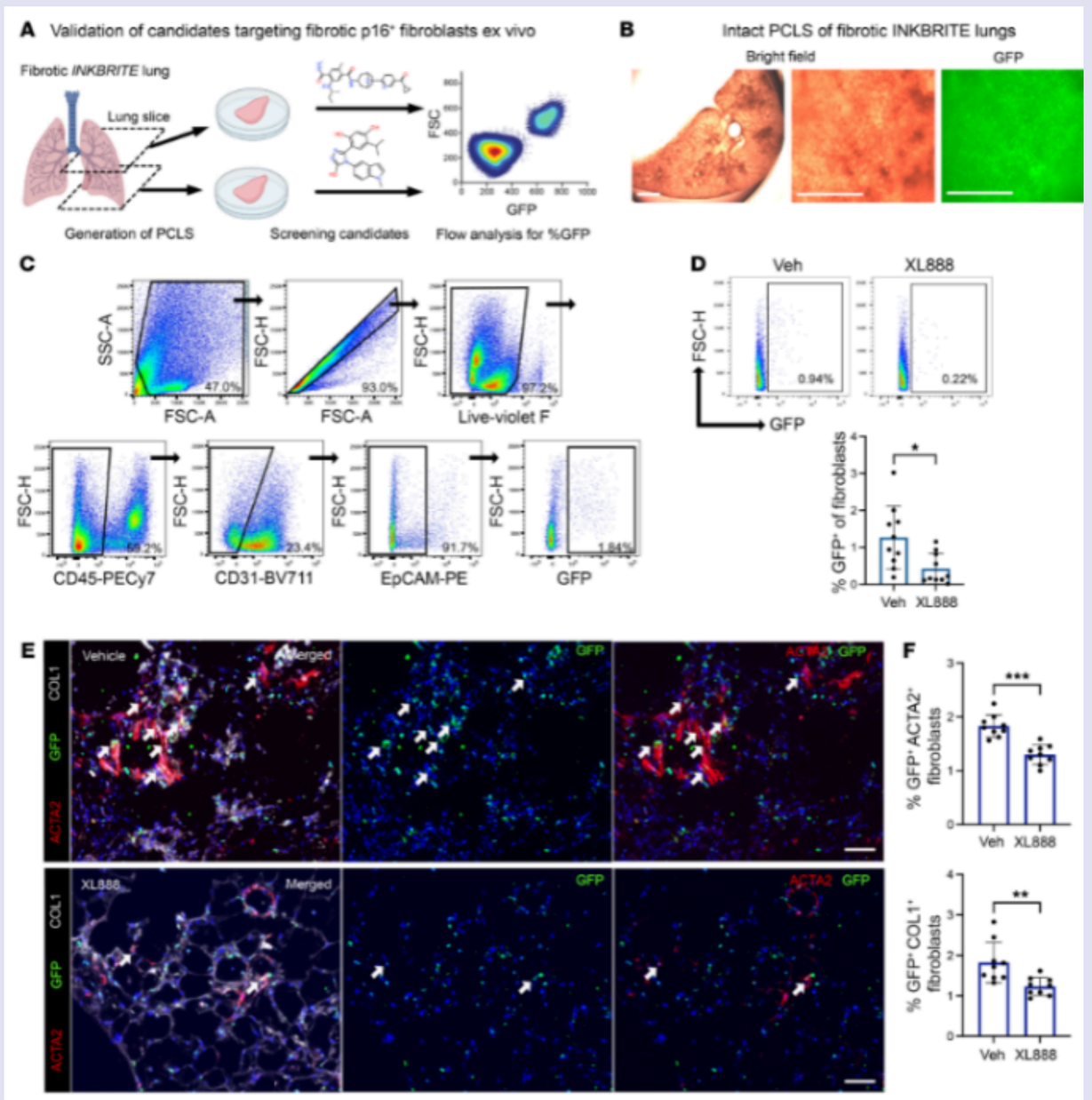


Fig. 5. Validation of Candidate Senolytic Compounds Using Mouse PCLS Derived from Fibrotic INKBRITE Lungs

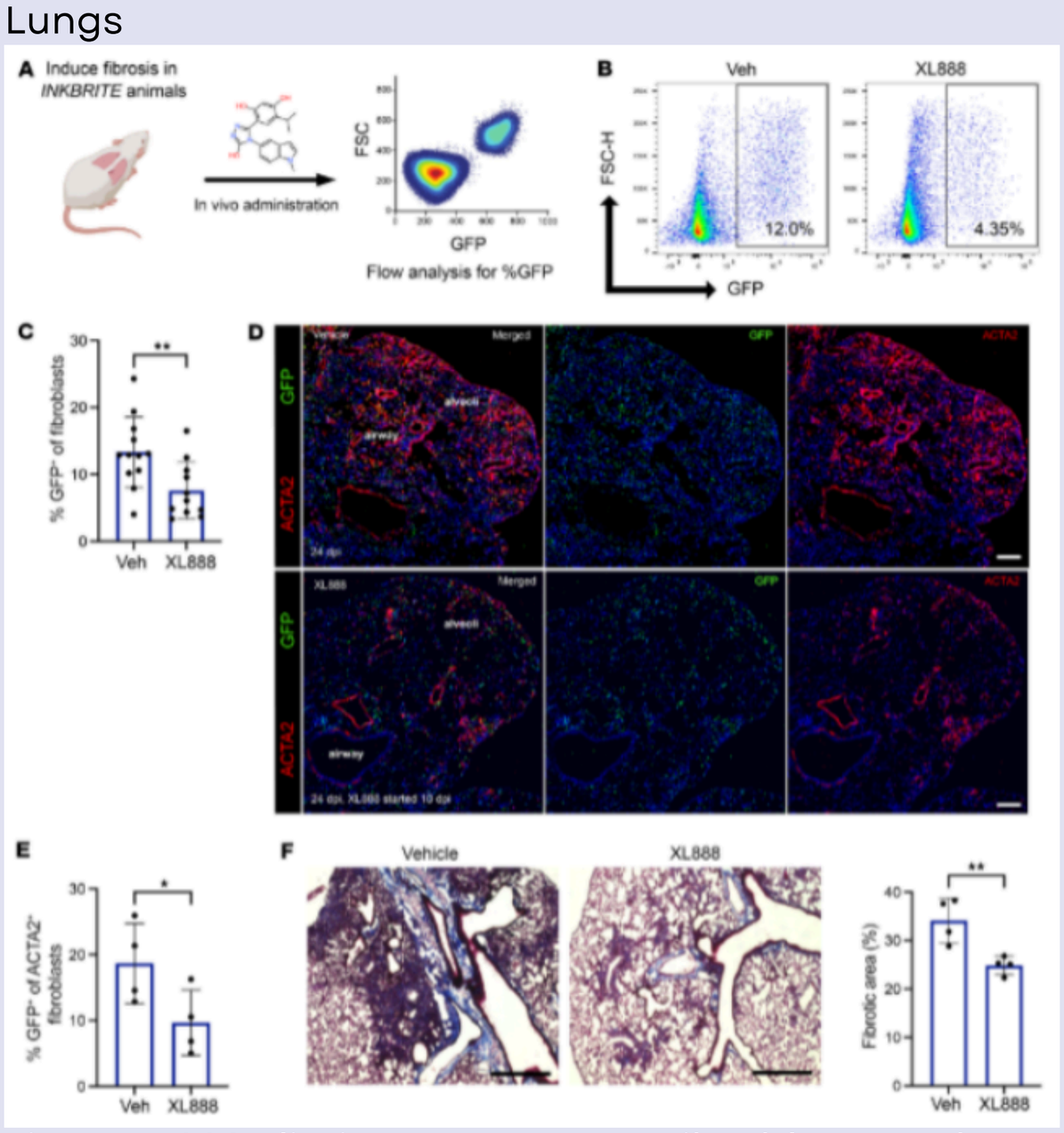


Fig. 6. XL888 Eliminates p16INK4a Fibroblasts and Attenuates In Vivo Fibrotic Remodeling

The research team performed a high-throughput screening Compounds were tested in fibrotic lung slices to confirm their efficacy in a physiological environment. The study found that the HSP90 inhibitor XL888 exhibited the most potent effect, significantly reducing the number of p16INK4a + fibroblasts in the lung slices.

The efficacy of XL888 was ultimately validated in a mouse lung fibrosis model. Treatment with XL888 significantly reduced the number of p16INK4a + fibroblasts and the extent of fibrotic remodeling. This effect was confirmed through flow cytometry, immunohistochemistry (IHC), and collagen content analysis.

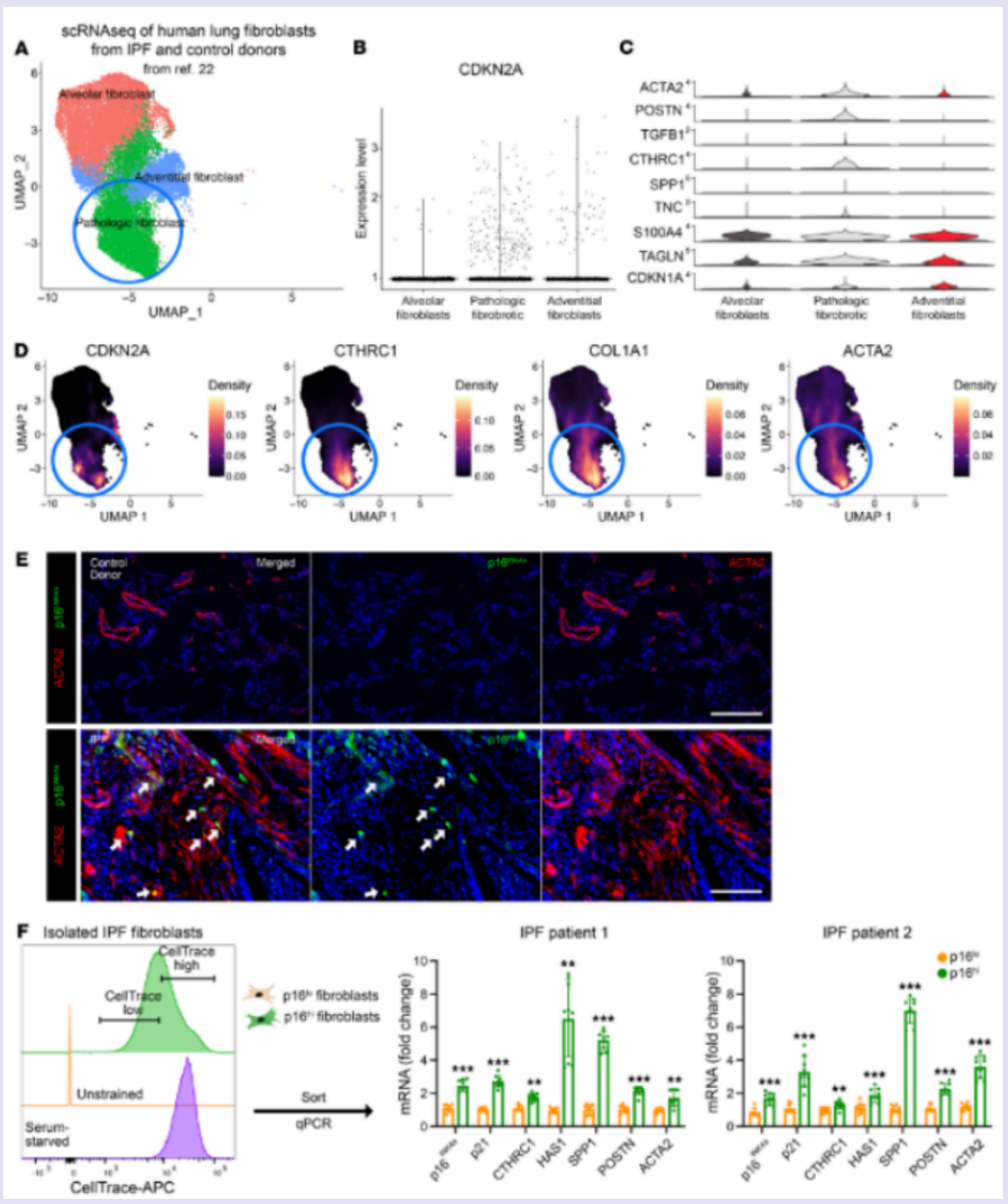


Fig. 7. Human p16INK4a Fibroblasts Contribute to Pathological Fibroblasts in IPF

The study further tested XL888 on human lung fibroblasts and PCLS models derived from patients with idiopathic pulmonary fibrosis (IPF). The results confirmed that XL888 selectively cleared human p16INK4a + fibroblasts, demonstrating its potential in the treatment of human fibrosis.

Summary

This study focused on the pathogenic role of senescent cells in pulmonary fibrosis and developed a highly efficient and precise in vivo screening platform to identify senolytic compounds targeting p16INK4a + senescent cells. By combining a fluorescence reporter system (INKBRITE), single-cell RNA sequencing (scRNA-Seq), and immunohistochemistry (IHC), the heterogeneity of p16INK4a + fibroblasts in fibrotic lungs was characterized, confirming their key pathogenic potential in the fibrotic response. In vitro experiments showed that p16INK4a overexpressing fibroblasts significantly upregulated pro-fibrotic genes upon TGF-β1 stimulation. In vivo studies demonstrated that p16^INK4a^ gene knockout significantly reduced fibrosis, verifying its critical role in fibrosis.

Using the high-throughput screening platform, the study identified the HSP90 inhibitor XL888 from 2000 candidate compounds, which was validated through ex vivo tissue slices (PCLS) and mouse models. Results showed that XL888 selectively cleared p16INK4a + fibroblasts and attenuated fibrotic pathological remodeling. Additionally, its efficacy was confirmed in human IPF samples.

This study presents a clear approach with significant technological innovation, proposing an integrated strategy from disease models to clinical validation, offering new perspectives for the treatment of fibrosis and other age-related diseases. By systematically evaluating the efficacy and selectivity of senolytic compounds both in vitro and in vivo, the study establishes a technical benchmark for drug development and lays the foundation for further clinical applications.

Reference

[1] Lee, J. Y., Reyes, N. S., Ravishankar, S., Zhou, M., Krasilnikov, M., Ringler, C., Pohan, G., Wilson, C., Ang, K. K., Wolters, P. J., Tsukui, T., Sheppard, D., Arkin, M. R., & Peng, T. (2024). An in vivo screening platform identifies senolytic compounds that target p16INK4a+ fibroblasts in lung fibrosis. The Journal of clinical investigation, 134(9), e173371. https://doi.org/10.1172/JCI173371

[2] Burd CE, et al. Monitoring tumorigenesis and senescence in vivo with a p16(INK4a)-luciferase model. Cell. 2013;152(1-2):340-351.

[3] Cai, Y., Song, W., Li, J., Jing, Y., Liang, C., Zhang, L., Zhang, X., Zhang, W., Liu, B., An, Y., Li, J., Tang, B., Pei, S., Wu, X., Liu, Y., Zhuang, C. L., Ying, Y., Dou, X., Chen, Y., Xiao, F. H., ... Liu, G. H. (2022). The landscape of aging. Science China. Life sciences, 65(12), 2354-2454. https://doi.org/10.1007/s11427-022-2161-3

SMART MAGAZINE AUTHOR: Dora EDITOR: Yates

Causes and Treatments of Aphasia

Introduction:

Aphasia is an acquired communication disorder caused by brain damage. It manifests as varying degrees of impairment in abilities such as language comprehension, expression, reading, writing, repetition, and naming.

Causes

ACurrent research on aphasia is primarily categorized into three theories: the Jakobson Regression Hypothesis (Jakobson, 1941), the Tree Pruning Hypothesis (Friedmann, 2001; Friedmann & Grodzinsky, 1997), and the Argument Structure Complexity Hypothesis (Thompson, 2003). The Jakobson Regression Hypothesis posits that aphasia represents a mirror image of language acquisition. For individuals with aphasia, language abilities acquired earlier in childhood are the last to be lost, while those acquired later are the first to be lost. This suggests a regressive relationship between language acquisition in children and language loss in aphasia.The Tree Pruning Hypothesis asserts that syntactic impairment in aphasia is essentially the result of pruning the inflectional tree. In other words, the higher the damaged node on the tree, the greater the number of functional categories affected, leading to more severe syntactic impairment.The Argument Structure Complexity Hypothesisproposes that the more complex the argument structure of a verb, the greater the difficulty individuals with aphasia face in understanding and producing that verb. It is recommended to include practical application examples of the theories：for instance, how the Jakobson Regression Hypothesis or the Tree Pruning Hypothesis is applied in the treatment of aphasia patients, and whether there are any case studies or experimental evidence to support their application.

Theories

ACurrent research on aphasia is primarily categorized into three theories: the Jakobson Regression Hypothesis (Jakobson, 1941), the Tree Pruning Hypothesis (Friedmann, 2001; Friedmann & Grodzinsky, 1997), and the Argument Structure Complexity Hypothesis (Thompson, 2003). The Jakobson Regression Hypothesis posits that aphasia represents a mirror image of language acquisition. For individuals with aphasia, language abilities acquired earlier in childhood are the last to be lost, while those acquired later are the first to be lost. This suggests a regressive relationship between language acquisition in children and language loss in aphasia.The Tree Pruning Hypothesis asserts that syntactic impairment in aphasia is essentially the result of pruning the inflectional tree. In other words, the higher the damaged node on the tree, the greater the number of functional categories affected, leading to more severe syntactic impairment.The Argument Structure Complexity Hypothesisproposes that the more complex the argument structure of a verb, the greater the difficulty individuals with aphasia face in understanding and producing that verb. It is recommended to include practical application examples of the theories：for instance, how the Jakobson Regression Hypothesis or the Tree Pruning Hypothesis is applied in the treatment of aphasia patients, and whether there are any case studies or experimental evidence to support their application.

SMART MAGAZINE AUTHOR: Dora EDITOR: Yates

Characteristics

The suprasegmental phoneme impairments of Chinese aphasia patients have also drawn the attention of researchers. As a tonal language, Chinese relies on syllabic tones to express intonation, meaning that intonation is conveyed through rising and falling tones without altering the underlying syllabic tones. Research on Chinese aphasia at the suprasegmental level mainly focuses on tone and intonation. Studies have shown that tones have independent representations, with tone errors most frequently occurring in the third tone. Additionally, the severity of impairment, error types, and distinctive phonetic features (distinctive traits) of tone and initial consonants in Chinese aphasia show similar patterns in their analysis.

Treatments

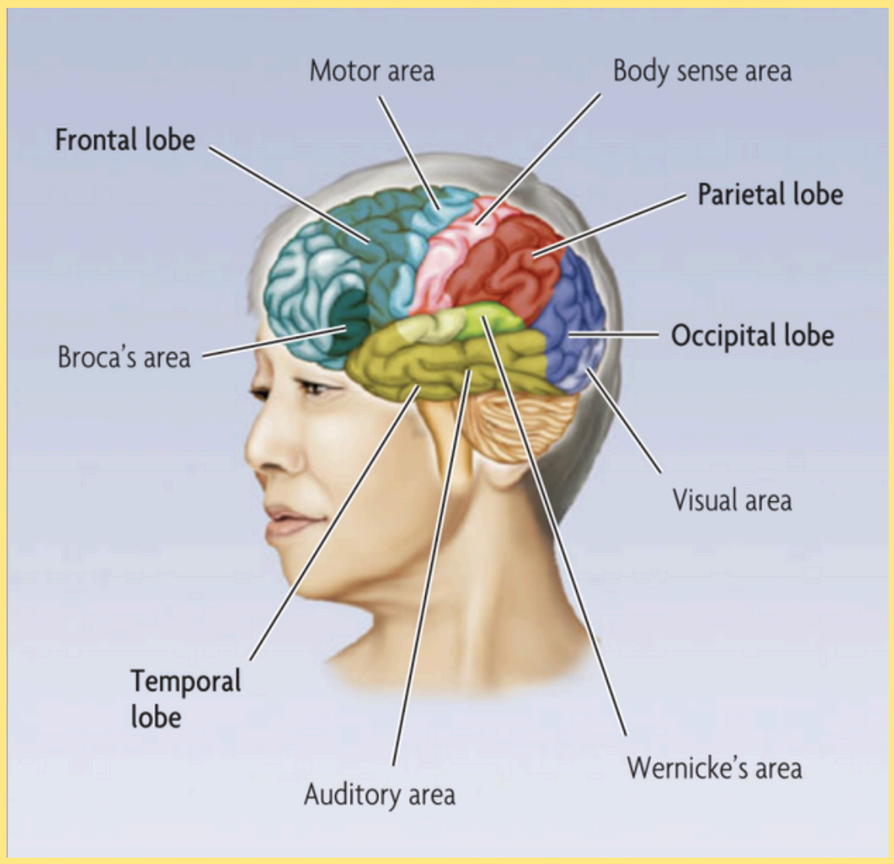
1. Studies have found that medication (such as Huiyu Dan and Huiyan Capsules) and acupuncture can improve speech function in patients with post-stroke aphasia. Among these, electroacupuncture has been shown to activate brain regions related to language processing in patients with motor aphasia following a stroke, aiding in the treatment of Chinese aphasia. While acupuncture demonstrates a certain level of efficacy, no clinical cases of long-term successful treatment have been reported to date. Transcranial magnetic stimulation (TMS) is another method that can be used to treat Chinese aphasia. In 2021, a case of pure word deafness aphasia was reported, where the patient underwent repeated TMS therapy.
2. After rTMS (repetitive transcranial magnetic stimulation) treatment, significant improvements were observed in auditory comprehension abilities, except for environmental sound recognition. Repetition and dictation abilities also showed marked improvement. Studies indicate that combining rTMS with computer-assisted therapy or synchronous speech therapy yields better outcomes compared to using rTMS alone.

The above outlines treatment approaches and future prospects for Chinese aphasia patients. For general aphasia patients, there are currently three main methods: Constraint-Induced Aphasia Therapy (CIAT), Multimodality Aphasia Therapy (M-MAT), and Music Therapy.
3CIAT (Constraint-Induced Aphasia Therapy) is a language game-based training method that uses only verbal communication and relies on patients' correct verbal responses.CIAT enhances treatment by prohibiting non-verbal communication methods, gradually increasing the difficulty of stimuli, and progressively forming more complex speech responses.This therapy was later adapted into a newer version called Intensive Language Action Therapy (ILAT). Research indicates that CIAT significantly improves quality of life and can alleviate aphasia symptoms at any stage of the condition.M-MAT (Multimodality Aphasia Therapy) is an intensive approach that integrates all available verbal and non-verbal strategies to enhance treatment efficiency. It is primarily used for patients with severe Broca’s aphasia. Compared to standard community care, M-MAT demonstrates superior therapeutic effects in word retrieval, functional communication, and quality of life.Music Therapyis an emerging interdisciplinary field combining musicology, medicine, and psychology. It enhances dopamine activity in the mesolimbic system, stimulates damaged brain language areas, regulates neuroplasticity within the language network, and promotes the recovery of speech functions. Neuroimaging studies reveal that music and language share overlapping brain networks, both activating the Broca’s area. As a result, intensive music training can aid in restoring language function and improving speech abilities in aphasia patients.What kind of improvements were achieved? Are there any experimental data or case studies available? I need comparative cases for reference.

Supplement:

Broca's aphasia and Wernicke's aphasia are two different types of aphasia. Broca's aphasia generally refers to motor aphasia, with speech expression impairments being the most prominent. It is mainly characterized by effortful, non-fluent speech, sparse word output, and a telegraphic style (mainly content words), though patients can express basic meanings.Wernicke's aphasia generally refers to sensory aphasia, characterized by fluent speech with a larger volume of speech, but with frequent errors and excessive words. What the patient says is often difficult for others to understand. They also have severe impairments in understanding spoken language, often answering questions incorrectly, and have abnormal repetition, naming, reading, and writing abilities. In comparison, the symptoms of Wernicke's aphasia are more complex, and treatment is more difficult.

Broca's area is located in the frontal lobe of the brain and serves as the motor center for language, primarily responsible for formulating speech production.
Thus, the main cause of Broca's aphasia lies in the patient's inability to fully express content after it is processed in the brain. The lesion in Wernicke's aphasia is not in "speech expression," but rather occurs during the processing of auditory input, where the brain has difficulty processing the information. Therefore, it is relatively more difficult to treat, with a lower cure rate.



Conclusion

In daily life, aphasia patients endure more suffering than we might imagine. In clinical practice, therapists should base their approach on the individual’s functional impairments, considering the patient's specific needs to choose the most suitable treatment method to aid in their recovery. In everyday life, society should show more understanding and care for aphasia patients, offering timely assistance when needed to help them overcome difficulties.

References

[1] 邱乐思,妥玉婷,汪洋,等.脑卒中后失语症治疗的研究进展[J].中国当代医药,2024,31(14):182-185.
[2] 王瑜元,孙长慧,白玉龙.卒中后失语症患者失语症类型及严重程度影响因素的回顾性分析[J].中国康复,2024,39(06):323-328.
[3] 常辉,王海燕.失语症研究的语言学转向[J].山东外语教学,2024,45(03):34-44.
[4] 刘佳,范琳.汉语失语症研究：回顾与展望[J].山东外语教学,2024,45(03):23-33.
[5] p1原AP Psychology and life教材
[6] p2原北京十一学校AP Psychology课程教案

SMART MAGAZINE AUTHOR: Kita EDITOR: Yates

Resistant starch – a carbohydrate that doesn't make you fat

Keywords: Resistant starch; carbohydrates

Abstract

Resistant starch（RS）is the general term of the starch and the starch degradation products that cannot be digested and absorbed by human body in 120 mins, but can be fermented in large intestine. Resistant starch has many health benefits, such as preventing diabetes, improving intestinal microenvironment, lowering blood sugar, lowering blood lipids and losing weight, which has aroused great interest among scholars in the fields of agriculture, food and medicine.

Introduction

When it comes to "carbohydrates", many people avoid them, fearing that eating too much will make them fat and raise their blood sugar, and even regard it as a "stumbling block" on their road to health. However, there is a type of "carbohydrates" that not only does not cause obesity, but also has the effect of reducing fatty liver. It is our protagonist today - resistant starch!

1 What is resistant starch?

Resistant starch, also known as indigestible starch, cannot be enzymatically hydrolyzed in the small intestine, but can undergo fermentation reaction with volatile fatty acids in the human gastrointestinal colon. Simply put, resistant starch is indeed real starch from a chemical structure point of view, but it cannot be broken down into glucose by the human body as an energy source.Of course, the small intestine cannot digest it, so it will smoothly enter the large intestine. The starch-loving species in the large intestine will welcome it very much and prosper because of "sufficient food", becoming the dominant bacteria. The short-chain fatty acids produced by these bacteria are beneficial for maintaining a healthy intestinal environment, preventing hyperlipidemia and colon cancer, etc. [1]

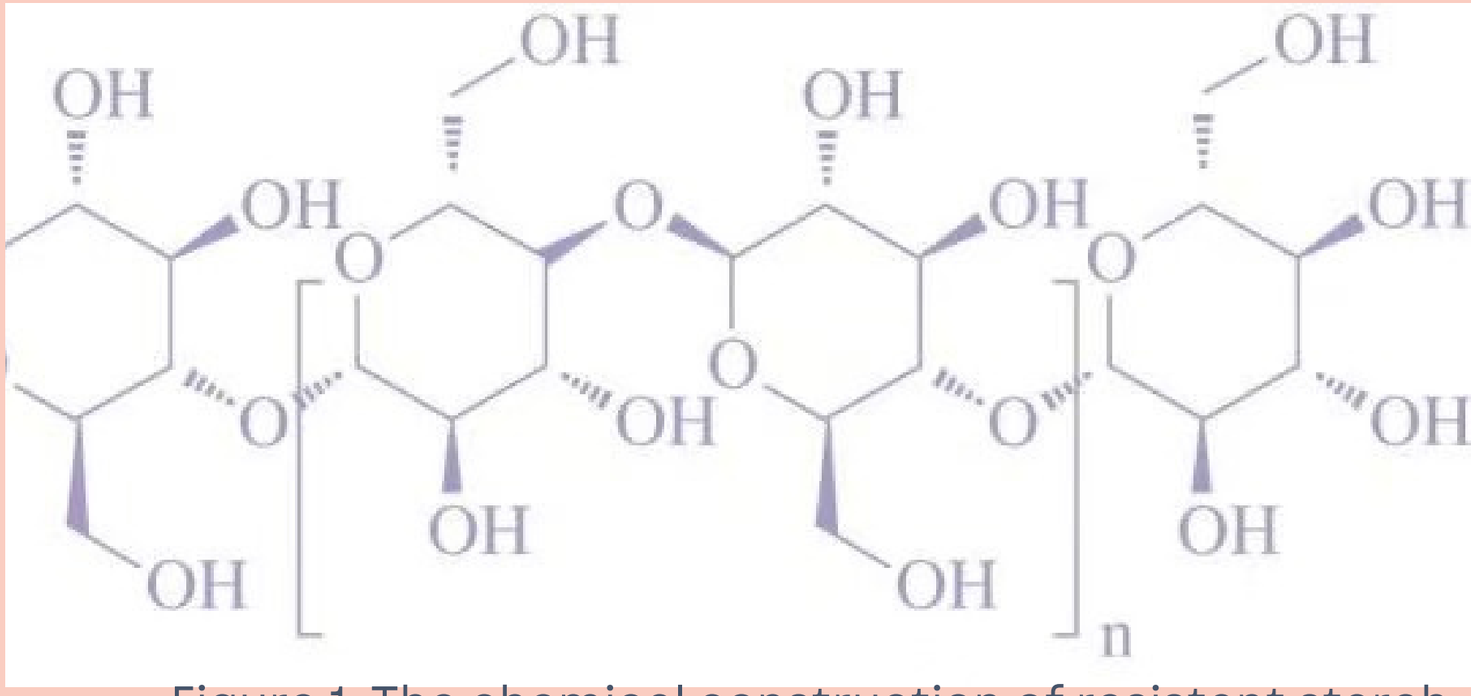


Figure 1. The chemical construction of resistant starch

2 Resistant starch’s benefits for human

In 2023, a study published in Cell Metabolism showed that a diet rich in resistant starch can change the composition of intestinal flora, reduce triglycerides and liver enzyme levels associated with liver damage and inflammation, and alleviate fatty liver. [2]

抗性淀粉含里	食品种类
≤1.0%	熟马铃薯、热米饭、高谷糠早餐麦片、小麦粉
1.0%～2.5%	普通早餐麦片、饼干、面包、冷米饭、冷稀饭
2.5%～5.0%	玉米片、大米碎片、油炸土豆片、爆豌豆
5.0%～15.0%	煮扁豆、煮蚕豆、生大米、玉米粉、豌豆
>15.0%	生马铃薯、生豆子、高直链玉米淀粉、青香蕉

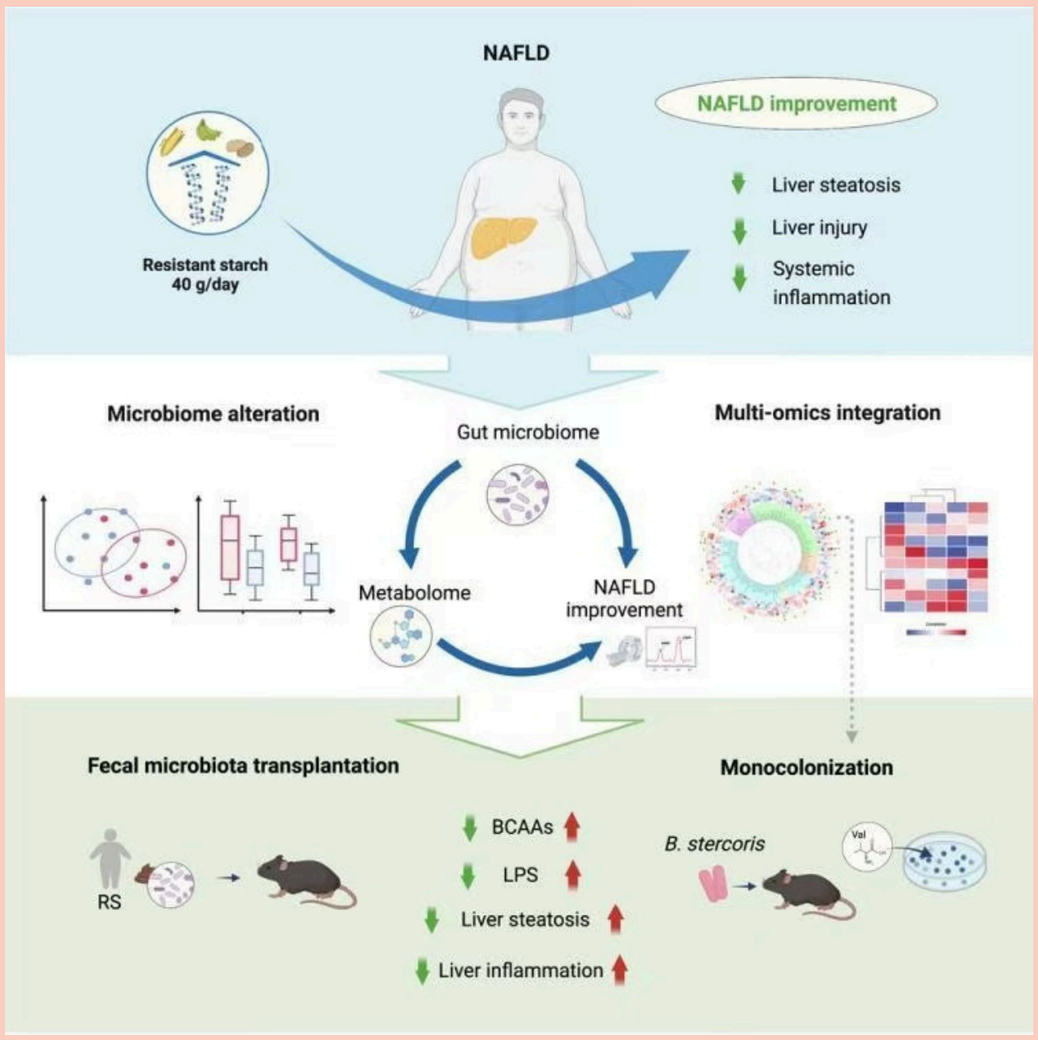
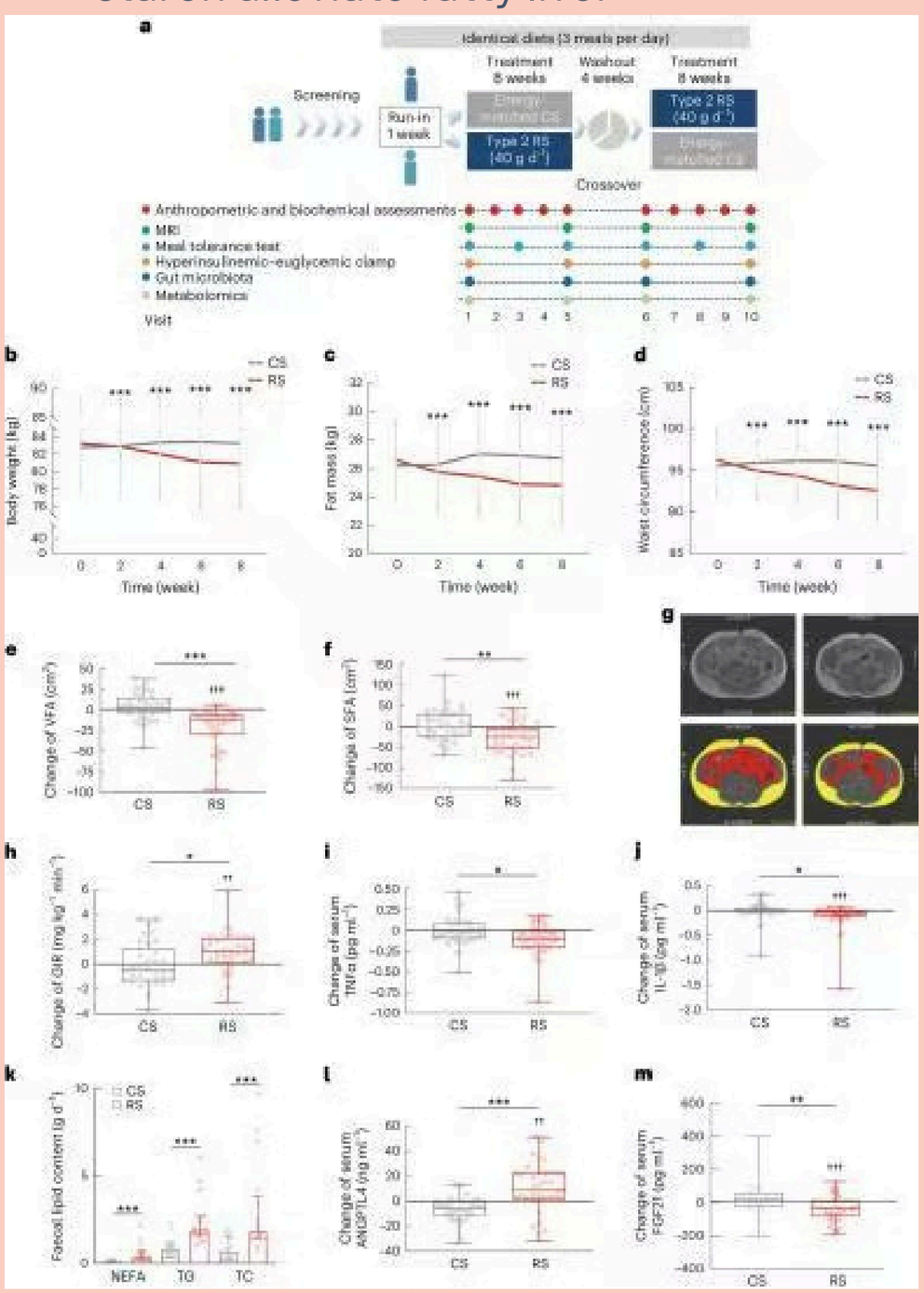


Figure 3. The mechanisms that resistant starch alleviate fatty liver



F igure 4. An 8-week intervention with resistant starch reduces obesity in overweight individuals

After a four-month clinical trial, researchers found that compared with the control group, resistant starch significantly reduced the triglyceride content in the participants' liver (absolute decrease of 9.08%, relative decrease of 39.42%), and the participants' weight, BMI, fat content, etc. also decreased significantly.

Not only that, the liver damage of the participants in the resistant starch experimental group was also improved to a certain extent, and the participants' total cholesterol, low-density lipoprotein and high-density lipoprotein all improved, alleviating dyslipidemia.

In February 2024, another study published in Nature Metabolism showed that only 8 weeks of resistant starch supplementation not only helped lose weight, but also improved the insulin resistance level of overweight individuals. [3]

The study found that participants who supplemented with resistant starch for 8 weeks lost an average of 2.8 kg in weight, with a significant decrease in fat content and waist circumference. In addition, the participants' glucose tolerance and insulin sensitivity were also improved accordingly.

3 How to improve the content of resistant starch in food?

1 Reheating the main dish after cooling

When foods with high starch content, such as rice, steamed bread, and potatoes, are cooked and refrigerated, the resistant starch content will increase significantly,and the glycemic index will decrease significantly.

After reheating, the resistant starch will still be partially retained. After reheating cold rice that has been refrigerated, the blood sugar response is still lower than that of fresh hot rice.

Under high temperature, starch will absorb water and gelatinize, the resistant starch content will decrease, and the food will be easier to digest and absorb, but correspondingly, the blood sugar response will also increase.

2 Choosing the cooking method which use less water

Choosing cooking methods with less water, such as baking and microwave heating, can effectively reduce starch gelatinization. The resistant starch content of baked potatoes is higher than that of boiled potatoes.

Conclusion

Through the introduction of this article, I believe everyone has a simple understanding of resistant starch, but I also advise everyone not to blindly increase the intake of resistant starch. If we balance the intake of resistant starch through appropriate food choices in daily life, we can make our diet structure healthier and more reasonable.

Reference:
[1]Englyst, H. N. & Cummings, J. H. Digestion of the polysaccharides of some cereal foods in the human small intestine. Am. J. Clin. Nutr. 42, 778–787 (1985).
[2]Resistant starch decreases intrahepatic triglycerides in patients with NAFLD via gut microbiome alterations.Cell Metabolism.SEPTEMBER 05, 2023.doi.org/10.1016/j.cmet.2023.08.002
[3]Resistant starch intake facilitates weight loss in humans by reshaping the gut microbiota.Nature Metabolism.26 February 2024.doi.org/10.1038/s42255-024-00988-y

SMART MAGAZINE AUTHOR:Molly Meng EDITOR: Hecate

Emerging Cancer Mutation Loci ——SWI/SNF Family

Keywords: SWI/SNF complex, gene mutation, targeted drugs

Abstract:

Systematic sequencing of cancer genomes has revealed high mutation rates in genes encoding chromatin regulatory proteins, one of the most compelling topics in cancer biology. Among these aberrations, mutations in the genes encoding subunits of the SWI/SNF chromatin remodeling complex are the most frequent, occurring centrally in nearly 25% of all cancers. It has been identified that at least nine genes encoding subunits of the SWI/SNF complex are recurrently mutated in cancer. Therefore, more and more studies are focused on understanding prognosis, especially the potential significance of treating mutations in genes encoding SWI/SNF subunits. In this article, investigators review the emerging data on the mechanisms by which mutations affecting the SWI/SNF complex promote cancer and describe the targeted therapies presented by these mutations, including the emerging immunotherapy against immune checkpoint inhibitors. The researchers also focused on clinical trials specifically targeting cancer patients with certain SWI/SNF gene mutations, and some related drugs were investigated.

SWI/SNF remodels chromatin

Inside the cell, the approximately 3 billion base pairs of the human genome are tightly associated with histones and other proteins, a structure called chromatin. In chromatin, the human genome is organized and compacted by wrapping 146-base pairs of DNA around histone octamers, forming structures called nucleosomes, such that approximately 3 meters of DNA is packed inside a nucleus that is only 5 μm in diameter on average. In addition, nucleosomes often block the binding of transcription factors responsible for activating or inactivating the expression of specific genes. Cellular machinery works in concert with transcription factors to mobilize nucleosomes to control gene expression, a process known as chromatin remodeling. The SWI/SNF family of chromatin remodeling complexes, also known as the BRG1 / BRM-associated factor (BAF) complex (BOX1), is a key regulator of nucleosome positioning. SWI/SNF is known to consist of three subfamilies: classical BAF (cBAF); Polybrominated biphenyl BAF (PBAF); Non-classical BAF (ncBAF), also known as GLTSCR1 or GLTSCR1L-containing and BRD9 containing (GBAF) complexes. All three complexes contain core subunits such as SMARCC1, SMARCC2 and the atpase SMARCA4 or SMARCA2, but also many variable subunits forming hundreds or thousands of distinct SWI/SNF complexes.

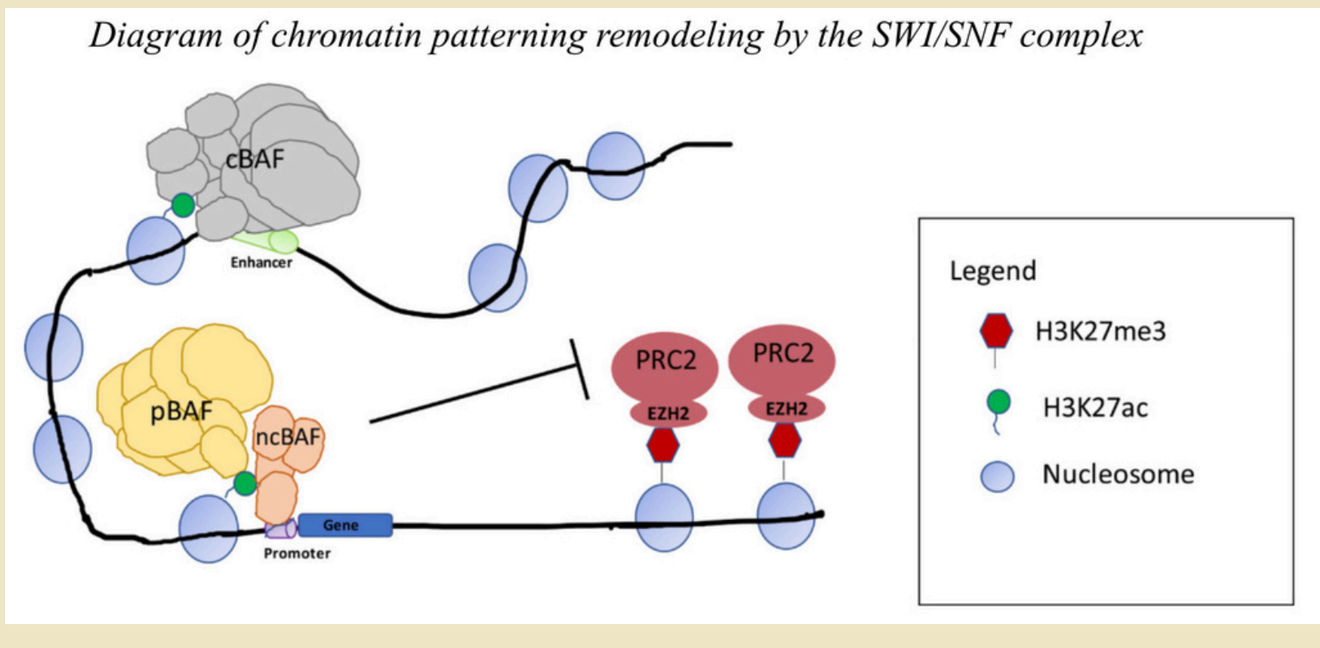


Figure 1
Diagram of chromatin patterning remodeling by the SWI/SNF complex

The complex contains a well-defined genomic region of action called an enhancer. These enhancers are short, non-protein-coding DNA elements that form binding sites fortranscription factors that regulate the transcriptional activity of neighboring genes. Enhancers account for only a small fraction of the genome, but SWI/SNF complexes are highly enriched at these sites and play an important role in regulating enhancer accessibility required for transcription factors to activate gene expression.

Mutations and mechanisms of SWI/SNF in tumors

Overall, at least nine different SWI/SNF subunits have been identified as recurrent mutations in multiple cancers (Figure 2), and altogether accounting for nearly 25% of all cancers.

Mutations in the genes encoding SWI/SNF subunits, including nonsense mutations, frameshift mutations, and deletion mutations, often indicate a loss-of-function phenotype. However, subsequent studies confirmed the possibility that SMARCB1 mutant cancers were not driven by loss of SMARCB1 protein itself, but by aberrant function of the residual SWI/SNF complex. For example, the SS18-SSX fusion, found in synovial sarcoma, conferred increased nucleosome mobilization activity on the SWI/SNF complex.

General carcinogenic factors such as radiation can cause a wide variety of cancers, but SWI/SNF subunit mutations are often associated with specific significant cancer phenotypes. For example, SMARCB1 inactivation is largely limited to the rare pediatric rhabdoid tumors described above and a few other types of cancers.

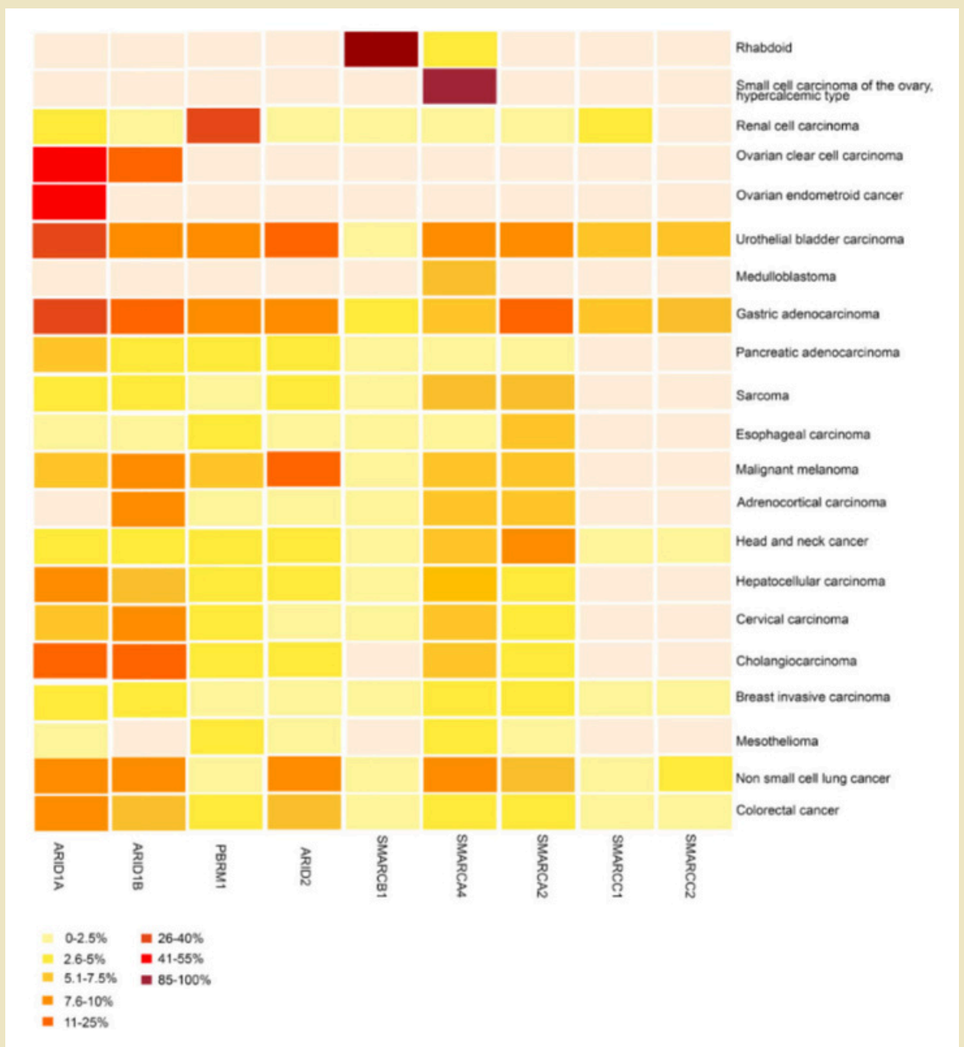


Figure 2
Mutation frequency of SWI/SNF subunits in human tumors

Prognosis of SWI/SNF-deficient tumors

The effect of SWI/SNF on prognosis is subunit-specific and/or context-specific. Notably, not only mutations, but also global changes in the expression of specific SWI/SNF subunits have been considered as prognostic markers for survival, and the relationship between their expression levels and prognosis changes with tumor type. For example, low expression of SMARCA4 and ARID1A proteins was associated with favorable outcomes in breast and bladder cancer patients, whereas loss of SMARCA2 and ARID1A expression was associated with poor overall survival in patients with hepatocellular carcinoma or cervical cancer.

The researchers found that mutations in some genes encoding SWI/SNF subunits often cause specific dependence on genes encoding other SWI/SNF subunits, suggesting that subunit mutations do not completely inactivate SWI/SNF function, but rather allow the loss of SWI/SNF subunits to be partially compensated by a counterpart. It is currently possible to inhibit SWI/SNF atpase activity by oral allosteric inhibitors or protein cleavage targeting chimeras. Protein cleavage targeting chimeras are bifactional molecules that use ubiquitin ligases to covalently link to target-binding ligands and directly target degraded target proteins. They have entered clinical trials.

Whether inhibition of EZH2, the enzymatic subunit of PRC2, affects the selection of SWI/SNF subunit mutations leading to cancer has been the subject of considerable research. Early genetic studies in Drosophila suggested that the SWI/SNF complex and Polycomb repressor complex have opposite gene regulatory functions, and subsequent studies found that mammals are evolutionarily conserved in this aspect. It has been shown that SMARCB1 mutations lead to local overdeposition of Polycomb repressive complexes, but the global activity of these complexes may be downregulated as the cell attempts to rebalance the gene expression profile. Based in part on clinical trial data, the FDA granted accelerated approval to the EZH2 inhibitor Tazemetostat for patients 16 years of age or older with metastatic or unresectable epithelioid sarcoma.

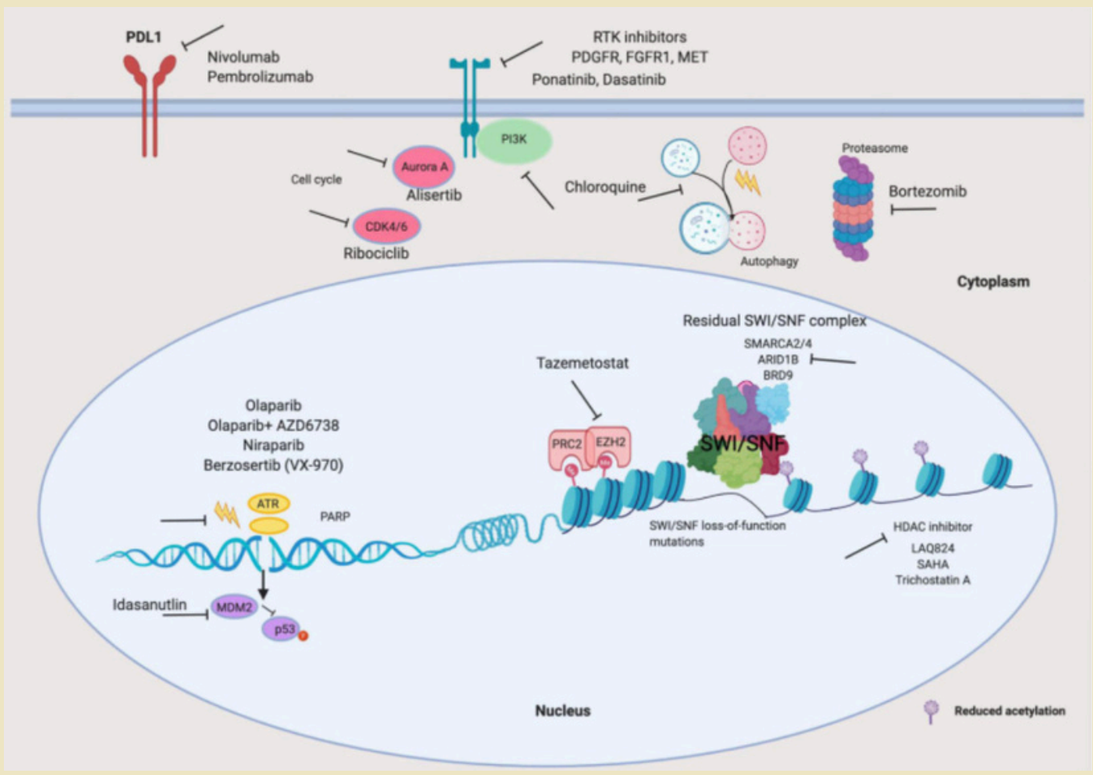


Figure 3

Translational mechanisms in SWI/SNF complex-deficient

Summary

Comparing to mutations in classical oncogenes and tumor suppressor genes, widespread SWI/SNF gene mutations have been discovered in cancer for only a decade, so our understanding of their mechanisms and corresponding therapeutic implications is still in its infancy. While it is now clear that inactivating mutations affecting a single SWI/SNF subunit can confer specific dependencies on other genes or pathways, whether any broad dependencies extend to all SWI/SNF cancers remains a critical question. Mutations in SWI/SNF subunits often increase the dependence on other components of the remaining SWI/SNF complex, so more and more research is being conducted around therapeutic targeting of the SWI/SNF complex itself. One caveat, however, is that whether inhibition of certain subunits can actually promote cancer development and/or growth remains to be determined.

Works Cited

Mittal, P., & Roberts, C. W. M. (2020). The SWI/SNF complex in cancer - biology, biomarkers and therapy. Nature reviews. Clinical oncology, 17(7), 435–448. https://doi.org/10.1038/s41571-020-0357-3IF: 81.1 Q1

SMART MAGAZINE AUTHOR: Nox EDITOR: Hecate

Turning to the Beginning of Life– Theoretical Basis and Current Methods of In Vitro Totipotent Stem Cell Culturing

Keywords: totipotent stem cells; pluripotent stem cells; in vitro culture

Introduction

As studies focusing on life cycles are taking further steps, scientists can now induce and obtain various tissues through a single cell. For instance, induced pluripotent stem cell (iPSC) technology, which won the Nobel Prize in Physiology or Medicine in 2012, is commonly employed in regenerative medicine and disease modeling research. Albeit iPSCs have helped achieve multi-directional differentiation, they lack totipotency, unable to differentiate into all types of cells in an organism. Therefore, in vitro culturing totipotent stem cells became a technical challenge in research of early embryonic development. Meanwhile, totipotent stem cells (TSCs) can differentiate into any type of cell. TSCs exist in the early stages after fertilization, usually the first few days of embryonic development. Compared to iPSCs, TSCs can generate organoids or complex tissues with adnexa support and thus cover the limitations faced by iPSCs in complex tissue generation. Furthermore, since TSCs can generate placental cells, they are unique tools for studying placenta-related diseases (e.g. gestational hypertension and placental dysfunction).

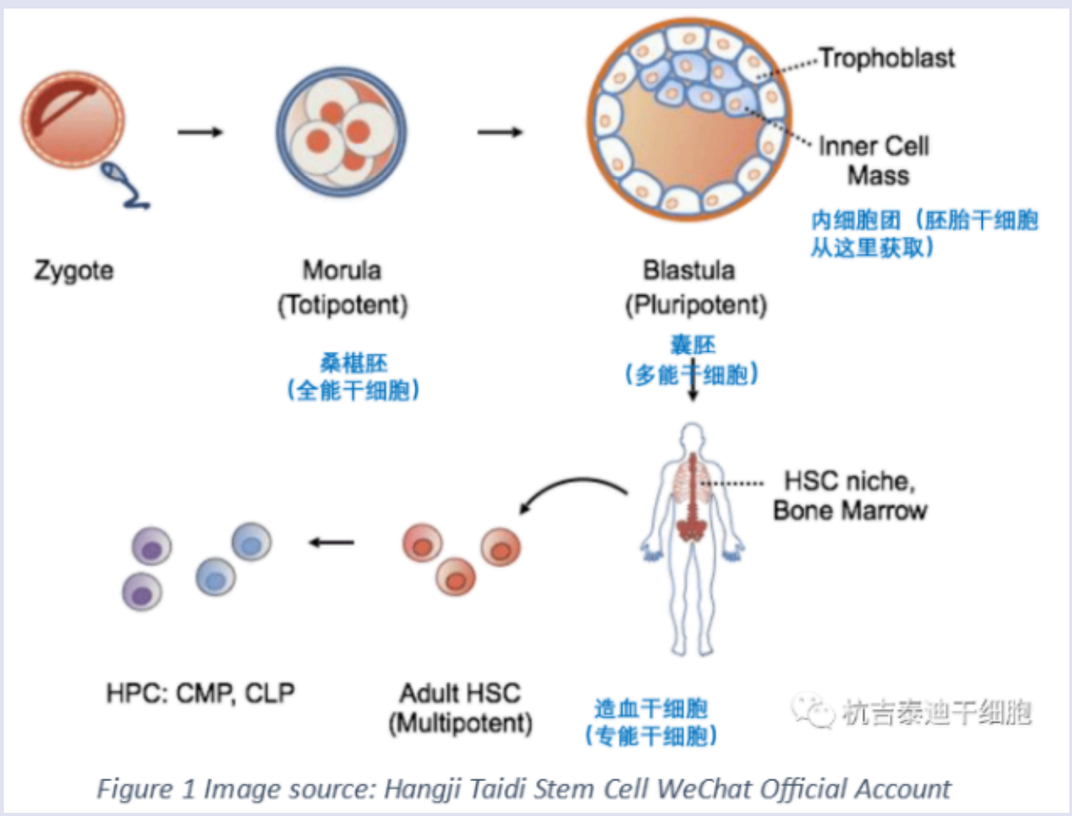


Figure 1 Image source: Hangji Taidi Stem Cell WeChat Official Account

Challenge in Culturing TSC

Previous laboratory observations revealed that pluripotent stem cell cultures contained a small number of cells with totipotency that is similar to 2C (two-cell) embryo stage in mice, suggesting the potential of in vitro culturing totipotent stem cell. However, totipotent stem cells' extremely brief existence in the animal life cycle makes it far more challenging to obtain them than obtaining pluripotent stem cells.

In mice, totipotent cells are limited to the zygote and 2C stages, while in humans and other mammals, this totipotent state extends to the 4-8 cell embryo stage. Subsequently, totipotent stem cells rapidly differentiate into outer trophectoderm (TE), primitive endoderm (PrE) (which later develop into placenta and yolk sac for maternal-fetal exchange), and epiblast (EPI) (which later develops into multiple embryonic organs). Although techniques for in vitro culture pluripotent stem cells are relatively mature, breakthroughs in totipotent stem cell culture are recent. Due to the extremely brief existence of totipotent stem cells (TSCs), scientists initially approached this challenge through studying pluripotent stem cells (PSCs). The researchers explored their differences and conversion mechanisms to achieve in vitro capture and maintenance of totipotent stem cells.

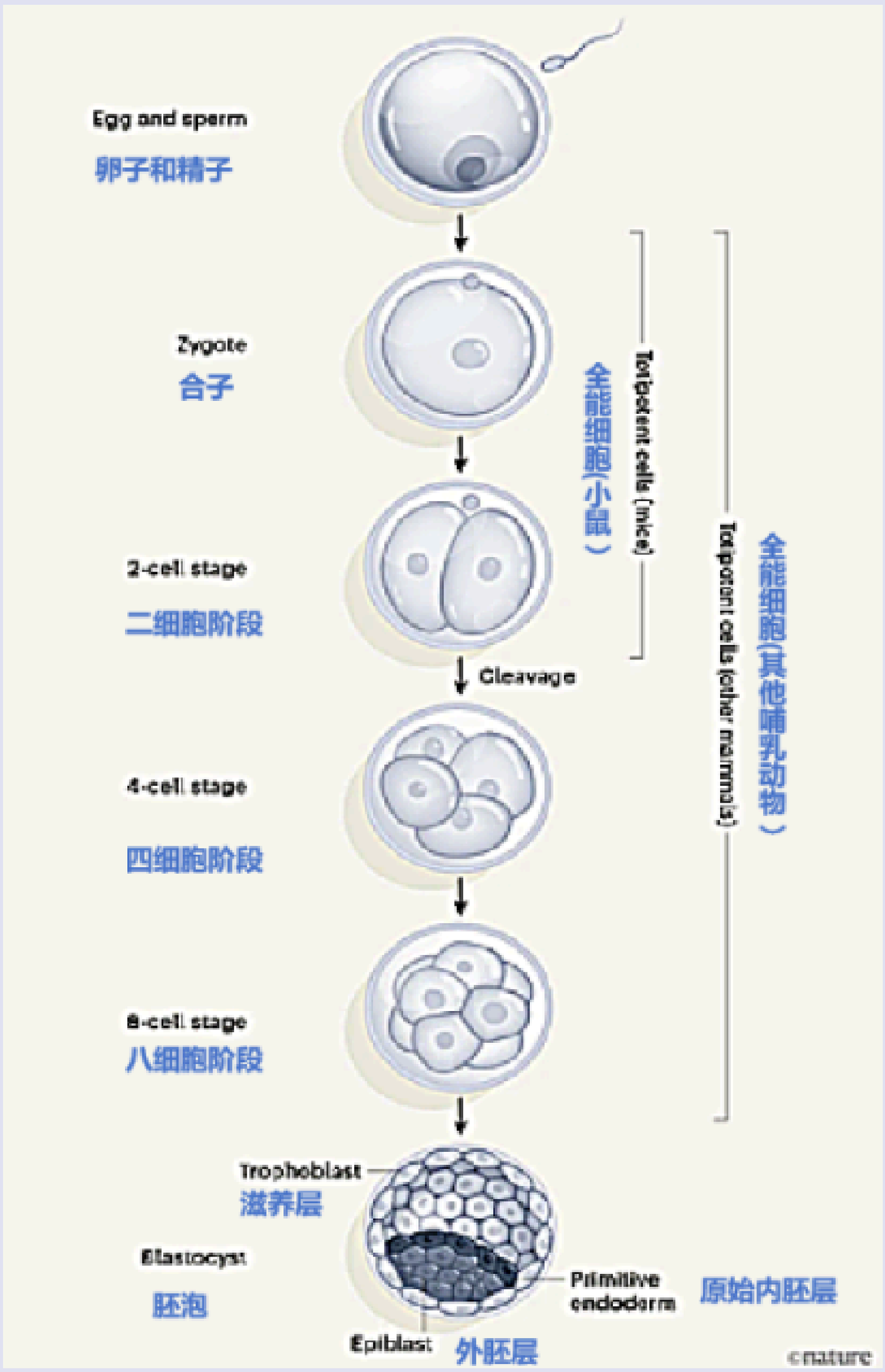


Figure 2 Image depicting early embryonic development stages - source: Nature, translated by Nox

Differences Between TSCs and PSCs

The differences between studying totipotent and pluripotent stem cells are fundamental for understanding their conversion mechanisms. Totipotent stem cells' molecular markers are closely associated with early-stage embryonic development, expressing genes such as Zscan4, Zfp352, DUX4, Dux, and Dppa2/4, reflecting their high similarity to early blastomere cells. In contrast, pluripotent stem cells express markers primarily related to the pre-implantation inner cell mass (ICM) state, with core pluripotency transcription factors like Oct4, Sox2, Nanog, and Klf4/5 maintaining their pluripotency. Regarding epigenetic characteristics, totipotent stem cells exhibit low levels of DNA methylation and specific histone modifications similar to early cleavage-stage cells, while pluripotent stem cells show higher DNA methylation levels and more complex epigenetic modifications, reflecting their intermediate developmental state. Overall, totipotent stem cells closely resemble 2-/4-cell blastocysts at the transcriptome level, possessing characteristics closer to the earliest stages of embryonic development, enabling them to differentiate into all embryonic and non-embryonic tissues, demonstrating broader developmental potential than pluripotent stem cells.

Regulatory Mechanisms of TSC-PSC Conversion

Understanding the regulatory mechanisms governing the conversion between totipotent and pluripotent stem cells has been a focal point in stem cell research. In 2020, Professor Gao Shaorong's team at Tongji University, collaborating with Professor Wang Jianlong's team at Mount Sinai School of Medicine (now at Columbia University Irving Medical Center), published research in Cell Stem Cell revealing the role of DUX-miR-344-ZMYM2-mediated MERVL activation in generating totipotency-like cells. The study established miR-344 as the first non-coding positive regulator of 2CLC expanded pluripotency and pre-implantation development, functioning through the DUX→miR-344-|Zmym2/Lsd1-|MERVL pathway.

In 2021, Shen Li's team at Zhejiang University used 3D genome sequencing and epigenomic studies to reveal dynamic changes and regulatory functions of higher-order chromatin structure during ESC to totipotent-like cell conversion. They found that chromatin structure becomes looser during this transition, with blurred A/B compartment boundaries, weakened TAD structures, and reduced chromatin loops.

In August 2023, Lin Chengqi and Luo Zhuojuan's team at Southeast University discovered that the young LINE-1 subset L1Md_Ts is marked by ELL3 and functions as an enhancer in mouse embryonic stem cells. In December 2023, Shuai Ling's team at Nankai University identified crucial roles of Dyrk1a and Catip genes in mouse ESC fate regulation.

Methods for Inducing TSCs from PSCs

1. Blocking Signal Pathways

Scientists initially succeeded in inducing totipotent stem cells by targeting signal pathways. In 2017, Liu Pengtao's team at the Sanger Institute successfully induced ESCs and iPSCs into Expanded Potential Stem Cells (EPSCs) by using specific small molecule inhibitors to block MAPKs, Src, and Wnt/Hippo/TNKS1/2 signaling pathways. In 2021, a team led by Wu Jun at UT Southwestern Medical Center and BGI-Shenzhen established stable XPSCs cell lines with "Formative" characteristics across multiple species by simultaneously activating FGF/Erk, TGF-β/Smad, and WNT/β-Catenin pathways.

2. Alternative Approaches to Inhibit Pluripotency-to-Totipotency Transition

Beyond blocking or activating signal pathways, researchers have achieved PSC-to-TSC conversion through methods such as blocking post-translational modifications and altering chromatin structure. In 2021, Du Peng's team at Peking University successfully captured and maintained mouse totipotent stem cells using the spliceosome inhibitor Pladienolide B. In February 2022, Wang Jichang's team at Sun Yat-sen University reprogrammed mouse ESCs into totipotent-like stem cells through chemically induced chromatin remodeling.

Conclusion

Research on totipotent stem cells enables scientists to better understand life's origins, cell fate determination mechanisms, and regulation of complex gene networks in early development. In regenerative medicine, totipotent stem cell research shows immense potential. Their ability to generate all cell types provides theoretical and practical foundations for organ regeneration and cell replacement therapy. If scientists can effectively control and maintain the totipotent state, it could lead to advanced tissue repair and organ transplantation technologies, fundamentally addressing tissue damage and organ shortage issues. Additionally, the low epigenetic modification state of totipotent stem cells provides crucial insights into cell fate transitions and reprogramming mechanisms, potentially advancing personalized medicine, anti-aging therapies, and genetic disease treatments.

References

1. Du, P., & Wu, J. (2024). Hallmarks of totipotent and pluripotent stem cell states. Cell Stem Cell, 31(3), 312-333.
2. Yang, F., Huang, X., Zang, R., Chen, J., Fidalgo, M., Sanchez-Priego, C., ... & Wang, J. (2020). DUX-miR-344-ZMYM2-mediated activation of MERVL LTRs induces a totipotent 2C-like state. Cell stem cell, 26(2), 234-250.
3. Zhu, Y., Yu, J., Gu, J., Xue, C., Zhang, L., Chen, J., & Shen, L. (2021). Relaxed 3D genome conformation facilitates the pluripotent to totipotent-like state transition in embryonic stem cells. Nucleic acids research, 49(21), 12167-12177.
4. Meng, S., Liu, X., Zhu, S., Xie, P., Fang, H., Pan, Q., ... & Lin, C. (2023). Young LINE-1 transposon 5′ UTRs marked by elongation factor ELL3 function as enhancers to regulate naïve pluripotency in embryonic stem cells. Nature cell biology, 25(9), 1319-1331
5. Zhang, W., Sun, S., Wang, Q., Li, X., Xu, M., Li, Q., ... & Shuai, L. (2023). Haploid-genetic screening of trophectoderm specification identifies Dyrk1a as a repressor of totipotent-like status. Science Advances, 9(51), eadi5683. .
6. Baker, C. L., & Pera, M. F. (2018). Capturing totipotent stem cells. Cell stem cell, 22(1), 25-34.
7. Yang, J., Ryan, D. J., Wang, W., Tsang, J. C. H., Lan, G., Masaki, H., ... & Liu, P. (2017). Establishment of mouse expanded potential stem cells. Nature, 550(7676), 393-397.
8. Yu, L., Wei, Y., Sun, H. X., Mahdi, A. K., Arteaga, C. A. P., Sakurai, M., ... & Wu, J. (2021). Derivation of intermediate pluripotent stem cells amenable to primordial germ cell specification. Cell stem cell, 28(3), 550-567.
9. Mazid, M. A., Ward, C., Luo, Z., Liu, C., Li, Y., Lai, Y., ... & Esteban, M. A. (2022). Rolling back human pluripotent stem cells to an eight-cell embryo-like stage. Nature, 605(7909), 315-324.
10. Xu, Y., Zhao, J., Ren, Y., Wang, X., Lyu, Y., Xie, B., ... & Deng, H. (2022). Derivation of totipotent-like stem cells with blastocyst-like structure forming potential. Cell Research, 32(6), 513-529.
11. Hu, Y., Yang, Y., Tan, P., Zhang, Y., Han, M., Yu, J., ... & Ding, S. (2023). Induction of mouse totipotent stem cells by a defined chemical cocktail. Nature, 617(7962), 792-797.
12. Shen, H., Yang, M., Li, S., Zhang, J., Peng, B., Wang, C., ... & Du, P. (2021). Mouse totipotent stem cells captured and maintained through spliceosomal repression. Cell, 184(11), 2843-2859.
13. Yang, M., Yu, H., Yu, X., Liang, S., Hu, Y., Luo, Y., ... & Wang, J. (2022). Chemical-induced chromatin remodeling reprograms mouse ESCs to totipotent-like stem cells. Cell Stem Cell, 29(3), 400-418.
14. Strelez, C., Perez, R., Chlystek, J. S., Cherry, C., Yoon, A. Y., Haliday, B., ... & Mumenthaler, S. M. (2023). Integration of patient-derived organoids and organ-on-chip systems: Investigating colorectal cancer invasion within the mechanical and GABAergic tumor microenvironment. bioRxiv.

The CHINESE VERSION

English Version in the Front

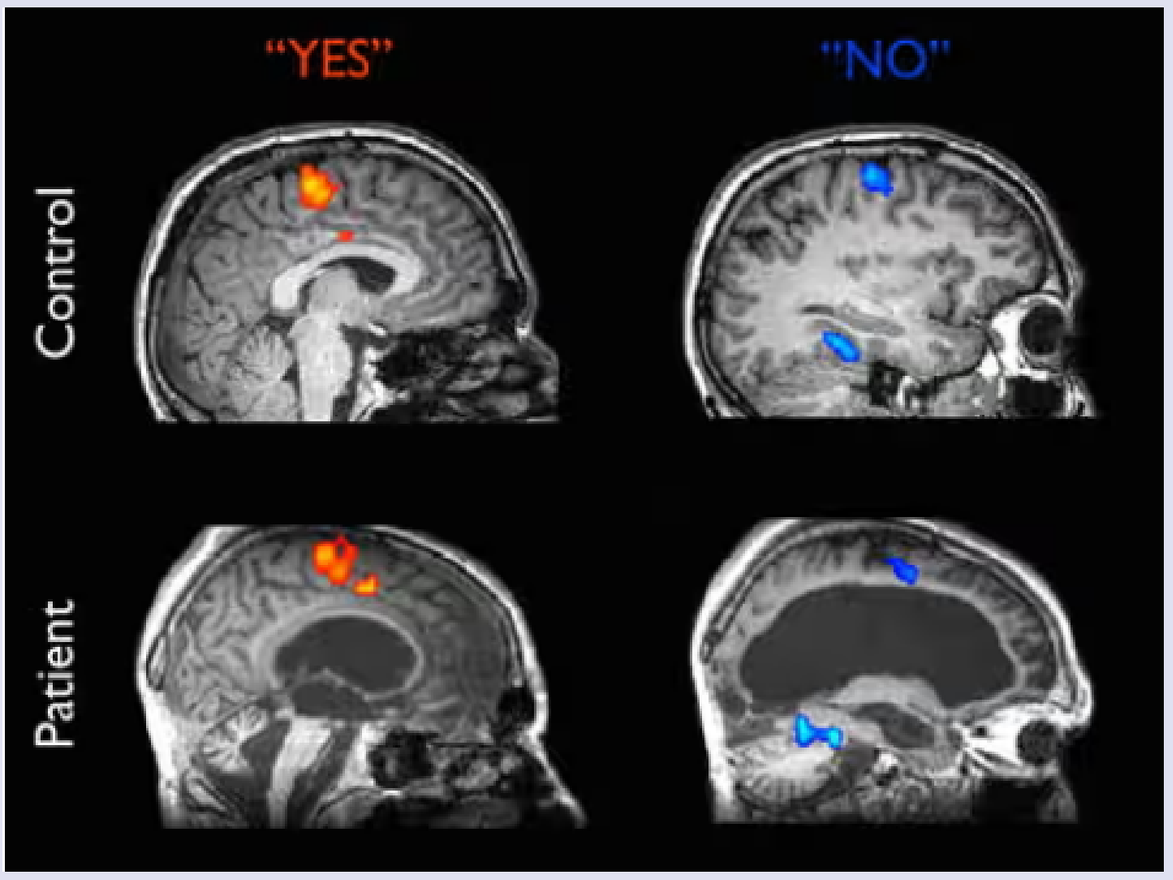
SMART MAGAZINE AUTHOR: Evelyn Yi EDITOR: Hecate Ye

植物人状态下的意识

关键词: 植物人状态；意识；神经成像；fMRI；脑电图

导言：

植物人是否仍然具备意识？植物人状态通常被描述为一种“清醒的无意识”状态，因 此我们往往会假设答案是否定的。此外，临床上将植物人状态（无意识）与微意识状态（有 意识）区分开来，意味着被诊断为植物人状态的人应该完全没有意识，否则就应被归类为微 意识状态。然而，由于植物人状态的诊断是基于可观察的行为，并依此制定了具体的临床 标准，因此符合这些标准的患者仍然有可能保留一种未被检测到的意识。事实上，最近的 一些研究利用先进的功能神经影像学技术发现，部分被诊断为植物人的患者实际上确实保 留了隐蔽的意识。



什么是植物人状态?

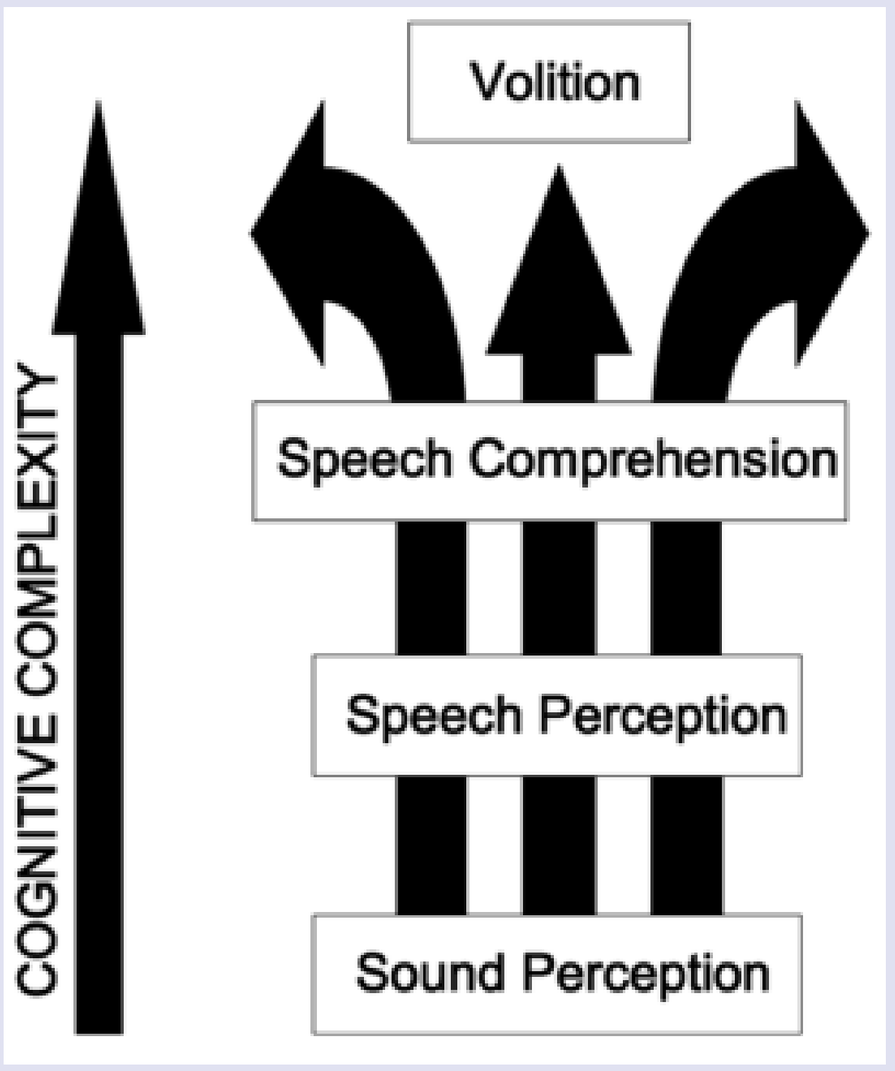
植物人状态（VS）不同于昏迷，它指的是一种拥有昼夜循环的睡眠和苏醒，但缺乏意 志行为和意识的状态。长期处于植物人状态的患者可能会表现出复杂的反射行为，例如眼 球运动、打哈欠以及对有害刺激（如疼痛）的不自主反应（如收回肢体），但他们缺乏持续 的、有目的的反应，这表明他们对自身及周围环境没有意识。经过反复检查，如果未能发现 患者对视觉、听觉、触觉或有害刺激有持续的、自愿的反应，也没有语言理解或表达能力 的证据，就可以确诊为植物人状态。

植物人状态通常是由严重的脑损伤造成的，这种情况下，大脑中负责高级认知功能 （如思考、推理、自主行为和信息处理）的部分会出现功能障碍。尽管这些高级脑功能丧失， 但下丘脑和脑干仍然可以正常工作，从而维持一些基本的自主生存功能，如调节呼吸、心 率、睡眠-觉醒周期和体温。相比之下，昏迷则通常涉及大脑和脑干的功能受损，限制了患者 在没有医疗干预的情况下执行自主神经功能的能力。

测量植物状态患者的认知功能

正电子发射断层扫描（PET）和功能磁共振成像（fMRI）等功能神经成像技术可用于 检测标准临床评估所忽略的隐蔽认知功能。通过这些神经成像技术进行的研究能够证实某 些残余的感知能力。例如，研究人员开发了一系列分层评估，旨在测量最简单的听觉信息处 理到更高级的认知功能，以确定患者的认知水平。

在最低的层次的声音感知， 是通过比较患者对所有听觉刺激（例如语音和白噪声）的 反应与对寂静的反应来进行评估的。确定声音感知后，研究进一步通过比较语音刺激与相 关噪声来评估语言感知。最高的认知水平则测量语言理解能力，通过比较模棱两可的句子 与没有歧义的句子来评估（例如，将“吱吱声/小溪来自天花板/密封处的横梁- the creak/creek came from a beam in the ceiling”与“她的秘密写在日记里- her secrets were written in her diary”进行比较）(Owen 等人)。利用这种方法，对一组七名植物人患者进行的研究发现，其 中三名患者表现出语言处理功能。其中两名患者对语义模糊的比较做出了显著反应，表明 他们在语言理解的语义层面上进行了高阶处理。

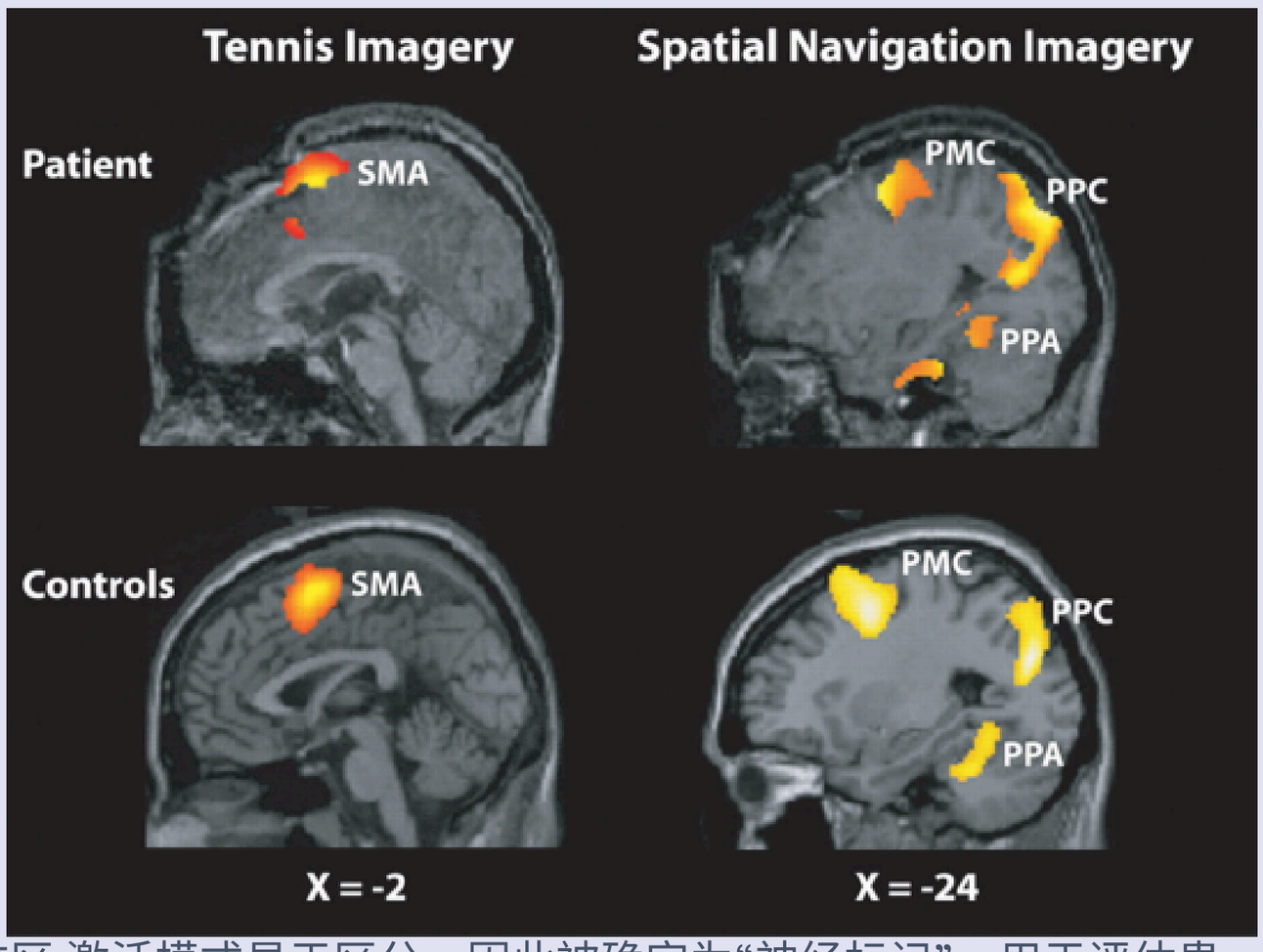


不过，需要指出的是，植物人拥有较高的认知功能只是个例，而非普遍现象。例如， 更大规模的研究表明，大多数植物人患者仅保留了最基本的感官处理功能，而对感知和意 识体验至关重要的高级处理区域（如次级体感皮层、岛叶皮层、后顶叶皮层和前扣带回皮 层等）仍然处于不活跃状态。此外，这些语言相关的大脑反应可能仍然是下意识的神经反 应，不需要有意识的觉知。因此，在尚不清楚正常人大脑对类似刺激的反应的情况下，这些 植物人的语言处理证据是否足以表明他们具有意识仍然存在疑问。

测量正常人的意识功能

为了研究在健康的实验对象中意识与高级语言处理之间的关系，戴维斯及其同事对 一组处于不同镇静水平（清醒、轻度镇静和深度镇静）的健康人进行了研究。志愿者在扫描 过程中聆听了以下内容：1) 含有歧义词的句子，2) 没有歧义词的句子，3) 与句子相关的噪 音。研究发现，无论镇静程度如何，三组志愿者在与语言感知相关的大脑活动上均存在显著 反应，这表明语言感知不受镇静剂的影响。然而，与语言压缩相关的额叶下部和颞叶后部的 额外反应在轻度镇静的状态下却未能观察到。由于语义处理似乎只能在清醒的志愿者中观 察到，因此可以推断，表现出与语义处理相关的大脑激活的植物状态患者可能具备一定的意识。

通过 fMRI 传递意识



即便如此，确认一个人是否有意识的最有力方式仍然是通过他们的口头交流或可识 别的行为符号（例如，眨眼表示“是”或“否”）来传达意识，但由于植物人无法进行有效的语 言和行为反应，因此，研究人员设计了通过大脑信号来表达意识状态的方法。

在神经专家阿德里安·欧文博士（Adrian Owen）的一项研究中，一名因交通事故受伤 的患者表现出植物人状态的行为特征，例如自发睁眼、睡眠/觉醒周期、不一致的反射行为 和缺乏自主运动反应。该患者被要求完成两个心理任务：“想象打网球”和“想象在家中参观 各个房间”。这些任务之所以被选择，是因为它们会激活不同的大脑区域。例如，想象打网 球会激活辅助运动区，而想象在家中走动则会激活海马旁皮层等区域。这两种任务的脑区 激活模式易于区分，因此被确定为“神经标记”，用于评估患者是否“理解指令、记住指令（在 扫描前的指令阶段），并根据指令执行特定且高度受限的心理任务”，这表明他们对外界刺 激有直接而自愿的反应（欧文等人）。

在随后的研究中，欧文博士进一步通过将“想象在家中参观”作为“是”的表示、“打网 球”作为“否”的表示，成功建立了医生与患者之间的双向交流。与斯科特·鲁特利（Scott Routley）的交流中，欧文博士成功获得了鲁特利的有意识回应。鲁特利十年前被诊断为植 物人状态，一直对周围环境没有知觉。为验证鲁特利的理解和回答能力，欧文首先提出了 “天空是蓝色的吗？”和“天空是黄色的吗？”等简单问题。然后，他进一步询问鲁特利是否 疼痛，鲁特利通过“打网球”的想象回答了“否”，表明他没有感到疼痛。

另一种方法：

另一种研究植物人隐蔽意识的方法是通过脑电图（EEG）检测他们对指令的反应能 力。2010年的一项研究中，研究人员测试了一些对外界无反应的患者，看他们是否能通过大 脑活动表现出意识的迹象。实验中，患者完成了两项想象任务：想象自己握拳和扭动脚趾。 每项任务以听觉指令开始，例如“每次听到‘哔’的一声，试着想象自己将右手握拳再放松， 或扭动所有脚趾再放松。”指令结束后，伴随一系列听觉信号，用来提示何时开始想象动 作。健康对照组进行了相同的任务，但被指示放空注意力，以此作为对比基线，便于评估患 者的脑电活动。结果显示，16名患者中有3人（19%）显著地回应了指令。这些研究结果表明 ，在被诊断为植物人状态的患者中，尽管没有明显意识表现，其中一些人仍能通过成功调节 脑电图对指令作出反应，展示出隐蔽的意识。

结论

尽管大多数植物人状态患者不会展现任何意识迹象，最近的研究表明，在确定病人 准确的意识状态时，有时需要作出超越传统的临床评估。这一发现更加证明了发展先进诊 断技术的需求，因为这些技术能够识别出此前被视为植物人状态的患者中存在的细微意识 迹象。通过改进意识评估方法，我们可以更好地理解这些患者的实际状态，确保他们获得适当的护理和支持。

引用

Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T. A., Fernández-Espejo, D., Pickard, J. D., Laureys, S., & Owen, A. M. (2011). Bedside detection of awareness in the vegetative state: A cohort study. The Lancet, 378(9800), 2088–2094. https://doi.org/10.1016/S0140-6736(11)61224-5 Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. Science (New York, N.Y.), 313(5792), 1402. https://doi.org/10.1126/science.1130197 Shea, N., & Bayne, T. (2010). The Vegetative State and the Science of Consciousness. The British journal for the philosophy of science, 61(3), 459–484. https://doi.org/10.1093/bjps/axp046

SMART MAGAZINE AUTHOR: Olivia Qian EDITOR: Amanda

鸟类语言

摘要：

这篇文章主要探讨了科学家们所收集的百万份鸟鸣数据，并揭示了鸟鸣与其行为之间的联系。

关键词: 鸟类，语言，AI，地球物种计划（Earth Species Project, ESP）

背景信息：

ESP 是一个致力于“利用人工智能解码非人类交流”的非营利组织。目前，ESP的研究对象包括斑胸草雀（zebra finch）、乌鸦（Crows）和白鲸（beluga whales）等。

鸟鸣主要分为歌曲（song）与叫声（calls）两种，从持续时间来看有长短之分。鸟鸣的拟声词有tseets、chirrups、rreeyoos、seeew-soooos等。

Kleindorfer在本科期间接受了只有雄鸣禽会唱歌，而雌鸣禽不会的传统观念。然而，在后期的工作中，她发现雌性鸣禽的歌声与雄性的一样复杂，这一发现颠覆了她早期的观念。直到后来，她开始致力于研究那些被忽视或不为人知的鸟类叫声。

在本文中，科学家通过收集数百万份的鸟类叫声与行为关系的数据，透过利用AI算法研究数据从而得出规律。科学家们发现了鸟类语言比人类之前所认为的还要复杂。在研究过程中，他们发现，鸟鸣声具有学习和模仿的特征，其中还包含着语法，并有着思维辩证的能力。

I.鸟类语言的复杂性超乎想象

鸟类不仅仅会唱歌来吸引配偶或保卫领地，它们也会通知彼此捕食者或食物的位置。灰雁（greylag goose）就有十种不同的叫声，而大山雀（Tit）的词汇量更是超过两百种。

II.鸟类也有学习语言的能力

极品细尾鹪鹩（Superb Fairy Wren）作为一夫一妻制的鸟种，集体抚养幼鸟。Kleindorfer的研究团队在极品细尾鹪鹩巢中安装摄像头和麦克风，发现母鸟孵蛋时会发出类似“摇篮曲”的鸣叫声可能会吸引掠食者。研究小组进一步将孵化鸣叫声与雏鸟的乞食鸣叫声进行比较，发现每个乞食鸣叫声都与母亲孵化鸣叫声中的一个元素相匹配，雏鸟在孵化后乞食的叫声与母亲的孵化叫声有明显的相似之处。这表明，鸟类能在孵化后中学习母语。这一发现颠覆了传统的鸣禽学习理论。

Kleindorfer的团队还发现，每个鸟类家庭都有自己独特的“方言”(familect)，雏鸟会从父母那里学习这些独特的叫声。雏鸟倾向于向父母学习其独特的叫声元素，而避免学习父母共有的叫声元素，这一特征有助于它们在保持家庭联系的同时发展自己的个体特征。

III.鸟类具有抽象思维能力

学者Toshitaka Suzuki的研究表明，鸟类并不仅仅有对特定的声音做出反应的能力，它们似乎能够理解及生成一些抽象的概念。

Suzuki设计了一个实验，透过播放不同叫声并配合特定的动作来测试鸟类的反应。他的实验灵感来源于人类可以从模糊的图像中识别出具体的形象，例如想象云朵的形状。实验中，只有当Suzuki播放蛇的叫声并模仿蛇的移动方式移动棍子时，鸟才会像面对真实威胁一样做出反应，这表明鸟类可能具有对蛇的基本认知。Suzuki的这一发现强调了鸟类可能具备形成心理形象的能力。

IV.鸟类也懂语法

在2023年的一项研究中，Suzuki的研究发现：大山雀（tits）对鸣叫声的语序很敏感。例如，ABCD和DABC的叫声，即对于标准语序和被打乱语序的叫声，会让鸟类有不同的反应。同样，Suzuki对南非黑头雀（southern pied babblers）和栗冠拟椋鸟（chestnut-crowned babblers）的研究也得出了类似结果，这表明鸟类语言中可能存在某种语法规则。

V. 鸟类会使用象征性手势

Suzuki观察到雌性大山雀（Tits）在进入巢穴时会对雄性用翅膀做出类似“你先请”（After you）的手势（Sophisticated syntax）。在Suzuki看来，这表明这种拍打翅膀的动作不仅仅是一个简单的指示，而是一种象征性手势。这种非语音的交流方式，表明了鸟类也可能使用象征性手势来进行沟通。

VI.鸟类具有模仿和欺骗的能力

在一片不显眼的树林里，Maddie Cusimano注意到一只翠鸟(Kingfisher)正在潜水捕鱼，一只雏鹰(Eagle)则站在一棵光秃秃的树上。在这片区域，一种听起来像红尾鹰(Red-tailed hawk)的叫声反复出现，但很快他们意识到，这其实是一只松鸦（Garrulus glandarius）在模仿鹰的叫声。研究人员说道：他们有时会这样做，可能是为了吓跑其他掠食者，但声音模仿的确切原因还尚未知晓。

鸟类语言与人类语言的对比：

尽管鸟类的语言展现出惊人的复杂性和多样性，但依旧无法与人类语言的复杂性相比：

1. 递归性有限：语言学家 Chomsky 认为递归性是人类语言的核心特征，允许我们表达极其复杂的概念。鸟类语言目前没有表现出这种无限递归的能力，它们的鸣叫组合方式相对简单，表达的含义也较为有限。
2. 文化传承的复杂性：鸟类语言的传承方式和复杂程度远不及人类语言。人类语言的文化传承依赖于社会结构、教育体系和文字记录，而鸟类的文化传承则主要依赖于模仿和学习。
3．元语言能力的缺乏：人类可以使用语言来谈论语言本身，即拥有元语言能力。我们可以分析语言的结构、意义和功能，并用语言来定义和解释语言。

相关研究：

1. 神经科学的进展：科学家们开始使用更加先进的技术来研究鸟类大脑如何处理和产生鸣叫。
2. 鸣叫的学习与遗传：科学家们发现鸟类的鸣叫声既有先天遗传因素也有后天学习成分，这一发现挑战了我们对动物学习能力的传统认识。
3. 鸣叫的社会功能：鸟类的鸣叫不仅仅是为了吸引配偶，它们还用鸣叫来标记领地、警告同伴等。

总结：

这篇文章透过与鸟类语言与人类语言的比较，揭示了鸟类语言的复杂性，并指出了两者之间的差异。鸟类的生活并非缺乏情感，许多思维和语言尚未知晓，因此难以被人类理解。此研究不仅重新定义了我们对鸟类智慧的看法，同时也提醒我们应更加尊重和好奇地探索与我们共享地球的生物。我们该倾听鸟类的声音，重新思考这硕大的生物世界。

引用

https://www.newyorker.com/magazine/2024/10/21/how-scientists-started-to-decode-birdsong

SMART MAGAZINE AUTHOR: Chris TRANSLATOR: Lunette EDITOR: Hecate

阿尔兹海默症

引言

阿尔兹海默症（AD）的特征包括认知功能衰退，最初表现为记忆力的丧失，特别是对近期对话和时间的遗忘，以及定向力和计算力的下降。患者可能在熟悉的环境中感到困惑，对时间的感知也会变得模糊。随着病情的发展，语言能力可能会受到影响。患者难以找到适当的词汇，说话时可能会中断、重复，或者遇到命名困难，这些都严重影响了日常沟通。空间认知障碍也是一个问题，患者可能在熟悉的环境中迷路，或者在执行需要空间认知的任务时遇到挑战，如组装家具或理解地图，这增加了他们的安全风险。情绪和行为方面的异常也常见于患者，他们可能会经历无法解释的情绪波动、焦虑、抑郁，甚至幻觉和妄想，这些都会对他们的精神状态和行为产生负面影响。随着病情的进一步恶化，患者可能会失去执行基本自我照顾任务的能力，如穿衣、进食和如厕，这会导致他们的生活质量显著下降，并给家人和护理人员带来沉重的负担。这种病症多发于60岁以上的老年人。

摘要

阿尔茨海默症（AD）是以学习、记忆功能衰退为主要临床特征的一种进行性神经退行性疾病。该病多发于老年人，但目前发病年龄呈年轻化趋势，该病发病隐匿，进展缓慢，患者可逐渐失去生活自理能力，严重威胁其生命健康。本篇文章将从有关阿尔兹海默症的病理学、阿尔兹海默症的治疗方法、阿尔兹海默症的多靶点药物研究进展三方面展开论述。

第一方面——阿尔兹海默症的病理学

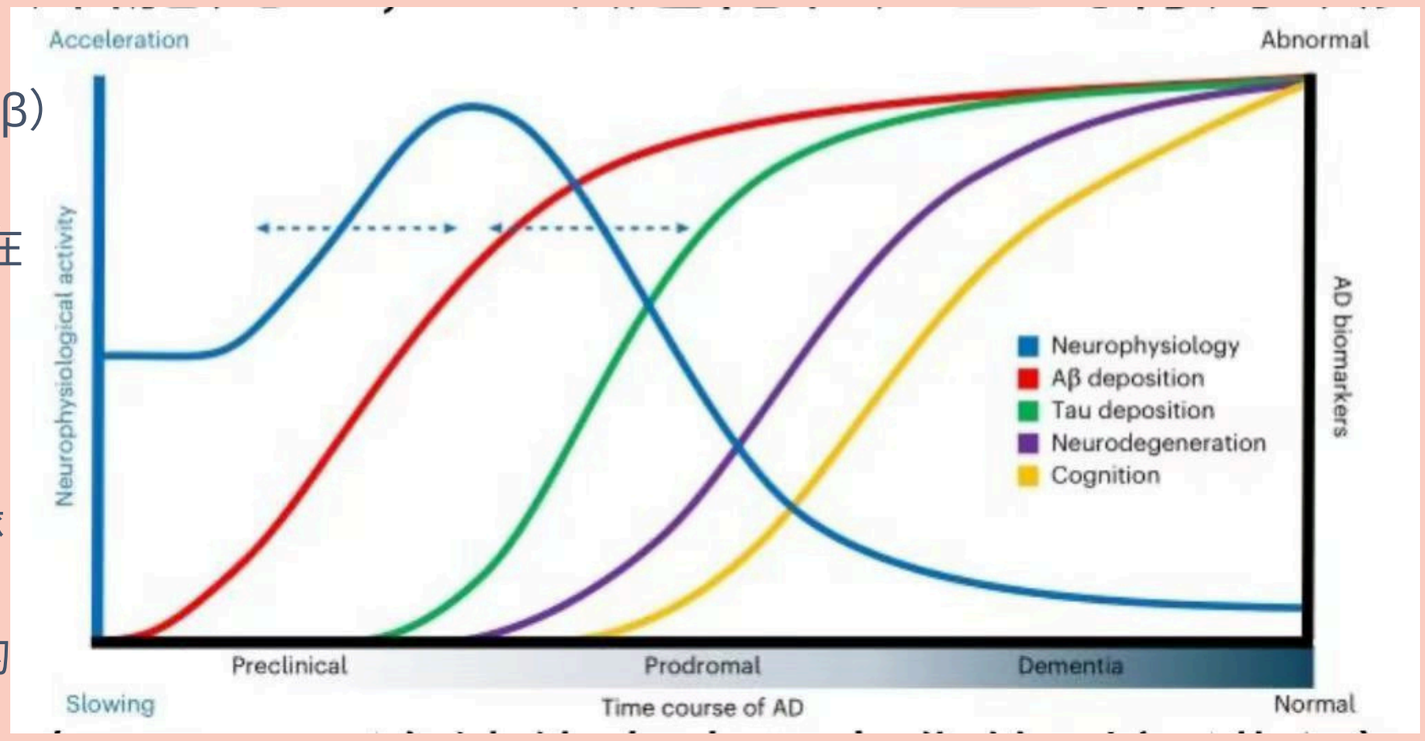
阿尔兹海默症（AD）的动物和计算模型表明，早期的淀粉样蛋白-β（Aβ）沉积物会促进神经元进入过度活跃状态，而随后的tau沉淀物随着行为缺陷的出现而表现出相反的抑制作用。

Aβ斑块沉积与tau沉积

AD的在组织病理学标志是大脑中β淀粉样蛋白（Aβ）斑块和过度磷酸化tau蛋白纤维缠结的积累。

Aβ斑块沉积可以在症状出现前二十年开始，最近在代谢基线活性高的皮质区域积累，例如楔前叶、内侧眶额皮质和后扣带回皮质，然后扩散到整个新皮质、脑干和皮质下核团。

Tau沉积首先在内嗅皮质中积累，然后扩散到边缘区域，最终扩散到新皮质。



这些有害作用的的一个可能机制是Aβ和tau蛋白的联合积累改变了神经生理信号，引发连锁反应中进一步的病理过程，促进疾病进展。动物模型表示，Aβ趁机会诱导神经元过度活跃的毒性机制，从而加剧Aβ病理本身。这种正反馈过程将促进tau蛋白病理学的积累和传播。这样的协同作用可能驱动神经元活动向相对低活动状态转变。在此阶段，神经元活动显著减弱，最终导致细胞死亡，组织退化和严重的行为改变。

早期Aβ和tau沉积可能通过破坏局部神经元群的兴奋/抑制平衡而产生因果效应，这反过来又改变了整个大脑网络的宏观神经生理频谱。疾病后期，Aβ和tau蛋白的积累会导致神经元活动逐渐从活跃转向低活跃，特别是在宏观尺度上表现为倒U型后的α带活动水平跨越AD连续体的轨迹。

通过对散发性AD痴呆家族史的无症状老年人进行毫秒级定时任务MEG源成像以及Aβ和tau蛋白的全脑定量PET成像，发现早期Aβ沉积与宏观神经生理学表现的过度活跃有关，表现为α波段活动增加和δ波段活动减少。并且在出现早期颞叶tau病理学的个体中，这些效应从震荡加速转变为缓慢，如α带减少和δ带活动增加。从而证明，从神经生理活动的加速到减慢的转变幅度与纵向认知能力下降相关。

相关研究数据表明，神经生理活动的变化确实广泛影响皮质并超出中颞叶区域，这可能是AD后期观察到的广泛放缓的前兆，并且发现，神经生理学动力学的这种转变本质上是由节律性大脑活动驱动的，而不是由宽带心律失常背景活动驱动的。

胆碱能神经元选择性变性

胆碱能神经元分泌的神经生长因子（NGF）发挥靶源性营养作用，能维持基底前脑胆碱能系统，而Aβ病理性沉淀会破坏NGF代谢通路，无法产生足量成熟NGF的同时降解增加、前体NGF积聚、酪氨酸激酶TrkA（神经生长因子受体）表达减少，最终使基底前脑神经元突触萎缩，胆碱能系统功能缺失，加重Aβ和P-Tau病理。在AD早期，伴随基底前脑胆碱能神经元变性，大脑皮质和海马的胆碱能突触减少，记忆力（尤其是情景记忆）发生进行性丧失.

神经炎症

小胶质细胞是中枢神经系统中的单核巨噬细胞，参与神经炎症的发生。当Aβ蛋白大量积聚超过阈值时，小胶质细胞监视和突出重塑的生理功能就被削弱，发生炎症和淀粉样前体蛋白(APP)加工的正反馈循环，使Aβ、神经元碎片等持续积累，由于M1型小胶质细胞不断产生促炎细胞因子和趋化因子，最终建立起慢性的和不可消退的炎症。

第二方面——阿尔兹海默症的治疗方法

在阿尔兹海默症（AD）早期，周细胞收缩毛细血管，增加其液压阻力并捕获免疫细胞，从而减少脑血流量（CBF）。目前缺乏减轻AD中周细胞介导的收缩的治疗方法。在疾病进展中早期用尼莫地平阻断Cav可改善CBF，减少白细胞在周细胞胞体的停滞并减轻脑缺氧。Cav阻滞也大大减少了人类皮质组织中淀粉样蛋白β（Aβ）引起的周细胞收缩/因此，在AD早期降低周细胞可能提供一种增强AD脑能量供应和认知功能的治疗策略。

抑制阿尔兹海默症模型的通道放松周细胞，改善脑血容量并减少免疫细胞停滞和缺氧

大多数阿尔茨海默病 (AD) 疗法旨在去除β淀粉样蛋白(Aβ)斑块或防止tau蛋白过度磷酸化，但未能阻止认知能力下降。其中一项目标靶点是脑血流量（CBF），AD受影响的大脑区域CBF减少约 45%，足以导致注意力丧失、有髓鞘轴突破坏、空间记忆缺陷和突触丧失。CBF减少与毛细血管通过时间异质性增加有关，从而加剧组织缺氧。临床前AD中较早开始的CBF减少表明，在突触或神经元丢失之前，血流变化对AD早期的认知变化具有因果影响，其起效速度比Aβ或tau沉积更快，并与认知能力下降相关。

在人类AD中，这种 CBF 减少与收缩周细胞的毛细血管收缩有关。这可能反映了Aβ刺激活性氧 (ROS) 的产生，从而释放血管收缩剂内皮素-1 (ET-1)。

周细胞的收缩方式

周细胞收缩是由细胞内钙浓度（）升高或激活Rho激酶通路引起的。

周细胞的收缩通过三种方式降低CBF。首先，它产生的毛细管直径减小，从而减少了可用于流动的横截面积，从而根据泊肃叶定律增加了阻力。其次，它通过促进血液中的细胞与血管壁的相互作用而导致血液粘度增加。最后，血细胞会卡在直径减小的血管中。这对于白细胞尤其重要，因为白细胞比红细(RBC)更大且不易变形。

减少 AD 周细胞收缩的药物应通过增加毛细血管直径、降低血液粘度和减少毛细血管阻塞来增加 CBF。它们可能会更长时间地维持正常的神经元功能，并延迟对神经元的不可逆转的有害影响。相关研究表明在AD小鼠模型中，尼莫地平降低了周细胞（），从而松弛整个毛细血管床的周细胞，扩张毛细血管并减少中性粒细胞和其他细胞造成的毛细血管阻塞。因此CBF增加，组织缺氧减少。

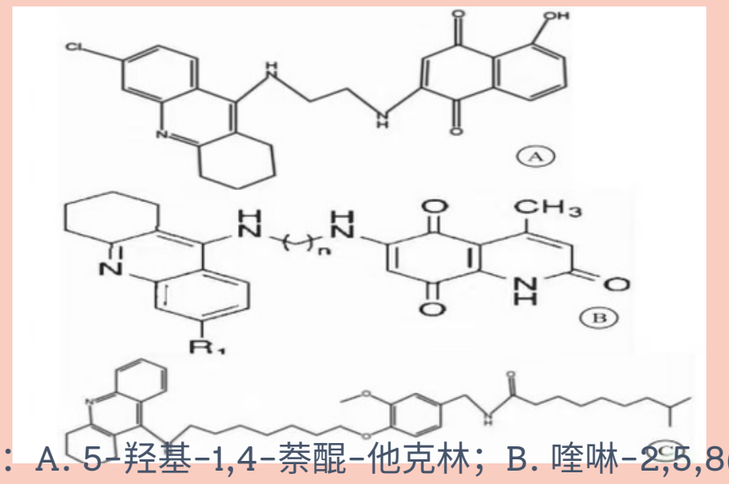
第三方面——阿尔兹海默症的多靶点药物研究进展

目前临床上已经获批治疗AD的药物只有胆碱酯酶（ChE）抑制剂（如多奈哌齐、加兰他明）以及N-甲基-D-门冬氨酸（NMDA）受体拮抗剂（如美金刚）。然而，临床应用表明，上述药品随能缓解AD症状，但不能有效阻滞病程，且会引起幻觉、头晕以及肝毒性等严重毒副作用，导致长期疗效不理想。而近年来，多靶点药物凭借其具有能针对多个病理环节和致病靶点，平衡多个病理因素，在保证药效的同时能有效减少药物毒副作用等优势，成为了AD相关药物设计的重要方案。

抗阿尔兹海默症的多靶点药物

多靶点药物主要由对化合物库进行高通量筛选，或是基于构效关系、药效团、蛋白结构、内源性配体等设计而得到的靶向不同靶点、代谢稳定的单分子药物，相较于单靶点药物和固定计量联合药物有特定的优势。

• 他克林类化合物

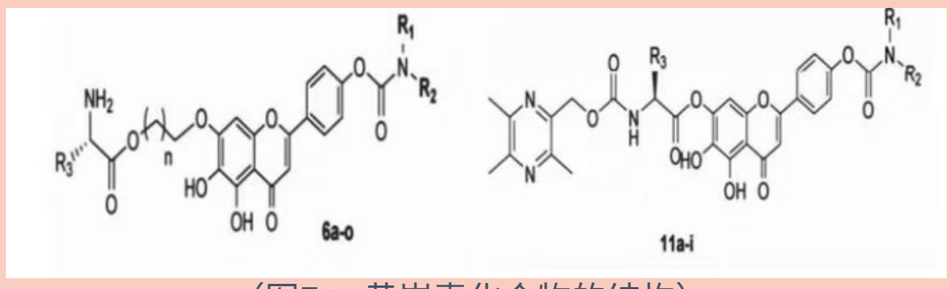


注：A. 5-羟基-1,4-萘醌-他克林；B. 喹啉-2,5,8(1H)-喹啉三酮-他克林；C. 化合物5s

• 喹诺酮类化合物（铁螯合剂）

铁的积累和沉淀以及铁依赖的氧化应激会引起多种中枢神经系统退行性疾病，金属螯合物具有防止金属诱导产生的活性氧、氧化应激和Aβ肽聚集的潜力。

• 黄岑素类化合物（黄酮类化合物）

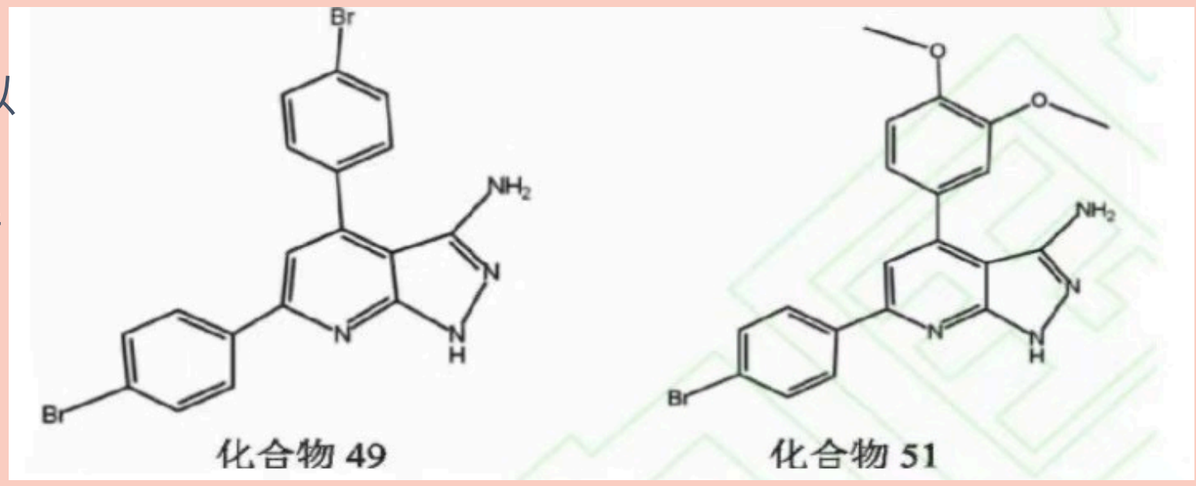


（图3： 黄岑素化合物的结构）

• 吡唑吡啶支架化合物

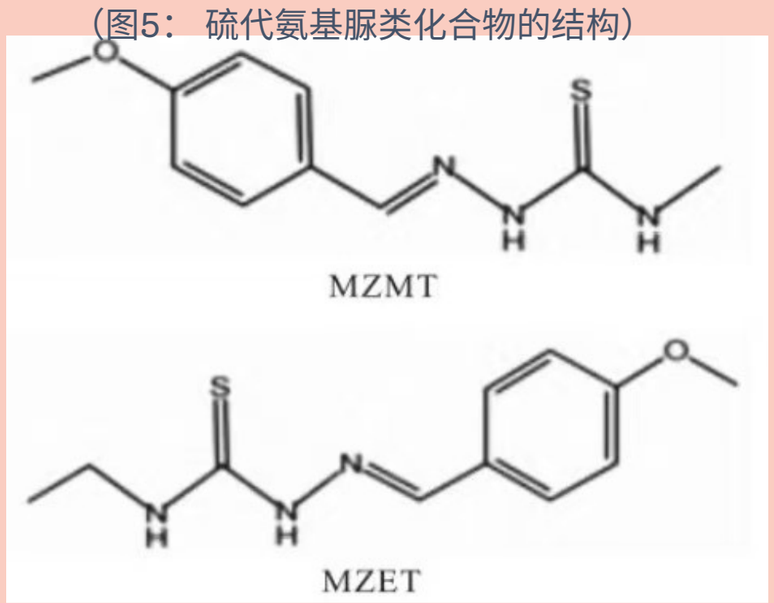
有研究者通过对吡唑吡啶的4位和6位进行了不同取代的苯基部分修饰，合成了一系列多靶点抗AD吡唑吡啶支架化合物，进行活性评估和毒性检测，其中化合物49和51表现出了显著的改善AD的活性的能力。

吡唑吡啶支架化合物同时抑制Aβ聚集，防止Aβ依赖性神经毒性；也通过抑制GSK-3β生成抑制Tau蛋白的过度磷酸化以及神经纤维缠结形成。此外，它们还具有螯合、、等金属的能力，能防止AD患者脑内的氧化损伤，且具有良好的血脑屏障穿透性，符合Lipinski规则，表明具有成为良好口服抗AD药物的潜力。



化合物 49　　化合物 51

（图5： 硫代氨基脲类化合物的结构）



• 硫代氨基脲类化合物

硫代氨基硫脲因其已知的多种关于抗AD的药理活性及硫代氨基硫脲类似物具有的金属螯合剂的性质，成为设计抗AD多靶点药物的基础分子。一些硫代氨基脲类化合物具有抑制NMDA受体的能力，抗氧化，抵消活性氧生成的神经保护作用以及能通过增强细胞自噬量而促进Aβ清除的能力。

• 噻唑烷二酮类化合物（TZDS）

近期发现TZDS同时，且有较高的靶向特异性，作为PPARγ的激动剂，通过拮抗炎症相关转录因子和活化T细胞来抑制神经炎症。临床监测也表明TZDS能够同时调节多种AD相关病理途径，有效抑制慢性炎症，保护神经元免受损伤。

• 喹啉-O-氨基甲酸酯类化合物

喹啉具有广泛的生物活性，已有部分喹啉衍生物被证明具有抑制胆碱酯酶、抗氧化、抗炎等神经保护作用，且已进入临床试验。

• 类胡萝卜素化合物

类胡萝卜素化合物由于具有共振双键的聚异戊二烯结构而具有独特的药理活性，作为一类脂溶性分子已被发现具有良好的抗氧化和抗炎作用，能够保护大脑免受氧化应激、神经炎症和线粒体功能障碍的影响。

参考文献

• Jonathan Gallego-Rudolf，Alex I. Wiesman, Alexa Pichet Binette.2024,.Synergistic association of Aβ and tau pathology with cortical neurophysiology and cognitive decline in asymptomatic older adults.nature neuroscience. https://doi.org/10.1038/s41593-024-01763-8
• Nils Korte, Anna Barkaway, Jack Wells.2024. Inhibiting Ca2+ channels in Alzheimer's disease model mice relaxes pericytes,improves cerebral blood flow and reduces immune cell stalling and hypoxia. https://doi.org/10.1038/s41593-024-01753-w
• 高晓娟.2024.阿尔兹海默症:认识老年痴呆症.山西科技报/2024年/5月/30日/第A03版
• 麻煜程,李汶阳,夏雨田.2024.阿尔兹海默病多靶点药物研究发展. https://link.cnki.net/urlid/51.1654.R.20240927.1743.002
• 王宇宇,朱丽,陈长梅.2024.药食同源物质抗阿尔兹海默症的作用及其机制.临床合理用药2024年9月10日第17卷25期

SMART MAGAZINE AUTHOR:Derek TRANSLATOR: Zeke EDITOR: Zeke

生物医用材料吲哚青绿

关键词: xxxxxxxxxxxxxxxxxxx

简介：

吲哚菁绿（Indocyanine Green, ICG）是一种具有优异生物相容性和生物降解性的近红外（NIR）光敏分子，广泛用于医学领域的荧光染料。尤其是在光动力疗法（Photodynamic Therapy, PDT）和光热疗法（Photothermal Therapy, PTT）中的应用，展现了其独特的优势与潜力。作为新兴的肿瘤治疗手段，PDT和PTT日益受到科学界的关注，而ICG因其多功能性和作用机制成为研究热点。

在NIR光照射下，ICG作为PDT中的荧光剂，可通过光激发产生活性氧（Reactive Oxygen Species, ROS），实现对肿瘤组织的靶向破坏。同时，ICG作为PTT的光敏剂，能够吸收特定波长的光并转化为热能，从而产生局部热效应，进一步增强其治疗能力。这种双重功能使得ICG在肿瘤治疗领域具有广阔的应用前景。

与其他染料相比，ICG在近红外光区域表现出优越的组织穿透性和较低的光漂白特性，使其在光学成像引导下的肿瘤治疗和抗菌治疗中效果显著。然而，ICG的水溶液稳定性、光学稳定性和多功能性仍面临挑战。为了解决这些问题，研究者们致力于开发基于ICG的复合纳米材料，尤其是在提高肿瘤治疗效果方面。

作为一种花青素类化合物，ICG在NIR区域表现出强吸收和荧光特性，广泛应用于肿瘤的诊断和治疗。术中ICG荧光成像技术能够精准识别实体瘤和转移瘤类型，为个性化手术方案提供支持。此外，ICG还可通过PDT的ROS生成和PTT的热效应引发癌细胞死亡。然而，其水不稳定性、光漂白性、光降解性和热降解性限制了临床应用。

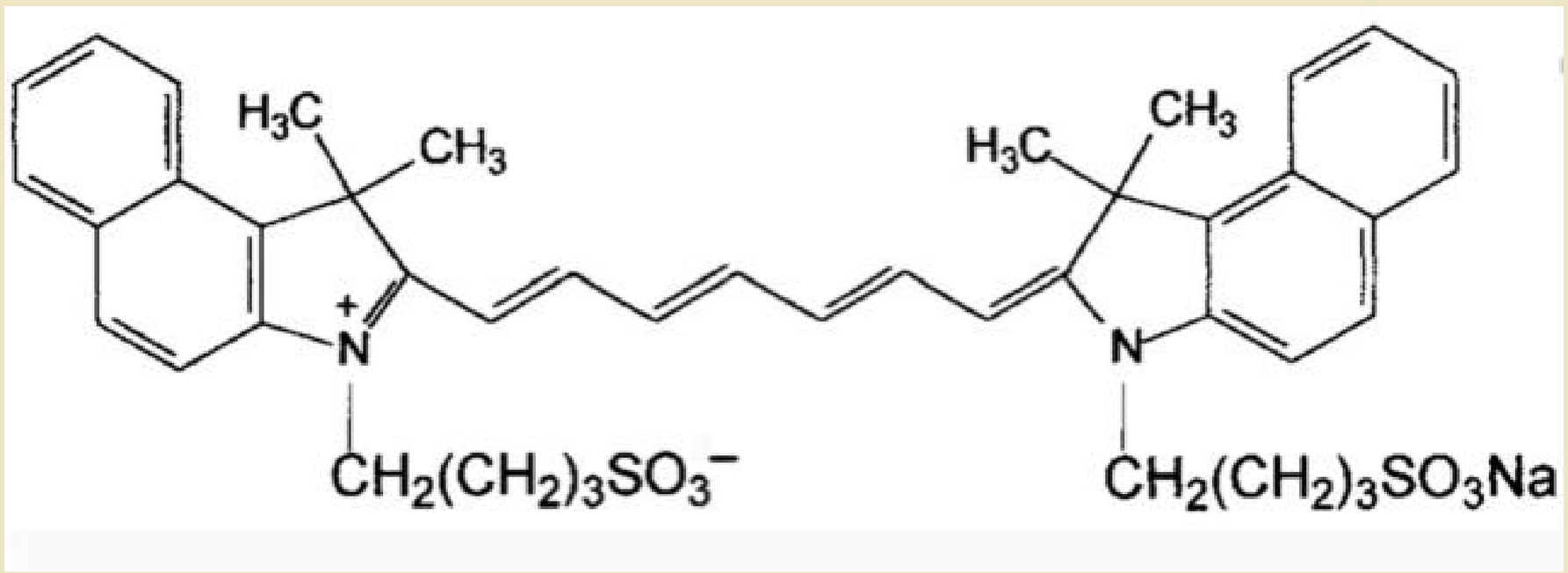
为克服这些限制，研究者们开发了多种策略，包括利用无机或聚合物纳米颗粒（Nanoparticles, NPs）、脂质体及杂交细胞膜对ICG进行封装。这些设计不仅显著提高了ICG的治疗稳定性和肿瘤靶向性，还增强了整体治疗效果。近年来，基于纳米平台的ICG复合结构已成为提高其生物相容性和多功能性的关键手段。

由于ICG的PDT、PTT及成像功能均依赖NIR光激发，如何高效利用光能并优化这些功能仍是研究的重点。此外，基于纳米载体的多功能治疗平台，为肿瘤患者提供了全新的治疗方案。随着研究的深入，ICG及其衍生物在肿瘤治疗领域的应用潜力将进一步拓展，为肿瘤精准诊疗带来更多可能性。

ICG的两亲性特性及其浓度依赖的光学性质

吲哚菁绿（Indocyanine Green, ICG）是一种独特的两亲性分子，兼具亲水和亲脂特性。其分子结构由两个主要的多环基团（benzindotricycin）组成，这些基团本质上呈现出亲脂性，并通过碳链相互连接。每个多环基团均携带一个硫酸盐基团，从而赋予ICG一定的水溶性。正是这种独特的两亲性结构，使得ICG能够与多种亲水性或亲脂性物质（如磷脂）形成显著的相互作用，大幅增强其在溶液中的荧光强度，并对其荧光量子产率产生重要影响。

在低于5μM的浓度条件下，ICG主要以单体形式存在于溶液中。然而，随着浓度的增加，尤其在超过100 μM时，ICG分子倾向于发生自聚集行为。单体ICG在吸收光谱中呈现约785 nm的峰值，而聚集体（ICG聚集体，IJA）则在约690 nm处显示出最大吸光度。



肉眼观察时，IJA呈现深绿色，与ICG单体的浅绿色形成鲜明对比。此外，与单体ICG相比，IJA在光谱特性上表现出约100 nm的显著红移。无论是IJA还是ICG，在多种介质中均可在约892 nm处观察到特征性的荧光峰。然而，两者在稳定性方面有所不同。IJA展现出较强的水稳定性，并且在盐浓度变化的情况下，其光谱几乎不发生显著波动。生理条件下，当ICG通过静脉注射进入体内后，分子易与血浆蛋白或脂蛋白结合，形成稳定的聚集体。这一聚集行为导致ICG的吸收光谱主峰发生红移，通常至约805–810 nm，并表现出更为稳定的光谱特性。

这些研究结果表明，ICG分子在水溶液或与蛋白质和脂质结合时，展现出显著的光学和稳定性差异。此外，ICG的荧光强度随着浓度的变化而显著改变，为探索其浓度依赖的生物学应用奠定了理论基础。这种特性不仅为ICG在荧光成像和治疗中的应用提供了新的视角，也为开发基于其分子结构特性的多功能诊疗平台提供了可能性。

吲哚菁绿在肿瘤治疗中的临床应用:

在光动力疗法中，ICG在近红外光的作用下能够产生活性氧（ROS），直接杀伤肿瘤细胞。多项临床研究显示，在结直肠癌、乳腺癌、肺癌等多种肿瘤的治疗中，ICG介导的光动力疗法显示出显著的疗效和生存率改善。

此外，ICG还作为光热疗法（Photothermal Therapy, PTT）的关键显影剂，通过吸收NIR光能并转化为热能，对肿瘤组织产生局部热疗效应。在肝癌、胰腺癌等恶性肿瘤的治疗中，ICG介导的PTT展示了良好的局部肿瘤控制率和显著的临床疗效。

为进一步提升ICG的光毒性，研究者们探索了其与其他光敏剂分子的联合使用。其中，酞菁锌（Zinc Phthalocyanine, ZNPC）因其高效的ROS生成能力成为关注的焦点，并被认为是与ICG联合使用的理想候选分子。例如，Chen等人利用超声辅助抗溶剂沉淀法，成功制备了无载体纳米探针ZNPC-ICG，并在其表面涂覆红细胞膜，构建了仿生纳米探针ZNPC-ICG@RBC。该系统通过单次NIR激光照射，即实现了光动力与光热联合治疗的协同效果，同时显著提升了ICG和ZNPC的生物稳定性和光学稳定性。

然而，在临床应用中，ICG面临肝脏快速清除的限制，这对其在体内的持久性和治疗效果构成挑战。针对这一问题，Du等人开发了ICG-PEG45，这是首例通过肾小管分泌途径代谢的NIR荧光团。ICG-PEG45能够选择性地在p-糖蛋白（P-gP）低表达的肾癌组织中积累，实现了高特异性的荧光成像诊断。该策略不仅为肿瘤的精准诊断和治疗提供了新思路，还可与其他成像技术（如计算机断层扫描，CT）结合，进一步推动诊疗一体化的发展。

综上所述，吲哚菁绿在肿瘤治疗领域展现出广阔的应用前景。尽管如此，为确保其安全性和疗效，仍需开展更多大规模临床研究和实际验证。随着研究的不断深入，ICG有望成为肿瘤诊疗中的核心工具，为患者提供更精准、高效的治疗方案。

吲哚菁绿的安全性评估

吲哚菁绿是一种常用于光动力疗法和光热疗法的光敏剂，但其安全性成为了人们关注的焦点。吲哚菁绿的安全性评估主要涉及其在体内和体外的毒理学评价、长期用药的安全性、以及对人体的潜在副作用。

现有研究表明，在适当剂量范围内，ICG对人体具有较高的安全性。体内毒理学研究显示，ICG仅在特定近红外（NIR）光照条件下才会产生细胞毒性，而在常规实验条件下使用的剂量对正常细胞无显著损伤。同时，长期用药的安全性评价也表明，ICG对主要器官和生理系统未表现出明显的累积性毒副作用。

然而，ICG在某些特定情况下可能引发不良反应。例如，过量使用或不适当的光照条件可能导致皮肤灼伤、光毒性反应等副作用。特别是在光动力疗法中，若光源波长、能量密度或光照时间未严格控制，可能加剧治疗区域的非特异性损伤。因此，在临床应用中，需谨慎控制ICG的给药剂量，同时优化光照参数，以最大限度地减少不良反应。

综上所述，ICG在PDT和PTT中的安全性在很大程度上取决于剂量、光照条件等关键因素。在合理使用的前提下，ICG是相对安全的光敏剂。然而，为了进一步降低潜在风险并确保其疗效，仍需在临床实践中加强对剂量及治疗参数的监测和管理，从而实现ICG在肿瘤治疗领域的更广泛和安全应用。

吲哚菁绿治疗的副作用及对策

吲哚菁绿作为一种常用的光敏剂，在光动力疗法和光热疗法中被广泛应用。然而，其治疗过程中可能出现一些副作用，包括皮肤灼伤、疼痛、色素沉着、水肿等。这些副作用可能给患者带来不适，甚至影响治疗效果。

为了减少吲哚菁绿治疗的副作用，一些对策被提出。首先，医务人员应严格遵守治疗操作规程，确保吲哚菁绿的正确使用和患者的安全。其次，在治疗前应对患者的皮肤情况进行评估，并对可能出现副作用的部位进行保护。同时，对于不同的副作用，还可以采取相应的处理方法，如皮肤灼伤可采取冷敷和使用外用药物等。综上所述，吲哚菁绿作为一种重要的光敏剂，在治疗过程中可能出现一些副作用，但通过严格的操作规程和患者评估，以及对副作用的对策，可以有效地减少其副作用的发生，保障患者的安全和治疗效果。在光动力疗法与光热疗法中，吲哚菁绿作为光敏剂具有广泛的应用前景。

通过文献综述可以得出结论：吲哚菁绿在光动力疗法中可以通过激发氧化应激反应产生毒性活性氧，对肿瘤细胞起到杀伤作用，同时对周围正常组织的伤害较小，具有较好的安全性。在光热疗法中，吲哚菁绿可以有效吸收光能并转化为热能，导致肿瘤组织的温度升高并达到破坏肿瘤的目的。因此，吲哚菁绿在肿瘤的光动力疗法和光热疗法中都具有潜在的治疗应用价值。

然而，对吲哚菁绿在临床应用中还存在一些问题需要解决。例如，吲哚菁绿的药物传递系统、生物分布、药物释放等方面的研究还不够深入。而且在临床试验中，对于不同类型的肿瘤使用吲哚菁绿的疗效、安全性等方面还需要进一步的研究和验证。因此，未来需要开展更多的临床研究，并结合不同的技术手段进一步深入研究吲哚菁绿在光动力疗法和光热疗法中的应用，以期为临床应用提供更可靠的证据和支持。

参考文献

[1] Yu B , Liu Q , Sun J ,et al.Phototherapy-based multifunctional nanoplatform for synergistic therapy against drug resistance bacteria: Progress, advances and challenges[J].Chemical Engineering Journal, 2024, 487.DOI:10.1016/j.cej.2024.150705.

[2] Wan Z , Mao H , Guo M ,et al.Highly Efficient Hierarchical Micelles Integrating Photothermal Therapy and Singlet Oxygen-Synergized Chemotherapy for Cancer Eradication[D].IVYSPRING INT PUBL,2014.

[3] H Lin,Z Lin,K Zheng,et al.Near-Infrared- II Nanomaterials for Fluorescence Imaging and Photodynamic Therapy[D].Advanced Optical Materials,2021

[7] G He,C Mei,C Chen,et al.Application and progress of nanozymes in antitumor therapy[D].International Journal of Biological Macromolecules,2024

[8] A S H , A C D B , A J W ,et al.Assemblies of indocyanine green and chemotherapeutic drug to cure established tumors by synergistic chemo-photo therapy - ScienceDirect[J].Journal of Controlled Release, 2020, 324:250-259.DOI:10.1016/j.jconrel.2020.05.018.

[9] TW Wong,SZ Liao,WC Ko,et al.Indocyanine Green-Mediated Photodynamic Therapy Reduces Methicillin-Resistant Staphylococcus aureus Drug Resistance[D].Journal of Clinical Medicine,2019

[10] Guan Wenchao,Gao Hongxia,Liu Yaqiong,et al.Application of magnetism in tissue regeneration: Recent progress and future prospects[D].,2024

[11] X Huang,J Wu,M He,et al.Combined Cancer Chemo-Photodynamic and Photothermal Therapy Based on ICG/PDA/TPZ-Loaded Nanoparticles.[D].Molecular Pharmaceutics,2019

[12] Q Zhang,X Wang,G Kuang,et al.Pt(IV) prodrug initiated microparticles from microfluidics for tumor chemo-, photothermal and photodynamic combination therapy[D].,2023

[13] C Huang,Z Zhang,Q Guo,et al.A Dual-Model Imaging Theragnostic System Based on Mesoporous Silica Nanoparticles for Enhanced Cancer Phototherapy[D].Advanced Healthcare Materials,2019

[14] Y Wang,NN Jin,J Zhang.Research progress of fullerene derivatives in photodynamic therapy[D].Applied Chemical Industry,2019

[15] FU Rong,C Yang,HU Yanyan,et al.Progress in preparation and application of core-shell structure nanocomposites with magnetism and fluorescence[D].Chemical Industry & Engineering Progress,2019

[16] Jingke Zhang,Hengxue Xiang,Zhiwei Cao,et al.Research Progress of Lignin-Derived Materials in Lithium/Sodium Ion Batteries[D].,2024

[17] Siqi Zheng,Min Bai.Application Progress of Ultrasound Elastography in the Evaluation of Diabetic Peripheral Neuropathy[D].,2024

[18] Y Chen,X Zhou,Y Li.Application and Progress of Microstructure and Mechanical properties Control Methods for Ultra-High Strength Steel in Rolling Process[D].Journal of Physics Conference,2020

[19] Yuhua Zhang,Lijie An,Jinli Shi,et al.Letter to the Editor Re: Research Progress of Music Therapy in Reducing Patient Pain Response and Its Intervention Effect Evaluation[D].,2024

[20] Xing-lu,PAN,Feng-shou,et al.Progress of the discovery, application, and control technologies of chemical pesticides in China - ScienceDirect[D].Journal of Integrative Agriculture,2019

[21] Jing Huang,Jinglan Yan,Taiyi Wang,et al.Research progress on central autonomic nervous mechanism of acupuncture at Neiguan point in the treatment of atrial fibrillation[D].,2023

[22] DR Sanchez-Ramirez,R Dominguez-Rios,J Juarez,et al.Biodegradable photoresponsive nanoparticles for chemo-, photothermal- and photodynamic therapy of ovarian cancer[D].Materials Science & Engineering C Materials for Biological Applications,2020

[23] Chen Jiang,Tianlong Ji,Qiao Qiao.Application and progress of artificial intelligence in radiation therapy dose prediction[D].,2024

SMART MAGAZINE AUTHOR:Molly Meng TRANSLATOR: Rick EDITOR: Amanda

AgRP 神经元促进摄食的生理学原理

关键词：AgRP蛋白，摄食量，温度，臂旁核

摘要

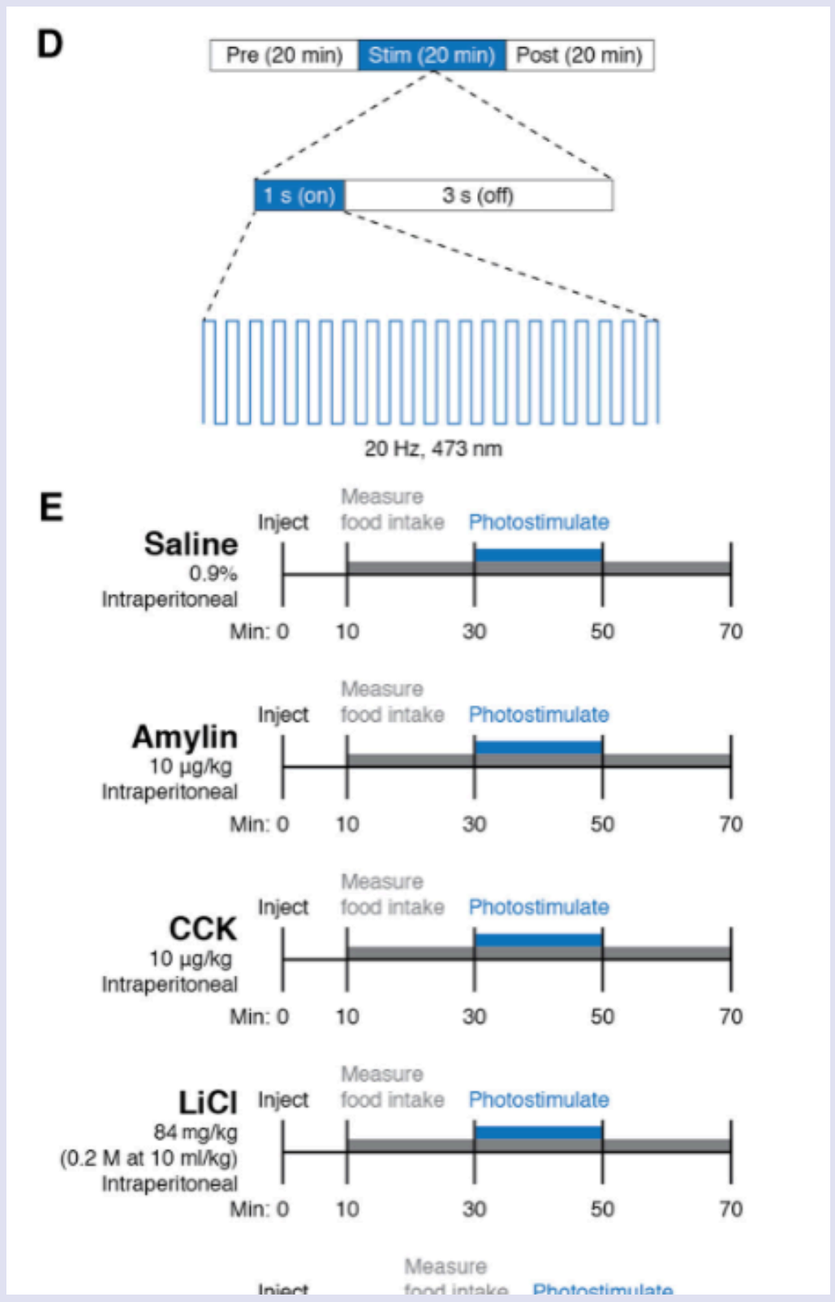
本文讲述的是下丘脑内表达刺鼠相关蛋白（AgRP）能有效增加摄食量，而臂旁核（PBN）内表达降钙素基因相关肽（CGRP）的神经元能有效抑制食欲。本实验证明通过限制进食及光刺激的方式能够诱导活化AgRP神经元从而克服胰岛淀粉样肽、胆囊收缩素（CCK）、LiCl的抑制食欲作用，从而验证了AgRP神经元能够克服厌食化合物引起的食欲抑制，降低PBN CGRP神经元活性的假说。

研究方法与设计

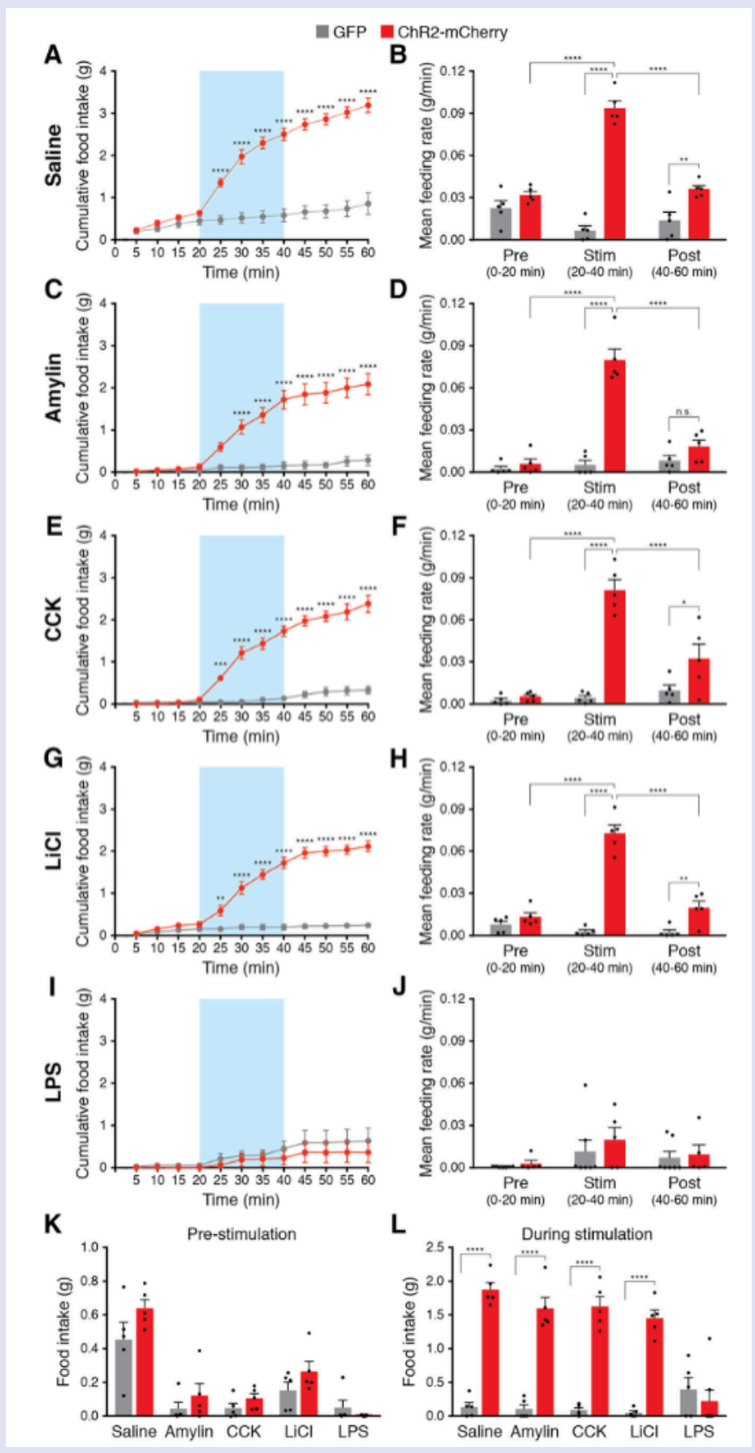
研究人员从AgRP神经元提升食欲时克服胰岛淀粉样肽、CCK、LiCl等的有效性、抑制臂旁核CGRP神经元活化导致的食欲抑制效应的有效性和对臂旁核CGRP神经元投射作用在各种食欲抑制条件下诱导摄食的有效性三个方面探究了AgRP的作用机制。

图一

光刺激（D）和注射食欲抑制剂（E）的实验流程



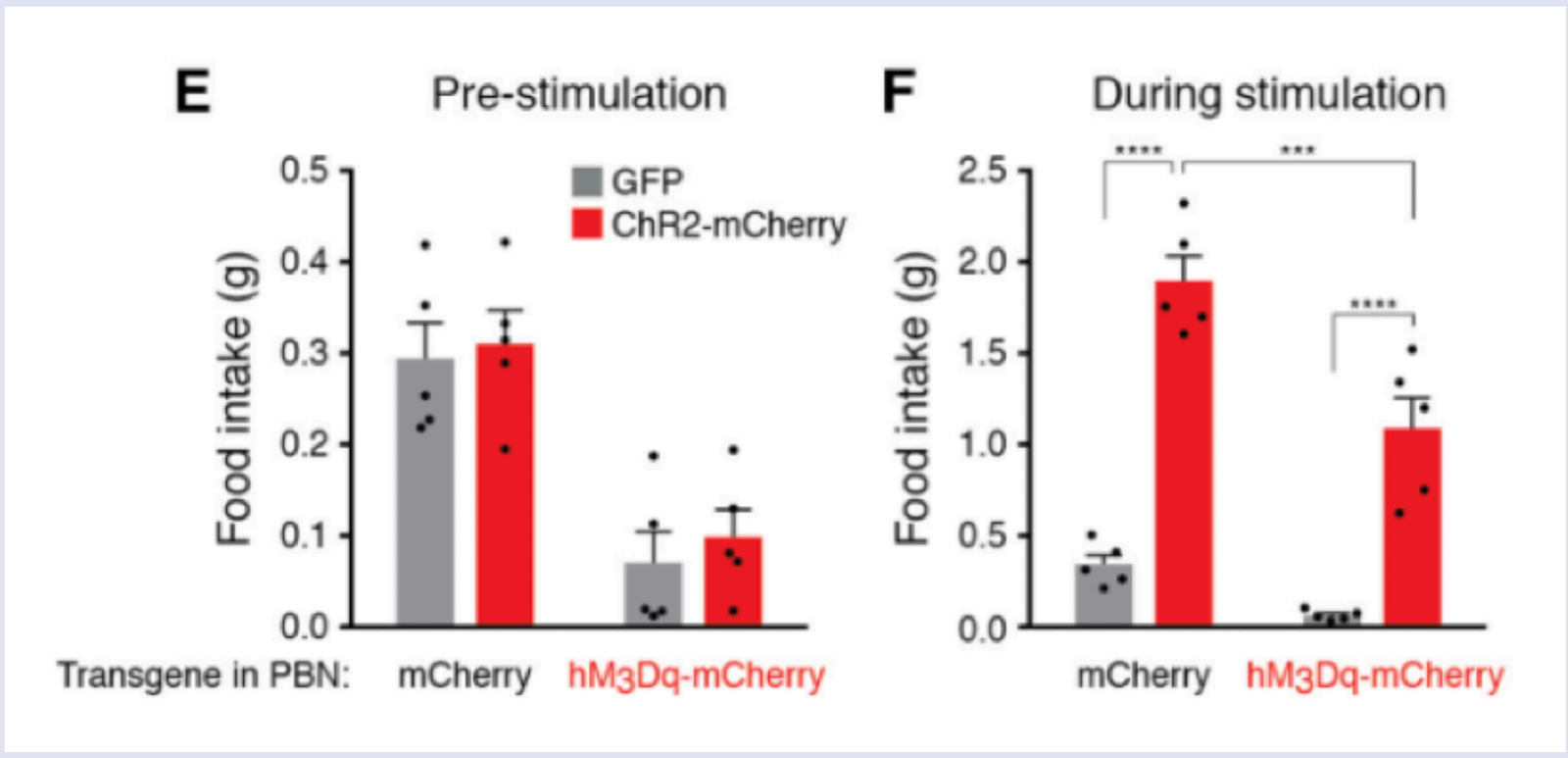
为了抑制食欲，研究人员给小鼠腹腔注射胰淀素(10 g / kg)、CCK (10 g / kg)、Li Cl (0.20 M ; 84 mg / kg)或LPS (50 g / kg)，所有剂量均已经先前研究使用以最大限度减少食物摄入量。对比可知，光激活AgRP后消除了胰淀素、CCK和LiCl的食欲抑制效果，使摄食量增加到与注射生理盐水刺激的动物相似的水平。



图二

AgRP神经元刺激足以增加非炎症性厌食化合物给药后的摄食记录

由于AgRP神经元在抑制能够激活厌食的臂旁核（PBN）CGRP神经元的化合物十分有效，如胰岛淀粉样肽、CCK、LiCl等方面研究人员尝试探究AgRP能否可以克服由直接激活PBN的CGRP神经元引起的食欲抑制。研究人员透过使用经过设计的受体hM3Dq和合成配体氯氮平- N -氧化物(CNO)，继而使用ChR2-mCherry或GFP转导AgRP神经元；同时使用hM3Dq-mCherry或mCherry转导PBN CGRP神经元，并对AgRPCre/Cre与CalcaCre/+杂交产生的AgRPCre/Cre-CalcaCre/+双基因敲入小鼠进行了注射（Calca编码CGRP）。结果显示，即使在PBN激活CGRP神经元的情况下，刺激AgRP神经元也有效增加了累积摄食量，这表明，在给予厌食化合物后，AgRP神经元刺激，有效降低了PBN CGRP神经元的活性。



图三
跨条件刺激AgRP神经元前及跨条件刺激AgRP神经元期间消耗的总食物

此外，在注射胰岛淀粉样肽、CCK、LiCl后，刺激AgRP对PBN的投射同样能够克服抑制食欲的效应并增加其摄食量。但与直接刺激AgRP神经元相同的是，刺激AgRP到PBN的投射不能克服注射LPS的抑制食欲效应，即无法增加炎症性厌食化合物给药后的摄食。值得注意的是，刺激AgRP神经元到PBN的投射使摄食量增加到与注射生理盐水相似的水平，其促进摄食效果低于直接光刺激AgRP神经元胞体。

总结

这项研究表明，在非炎症食欲抑制条件下，刺激AgRP神经元足以增加食物摄入量。AgRP神经元能够克服间接或直接刺激PBN中的CGRP神经元引发的食欲降低，但是在炎症食欲抑制条件下，刺激AgRP神经元不足以提高摄食量。AgRP神经元不仅主动参与引起觅食行为的下游环路，而且主动抑制有抑制食欲作用的臂旁神经元。最近的研究还表明，AgRP神经元通过向终纹床核、下丘脑外侧区、下丘脑室旁核和丘脑室旁核投射刺激摄食。

这一研究侧面证明了AgRP与PBN存在一定的联系，但是这还不足以证明AgRP和PBN之间存在单突触连接。由于PBN是一个包含许多遗传和功能上不同的细胞类型的异质性区域，未来还需进一步研究探寻AgRP和单个PBN神经元之间的连通性。我们的结果补充了相关发现，表明从AgRP神经元到PBN的投射可以克服各种形式的食欲抑制来增加摄食行为。

图四
刺激AgRP神经元向臂旁核的投射增加了给予非炎症性厌食化合物后的摄食

参考文献

Essner, R. A., Smith, A. G., Jamnik, A. A., Ryba, A. R., Trutner, Z. D., & Carter, M. E. (2017). AgRP Neurons Can Increase Food Intake during Conditions of Appetite Suppression and Inhibit Anorexigenic Parabrachial Neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience, 37(36), 8678–8687. https://doi.org/10.1523/JNEUROSCI.0798-17.2017

SMART MAGAZINE AUTHOR: Seraphina TRANSLATOR: Anaya EDITOR: Zeke

海藻盐酸

关键词：海藻酸盐；骨组织工程； 水凝胶

简介：

骨组织工程在修复骨损伤和疾病中占据重要地位。近年来，海藻酸盐复合水凝胶因其独特性质和潜在应用备受关注。本文综述了海藻酸盐的基本特性、局限性及其改进策略，尤其是通过制备纳米复合水凝胶、互穿网络复合水凝胶和三维生物打印材料以提升其性能的研究进展。同时，探讨了当前的挑战及未来研究方向。

一、海藻酸盐——一种独特的天然材料

海藻酸盐是一种从褐藻中提取的天然亲水性阴离子多糖，因其良好的生物相容性、可降解性、无毒性等特性，在骨组织工程中具有广阔的应用前景。

在温和条件下，海藻酸盐与二价钙离子交联形成三维网状水凝胶结构，为细胞提供类似细胞外基质的微环境。相关研究表明，小鼠前成骨细胞和人脂肪干细胞等多种细胞在海藻酸盐水凝胶中表现出优异的存活和增殖能力。在骨组织工程中，海藻酸盐可以在温和条件下与二价钙离子交联，形成具有开放网络结构的水凝胶。这种水凝胶能够为细胞提供一个类似于人体细胞外基质的微环境，促进细胞的营养物质和代谢产物的交换，为细胞的生存和生长提供良好的条件。研究表明，小鼠前成骨细胞、人脂肪干细胞和骨髓基质细胞等都能够在海藻酸盐水凝胶中存活并形成细胞外基质。

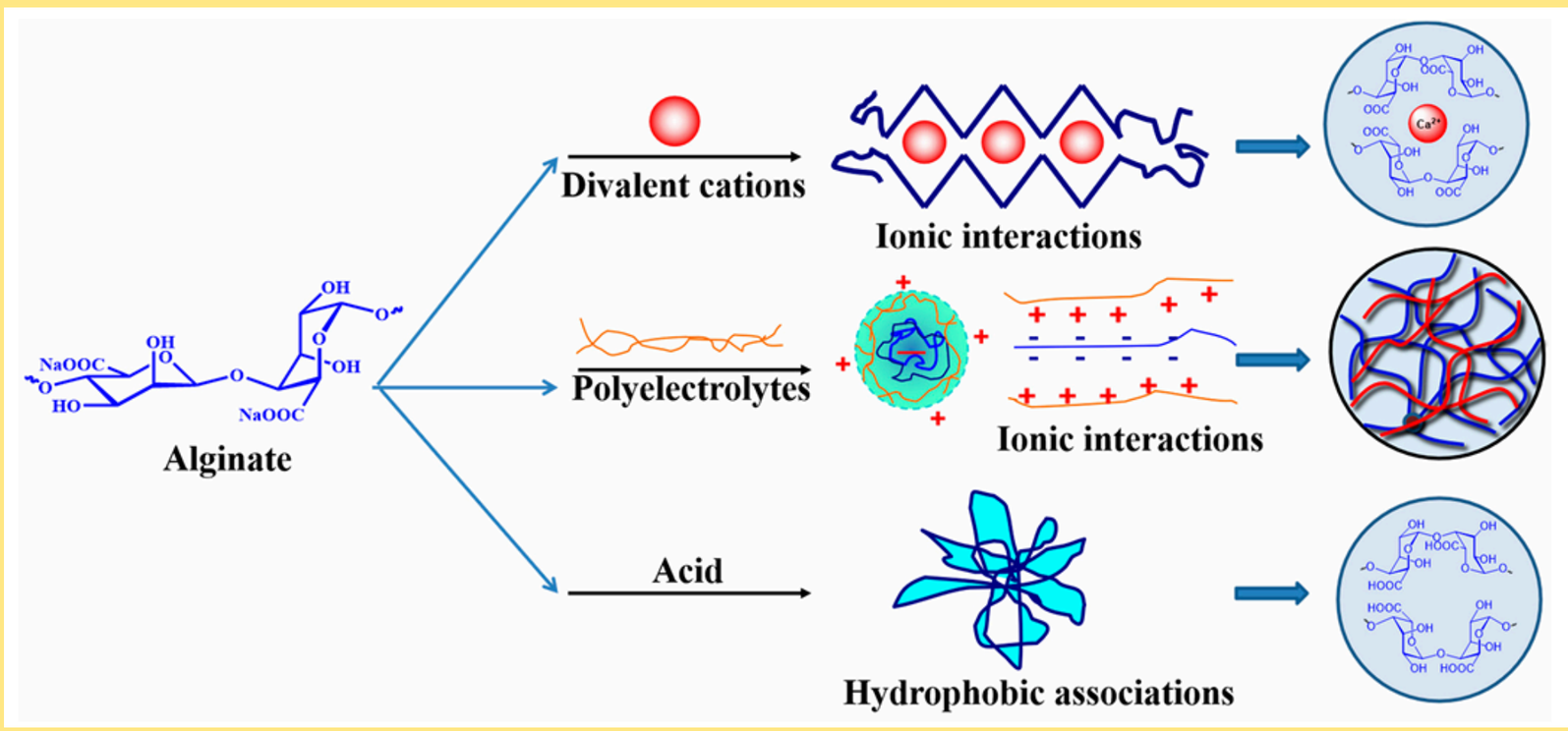


Figure 1. Schematic diagram of physically crosslinked alginate hydrogels.
图1. 物理交联海藻酸盐水凝胶示意图。

二、海藻酸盐水凝胶的局限性

单一的海藻酸盐水凝胶作为骨组织工程支架材料存在不足。它的机械性能不够理想，在生理环境中容易解体，且缺乏细胞特异性识别位点。这些缺陷严重限制了它在骨组织工程中的临床应用。

三、海藻酸盐复合水凝胶的诞生

为克服单一海藻酸盐水凝胶的缺陷，科学家们制备了海藻酸盐复合水凝胶。通过在海藻酸盐基质中按一定比例添加一种或多种其他材料，利用不同材料之间的协同作用实现优势互补，从而提高水凝胶的生物适用性。

（一）纳米复合水凝胶

纳米复合水凝胶是将纳米粒子与海藻酸盐聚合物结合而成的一种新型水凝胶。纳米粒子尺寸小，可更均匀地分布在聚合物基质中，从而赋予水凝胶更好的机械性能、弹性和耐热性。常见的纳米粒子包括羟基磷灰石、粘土、纤维素、纳米二氧化钛和二氧化硅颗粒等。这些纳米复合水凝胶在软骨再生等方面表现优异，例如一些研究中的纤维素纳米晶和聚乙烯醇纳米复合水凝胶展示出良好的机械特性和在组织工程及生物医学领域的应用潜力。

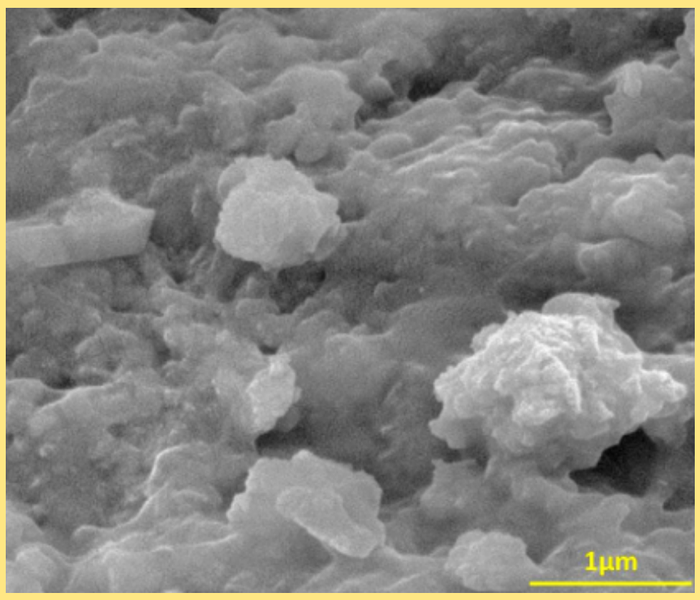


图2. 合成的 nHAp-GO 纳米复合材料的物理化学特征：
FESEM 图像

（三）三维生物打印用海藻酸盐复合水凝胶

随着技术的发展，三维生物打印技术为骨组织工程带来了新的机遇。海藻酸盐基生物墨水在这个领域展现出了巨大的潜力。通过将特定细胞注入海藻酸盐基水凝胶墨水，利用3D生物打印技术可以创建出具有可调降解性和无毒性的组织工程支架。这些支架能够模拟天然组织的微环境，为细胞的生长和分化提供良好的条件。例如，一些研究中通过添加生物活性玻璃纳米粒子或与胶原蛋白结合，显著提高了水凝胶的机械性能和细胞的增殖能力。

四、挑战与展望

尽管海藻酸盐复合水凝胶在骨组织工程中取得了显著的进展，但仍然面临一些挑战。例如，在制备方法上，目前常用的Ca^{2+}外源交联法存在不均匀交联和支架变形等问题，而且对海藻酸盐交联结构对支架降解和表面活性的影响研究还不够深入。此外，复合水凝胶对某些活性生物生长因子的控制释放对细胞分化和增殖的影响也需要进一步探索。

（二）互穿网络复合水凝胶

互穿网络复合水凝胶是由两个或多个聚合物分子链通过互穿和交联缠结形成的。这种结构使得不同的聚合物网络相互独立又相互交织，保留了各聚合物的独特性质，增强了复合水凝胶的物理特性。例如，通过将海藻酸盐与天然聚合物或合成聚合物混合，可解决纯海藻酸盐水凝胶生物活性低和机械性能差的问题。一些研究利用海藻酸盐和甲基丙烯酰化明胶制备的互穿网络复合水凝胶，通过进一步修饰还可以吸附骨诱导药物，对干细胞的成骨分化进行调控。

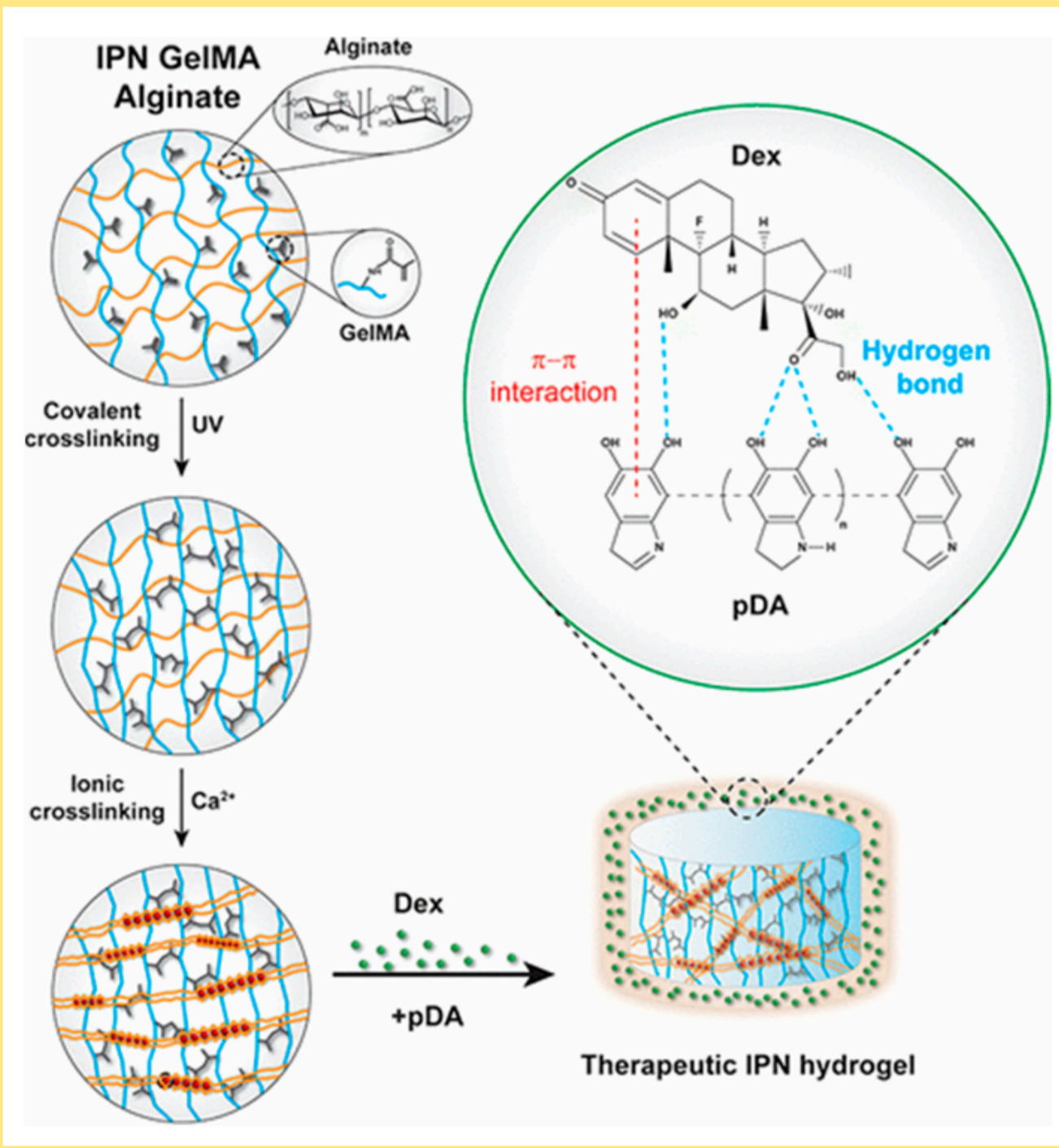


图3. 海藻酸盐/甲基丙烯酰化明胶互传网络复合水凝胶的机理图

随着科学技术的不断发展，我们对海藻酸盐复合水凝胶的研究也将不断深入。未来，我们有望通过进一步优化制备方法、深入研究其结构和性能之间的关系，开发出更加理想的海藻酸盐复合水凝胶材料，为骨组织工程的发展提供更有力的支持，为骨损伤患者带来更多的希望。

参考文献：

Fabrication and Biomedical Application of Alginate Composite Hydrogels in Bone Tissue Engineering A Review.
Alginate derivatization A review of chemistry, properties and applications.
Fabrication of Graphene Oxide and Nanohydroxyapatite Reinforced Gelatin–Alginate Nanocomposite Scaffold for Bone Tissue Regeneration.
Angiogenesis in bone tissue engineering via ceramic scaffolds A review of concepts and recent advancements.
Development of porous hydroxyapatite/PVA/gelatinaginate hybrid flexible scaffolds with improved mechanical properties for bone tissue engineering.

SMART MAGAZINE AUTHOR: Ariana TRANSLATOR: Yaqi EDITOR: Yates

什么是假基因

发现

1977 年，Jacq 等在非洲爪蟾基因组中发现了一段不转录的核苷酸序列，并且这段序列与编码 5S rRNA 的功能基因高度相似，但它却没有表达活性，因此被定义为假基因。

图一：非洲爪蟾

《遗传学名词》等中文书籍给出的假基因定义，是指与功能基因序列相似，但不产生有功能产物的基因，与真基因（功能基因）相对。因而假基因长期以来被认为是基因组中演化的遗迹和无功能的化石。为了能够快速识别出假基因，科学家们给了假基因一些特殊标识：在符号表示方面多用ψ表示，如ψPPM1K；也可在亲本基因后加一个大写字母P，如HMGA1-P。

定义

假基因是指与已知功能基因序列相似，但不产生有功能产物的基因。假基因与功能基因的表达属性相对，可以说是浩瀚基因组中的沉默区。假基因是基因组中与编码基因序列非常相似的非功能性基因组DNA拷贝，序列通常与对应的基因相似，但至少丧失了一部分功能，如基因不能表达或编码的蛋白质没有功能。一般认为，假基因最初是功能对生物生存并非必要的基因。随着突变的积累，编码区可能提前出现终止密码子、移码突变等情况，逐渐变为无功能的假基因。另外，拷贝数变异也可能产生假基因。

与基因相似与区别

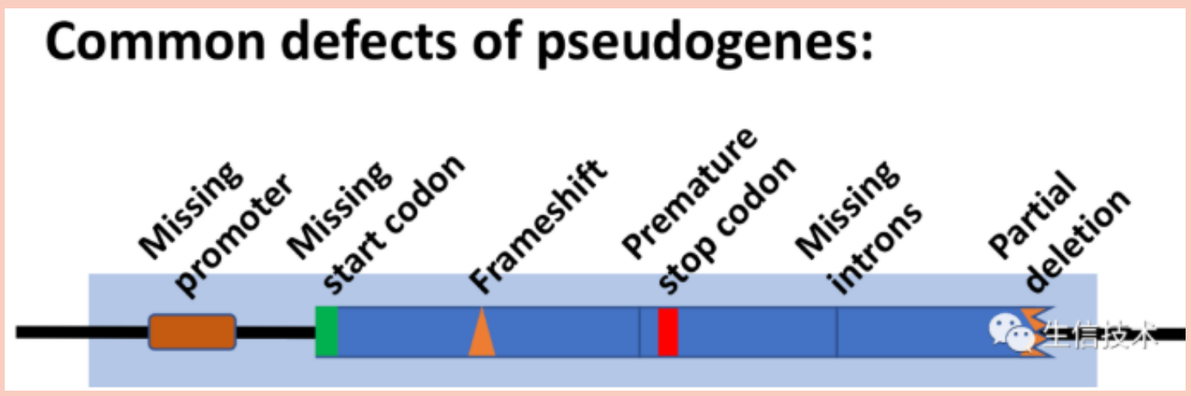
- 根据定义，基因是有机体的基本物理和功能单位，假基因是在进化过程中积累的功能基因的缺陷拷贝。
- 假基因和基因有什么相似之处?
- 两者都存在于基因组中
- 从结构上讲，它们是 DNA 的片段
- 它们是可遗传的遗传元素
- 它们会发生突变
- 两者都可以作为癌基因或肿瘤抑制因子
- 假基因和基因之间的主要区别在于：假基因是一种不编码蛋白质的非功能性遗传元件，而基因是一种编码蛋白质的功能性遗传元件。此外，假基因缺乏对翻译和转录非常重要的关键调控元件。相反，一个基因具有所有对翻译和转录非常重要的关键调控元件。因此，这是假基因和基因之间的另一个显著差异。

产生

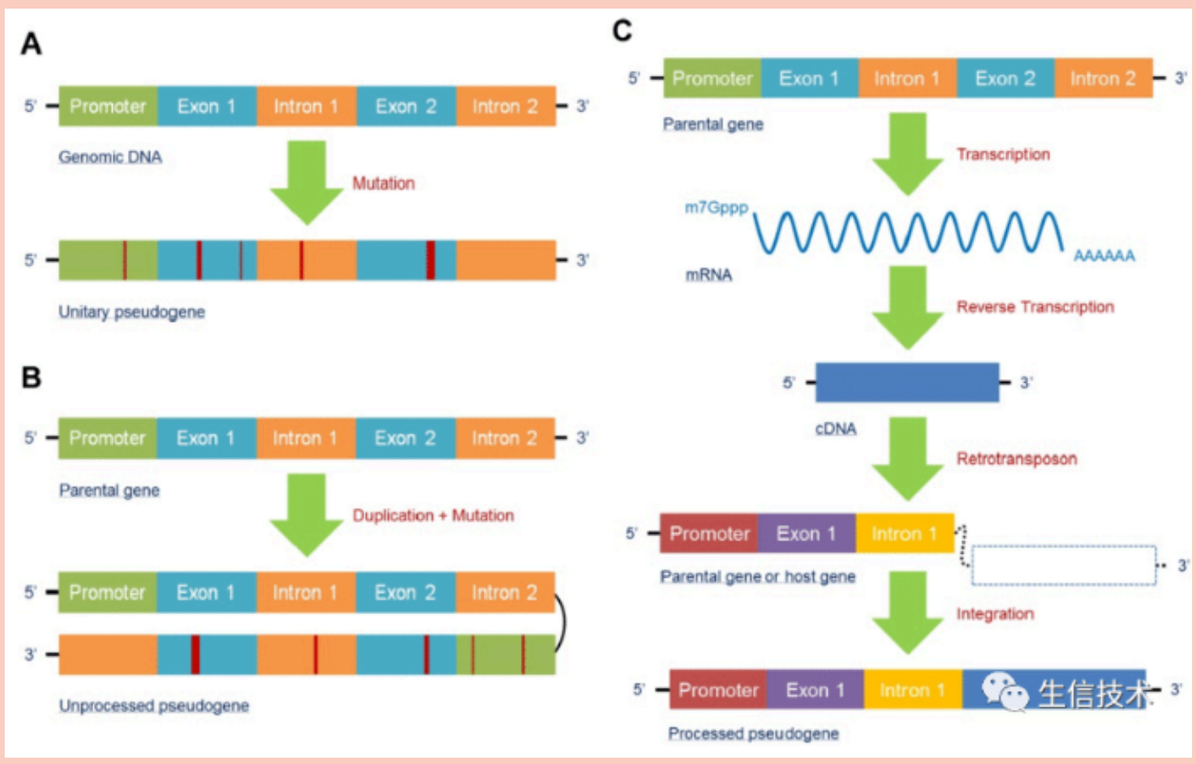
基因重复的最常见类型是产生与第一份拷贝邻近的第二份拷贝。重复基因可以趋异而产生不同的基因，或其一份拷贝可能会变成失活假基因。除非基因编码的产物在细胞中需要很高的浓度，否则有机体不太可能需要保留两份完全相同的基因拷贝。当重复基因的差异产生时，以下两种类型事件中的一类就将会产生。1）两个基因都将变成有机体所需的。

这种事件会在以下情况下发生：或者两个基因编码的蛋白质产生了不同的功能，或者它们在不同时间或者不同细胞类型中表达。2）如果上述事件不发生，那么其中一个基因很可能会变成假基因，因为如果它获得了有害突变后，由于缺乏纯化选择使它消亡，所以由于随机的遗传漂变，出现突变体的频率可能提高，并固定在某一物种中。

假基因通常缺乏对翻译和转录非常重要的调控元件。不同的生物过程都可能产生假基因，且没有专门的机制将它们从基因组中移除。最终，假基因可能会因偶然复制或 DNA 修复错误而从基因组中删除。否则它们会随着时间的推移积累不同的突变，不再被识别为以前的基因。可以通过基因组序列分析鉴定假基因。

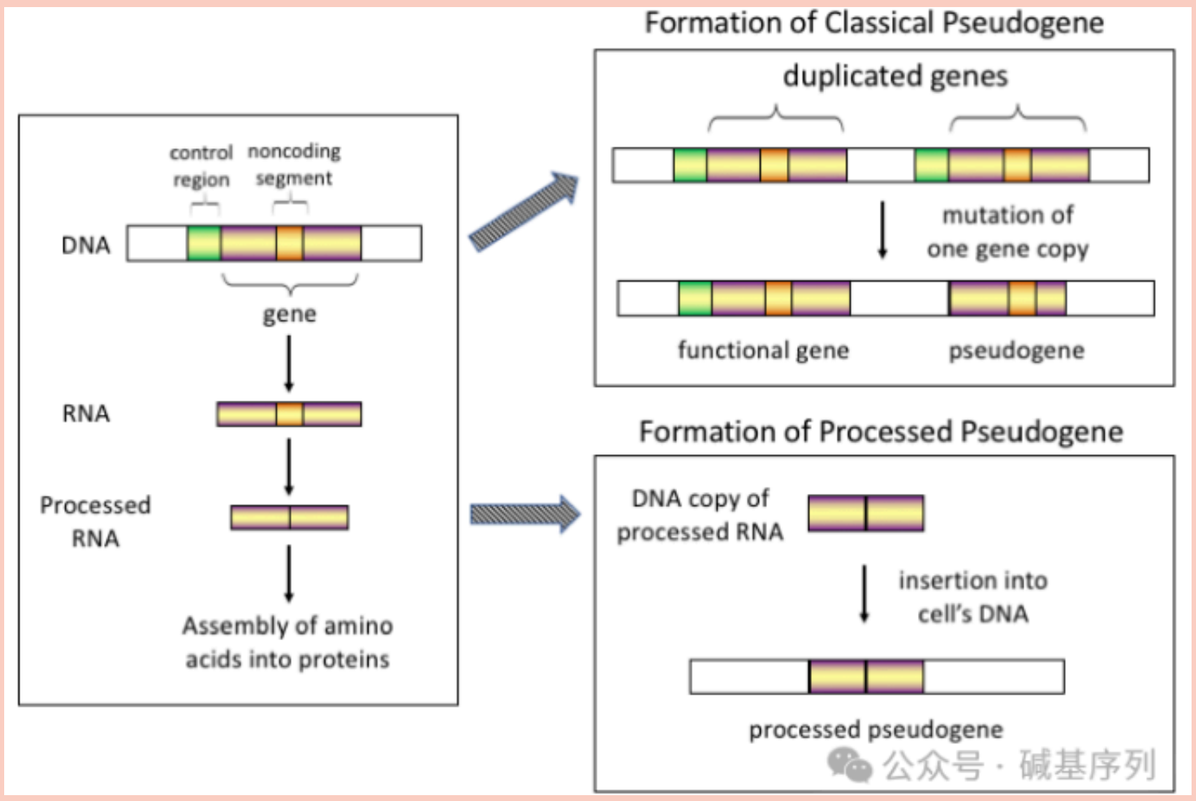


有时，由于启动子元件，假基因序列可以低水平转录成 RNA。这些启动子元件来自祖先基因或新突变。尽管这些假基因的大部分转录本没有功能意义，但有些会产生有益的调节 RNA和新蛋白质。

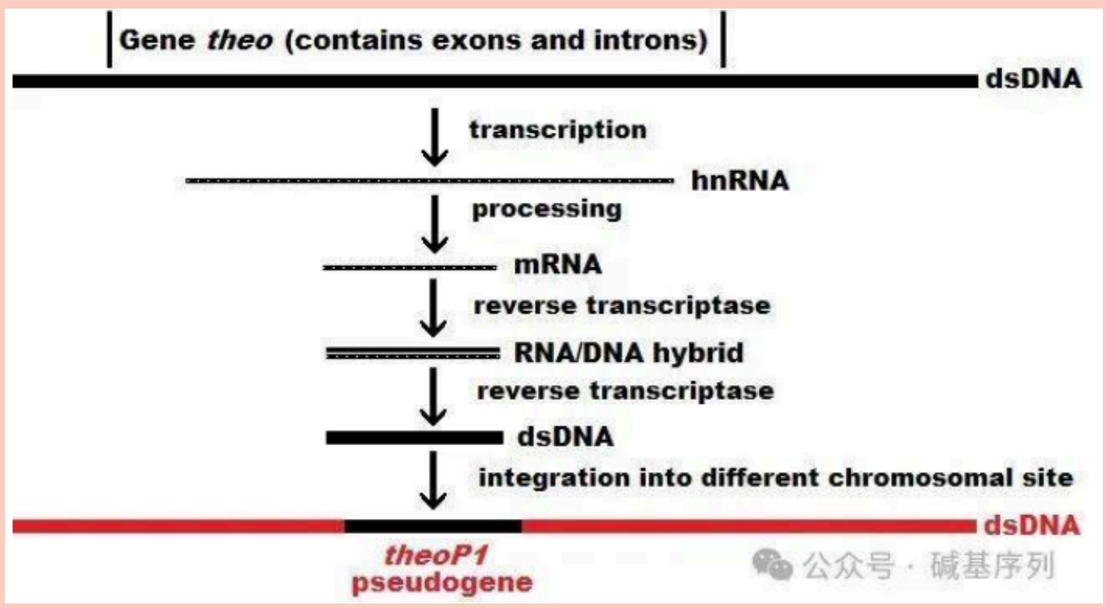


分类

假基因被定义为功能基因的拷贝，它们改变或丢失了一些区域，这样它们不能产生原有功能的多肽产物，可以是非功能性的，或产生了变异的功能，以及具有调节功能的RNA产物。例如，与它们的功能对应物相比，有些假基因存在移码突变或无义突变，使基因蛋白质编码功能丧失。根据其起源的这种模式可划分出两类假基因。



已加工的假基因来自成熟mRNA反转录而成的cDNA，随后通过反转录转座子被整合进入宿主或亲本基因组中。当活性反转录酶存在细胞中，如在活性反转录病毒感染时或反转座子具有活性时，可能会对转录物进行加工，使mRNA向外传递信息时随机返回基因组且功能丧失成为假基因，其结果是已加工的假基因通常缺乏正常表达所需的调节区。所以，尽管它初期是包含功能多肽的编码序列，而一旦形成，它就失活了。这样的假基因还缺乏内含子，可能还包含残留的mRNA的poly(A)尾和两侧反转录因子插入的特征性直接重复序列。处理过的假基因可以远离它们的对应物或在不同的染色体上找到。



未加工的假基因来自多重拷贝或单一拷贝基因的中一份拷贝的失活突变，或一个活性基因的不完全重复。其形成机制常常与串联重复相关。如果一个基因整体重复，包括调节区，那么此时即存在两个活性基因的拷贝，而一份拷贝上的失活突变不易受到负选择的影响。这样，基因家族就出现了未加工的假基因，如珠蛋白基因家族中几个假基因的存在就很好地证明了这一点。或者，一个活性基因的不完全重复，形成无调控区和(或)编码序列的拷贝，导致其转录和翻译能力的丧失，在同一基因组中没有完全功能的对应物。

作用

从分子进化论的角度来说，失去功能的基因在漫长的演化中没有被修正或删除，意味着其似乎对人类生存中并无过多影响，一度被看作是遗传演化的废料，但越来越多的研究证明了假基因与疾病的发生发展存在关联，还有很多研究证实了假基因和肿瘤、内分泌疾病等有关联。

随着研究深入，人们发现假基因在基因表达、基因调控、产生基因多样性等方面都扮演着极为重要的角色。甚至在标准参照基因组里一些被认为是假基因存在的片段，在某些个体中都会正常表达。研究发现假基因主要行为可能来自于：与功能基因竞争性结合 miRNA，从而调控功能基因的表达；产生内源性小干扰 RNA 抑制功能基因的表达；有的假基因可以编码部分具有功能的蛋白质；失活的假基因有时可重生，对新基因的产生及功能扩展有所贡献。

检测

假基因在一些疾病诊断中是关键。由于假基因和功能基因的序列相似度很高，在疾病检测中会干扰检测结果且影响结果判读。另外，假基因也可为人们认识和应对疾病提供新的角度和方式。

例如：21-羟化酶缺乏症是先天性肾上腺皮质增生症（CAH）中最常见的类型， CYP21A2编码有活性的21-羟化酶，CYP21A1P转录无活性的21-羟化酶，为假基因。

使用NGS二代测序技术对人类基因进行测序时，由于真、假基因序列的高度相似性，假基因的干扰会影响变异最终判定的结果。就需要使用其它方法如long-PCR、巢式PCR、MLPA等多重技术进行检测。

再如脊髓性肌肉萎缩症 (SMA)，致病基因是可以产生SMN 蛋白的SMN1，也存在序列同源性>99.9%的高度同源基因SMN2，两者仅有5个碱基存在差异。SMN2仅产生截短不太稳定的 SMN 蛋白，约占10%的SMN1全长转录产物，属于准“假基因”。重要的是，SMN2拷贝数的检测结果可作为患者诊断后的治疗、临床管理和预后评估的参考指标，一般患者携带SMN2拷贝数越多，临床症状越轻.

随着近年来分子生物学技术和高通量测序技术的发展，某些假基因被发现能够转录甚至翻译产生完整的蛋白，并具有重要的功能，如原癌基因的激活、三维基因组构象调控，参与个体的生长发育进程。尽管个别有功能的假基因被报道，假基因整体的表达和演化调控仍然是未知的，其演化起源时间、表达活性以及在发育和癌症中的功能等问题仍然有待探究。

针对这些假基因或高度同源基因的检测，三代测序技术优势凸显。具有长读长的第三代单分子实时测序技术可以直接获得基因全长转录本，同时极高的精准度也能实现对高度相似序列的区分，在假基因相关的遗传病筛查和诊断中具有很高优势。测序技术的精进使假基因的真面目及其他未知奥秘得以被揭露，也为攻克疾病和科学研究带去新的活力。

参考文献

[1] JACQ C, MILLER JR, BROWNLEE GG. A pseudogene structure in5S DNA of Xenopus laevis Cell [J]. Cell, 1977, 12(1) : 109 – 120.

[2] 刘慧，邹枨，林凤.假基因鉴定及其功能分析.生物工程学报，2013，29（5）：551-567.Liu H, Zou C, Lin F. Identification and function analysis of pseudogenes. Chin J Biotech, 2013, 29(5): 551-567.

[3] 刘国庆，白音宝力高，邢永强.假基因研究进展[J].生物化学与生物物理进展，2010（11）：1165-1174.6]

[4] 宋昉等. 脊髓性肌萎缩症遗传学诊断专家共识. 中华医学杂志2020年11月3日第100卷第40期.

SMART MAGAZINE AUTHOR: Ariana EDITOR: Amanda

Y染色体对自闭症谱系障碍的影响

导语

自闭症谱系障碍（ASD）是一种人类神经发育疾病，其主要特征表现为社交互动和沟通功能受损，行为、兴趣和活动模式的受限与重复。在自闭症的临床科研活动中发现男性患有自闭症的人数远远大于女性，而比例接近4：1，女性的保护性效应一直被认为是这一现象的主要解释。因此科学家们猜测，尽管自闭症的基因也许与Y染色体相关，但对这一假设的遗传学和流行病学调查，目前为止并不能完全有效解释ASD在两性之间流行率和患病率的巨大差异。

研究介绍

研究介绍

2024年10月15日，一篇发表在国际杂志NatureCommunications上题为“A genome-first study of sex chromosome aneuploidies provides evidence of Y chromosome dosage effects on autism risk”的研究报告中，来自美国格伊辛格卫生医疗系统等机构的科学家们研究发现，Y染色体与机体自闭症风险的增加有关，额外的Y染色体使得个体自闭症发生的几率几乎翻倍，而这一发现这或许为自闭症为何在男性群体中更普遍提供了新的解释。


nature > nature communications > articles > article

Article | Open access | Published: 15 October 2024

A genome-first study of sex chromosome aneuploidies provides evidence of Y chromosome dosage effects on autism risk

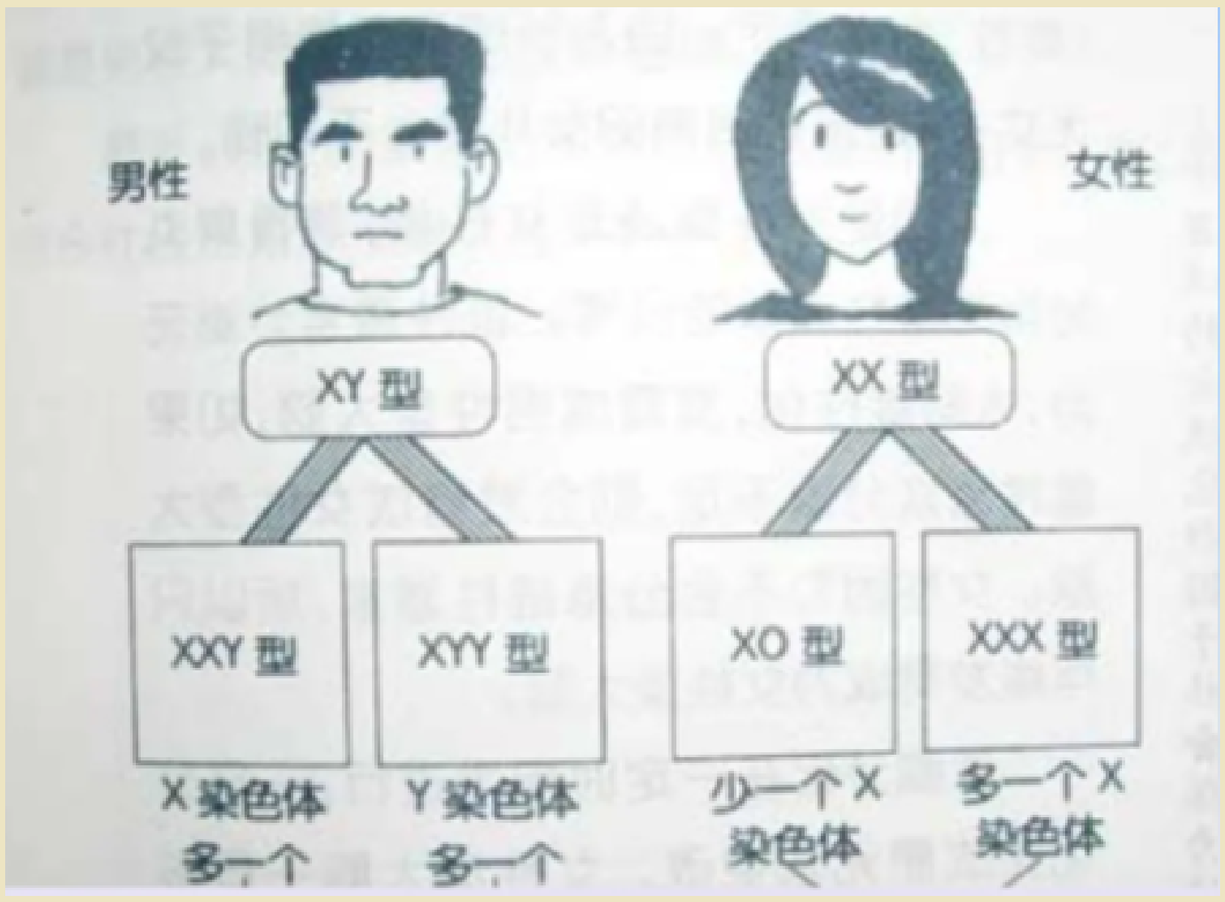
Alexander S. F. Berry, Brenda M. Finucane, Scott M. Myers, Lauren K. Walsh, John M. Seibert, Christa Lese Martin, David H. Ledbetter & Matthew T. Oetjens

Nature Communications **15**, Article number: 8897 (2024) | Cite this article

774 Accesses | **27** Altmetric | Metrics

研究方法

该研究团队通过系统评估了 ASD 责任阈值模型的几个关键预测，从而发现了几条反驳女性保护作用的证据。因此。他们呼吁研究人员需要开发一个替代的概念框架来调查观察到的 ASD 性别差异。性染色体非整倍体 （SCA） 的研究提供了一种创新策略，以进一步阐明基因组因素（包括女性保护作用）导致 ASD 中观察到的性别比偏斜。



几十年来，多项 SCA 研究已充分证明其与神经发育障碍（包括 ASD）患病率的增加有关。尽管许多研究的目的是描述特定 SCA 对神经发育的影响，但对性染色体补体的更全面分析，其中包括 SCA 之间的检查，可以有效揭示 X 和 Y 基因剂量的相对贡献的对比。研究人员汇总了四种最常见的 SCA （45X、47XXX、47XXY 和 47XYY） 中报告的 ASD 临床患病率，并提出了一个模型来解释性染色体剂量与 ASD 风险之间的关系。

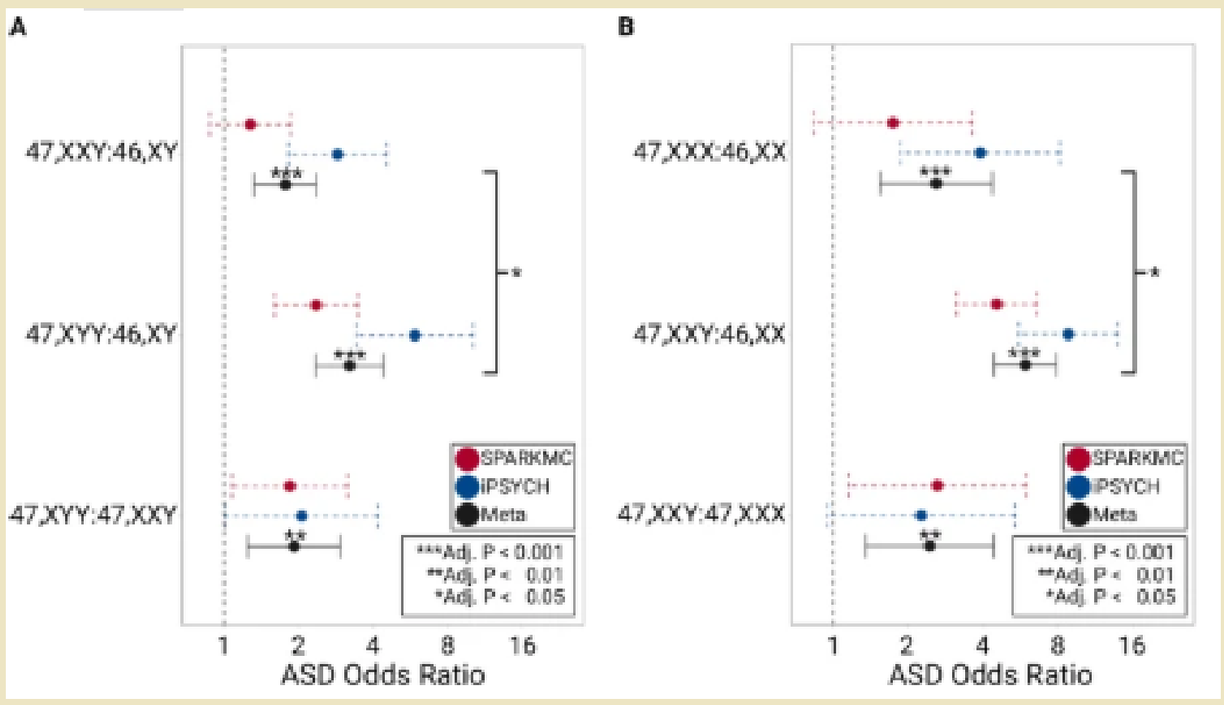
该模型由三个中心假设提供信息：

（1） ASD 风险随着 Y 染色体的每次添加而增加，称为“额外的 Y 效应”；

（2） 每次添加 X 染色体时，ASD 风险的变化很小或没有变化，称为“额外的 X 效应”；

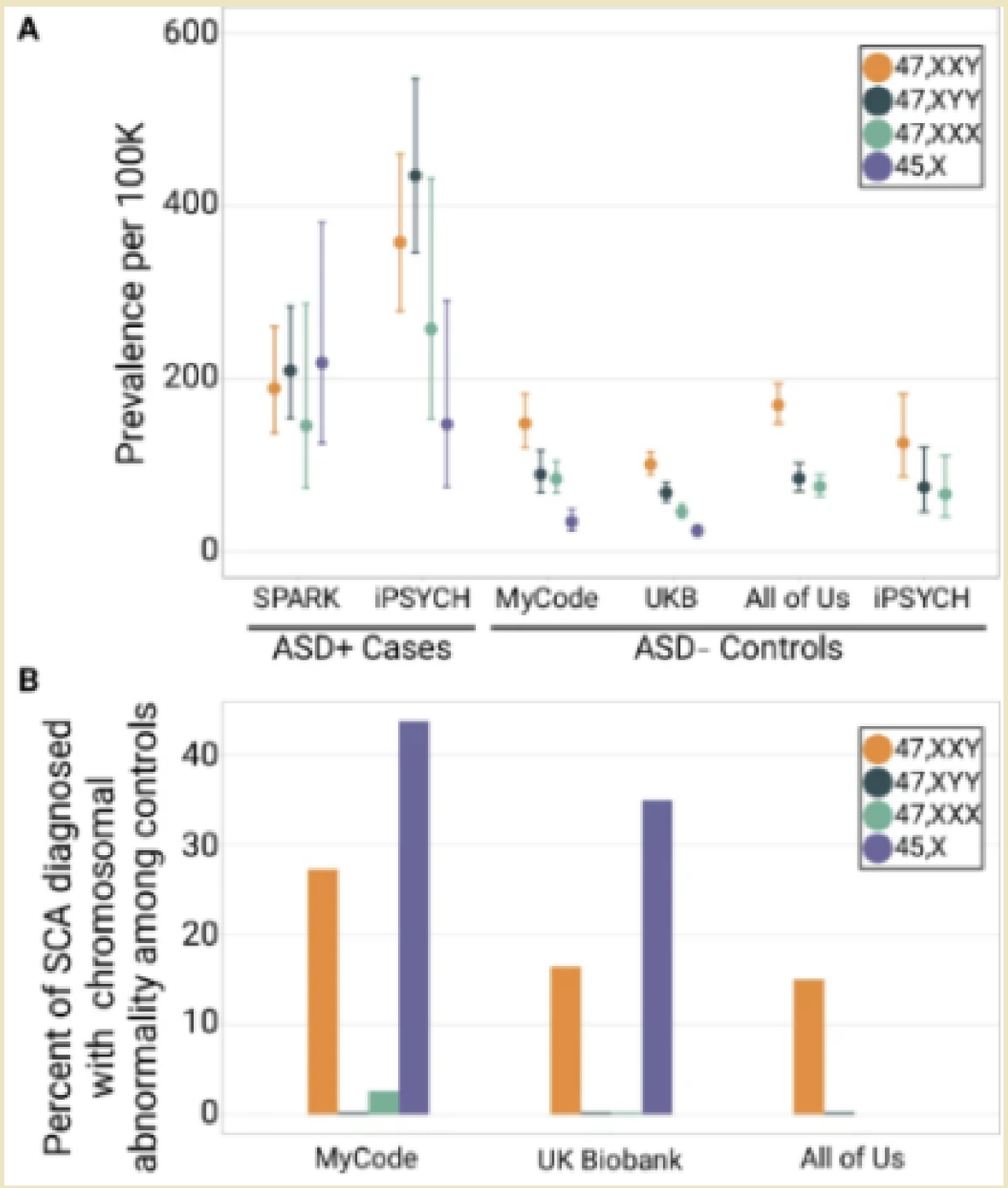
（3） X 染色体的单倍体不足会增加 ASD 风险。

虽然是描述性的并且尚未得到统计验证，但这种概念化为使用 SCA 研究来告知 X 和 Y 基因剂量对 ASD 风险性别差异的影响提供了一个框架。最近在丹麦进行的一项人口研究iPSYCH-SCA 检查了 SCA 与患神经精神疾病（包括 ASD）风险之间的关联。尽管该研究广泛地将 SCA 确定为神经精神疾病的重要危险因素，但它没有检查具有额外 X 染色体与额外 Y 染色体对 ASD 的比较影响。



析之间与更大的额外 Y 效应一致，因为 47 的个体相比，XYY 的风险高于 47XXY。同样，与 47XXX 相比，47XXY 与 ASD 相关的可能性显着更高 。

总体而言，性染色体剂量与 ASD 之间的风险模式与 iPSYCH 研究报告的风险模式基本一致。性别匹配比较中效应大小的排名顺序在研究中是一致的：45X 对 ASD 风险的影响最大，其次是 47XYY，47XXY 和 47XXX。



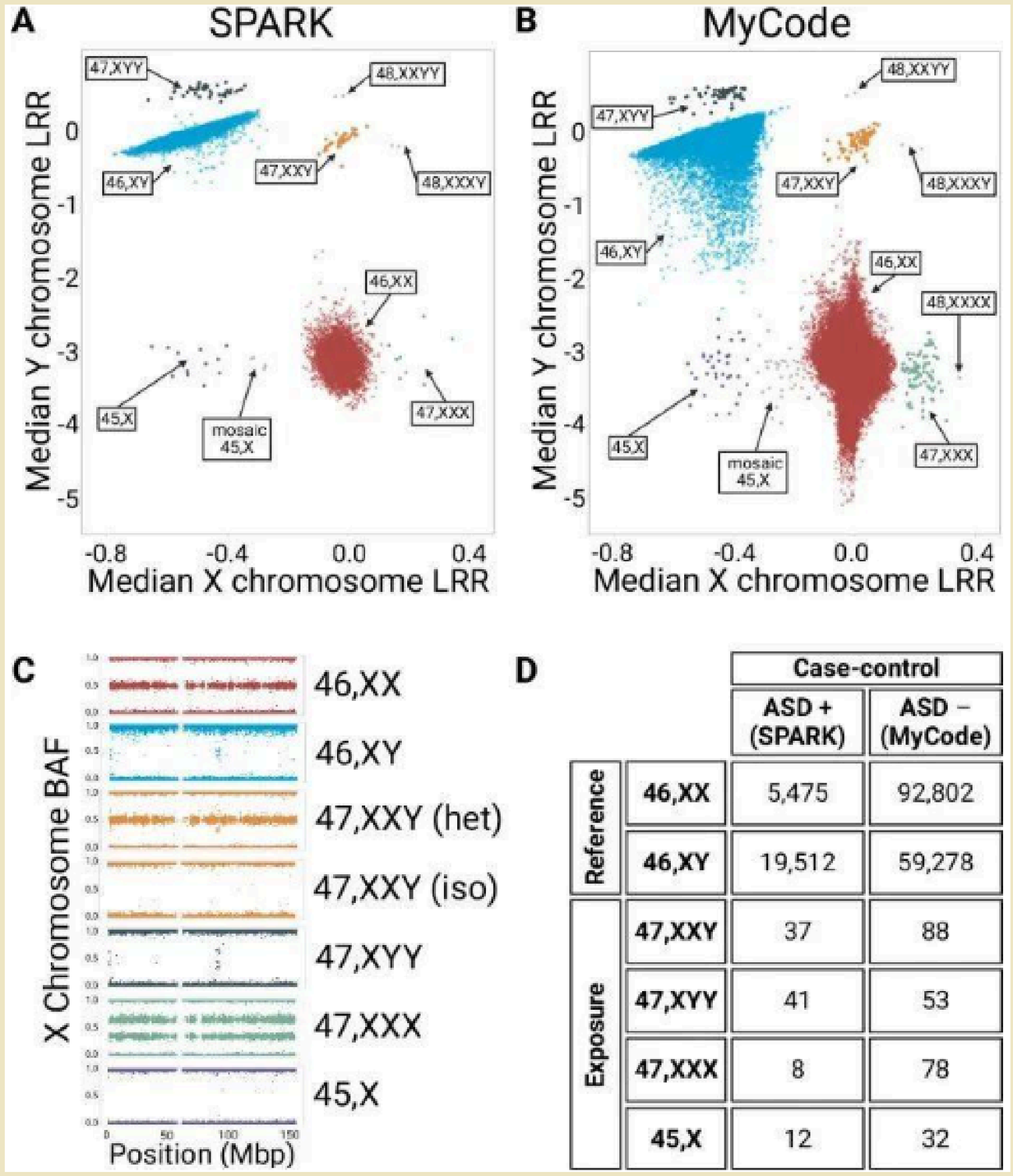
研究发现

在分别进行对 47XXY 和 47XYY 相对于 46XX 和 46XY 的分析中，研究人员模拟了多余的 Y 染色体与 ASD 风险之间的关联，以测试额外的 Y 效应。他们发现47XYY 和 47XXY 都与 ASD 风险增加显著相关，47XYY 的影响明显大于 47XXY 的影响；同时，47XXY 和 47 XXX 都与 ASD 风险增加相关，47XXY 相关的风险估计显著大于 47XXX 。而 47XXX 与 46XX 和 47XXY 相比，与 ASD 相关的可能性没有显着增加。同样，他们还通过对 45X 相对于 46XX 和 46XY 的 ASD 风险之间的关联进行建模，从而测试了单倍体不足的影响。发现45X 与 46XX 相比，X 与 ASD 相关的可能性显著更高，但与 46，XY 相比则不同。最后，在 SCA 分

X染色体的保护作用

遗传学上涉及男性和女性之间性染色体差异的一种常见假设是，典型的女性有两条X染色体，而典型的男性则拥有一条X染色体和一条Y染色体。一个主要理论认为，两条X 染色体之间的相互保护作用帮助降低女性患自闭症的风险，然而，截至目前，关于 X 染色体相互保护作用的相关证据并不充分。这项研究中，研究人员通过分析数据库中机体X或Y染色体数量异常的个体的ASD诊断情况，评估X染色体和Y染色体对自闭症风险的影响。该研究小组的目的在于，通过研究这种先天的染色体异常，来判断Y染色体是否增加了自闭症的发生率，以及X染色体是否具有降低自闭症发生率的保护作用。

研究发现，自闭症的性别失衡背后的潜在生物学机制远比现有‘女性保护作用’理论所能解释的更为复杂。需要进一步研究以阐明与多余Y染色体剂量相关的自闭症风险的生物学机制，以及它是否与自闭症的性别差异有关。

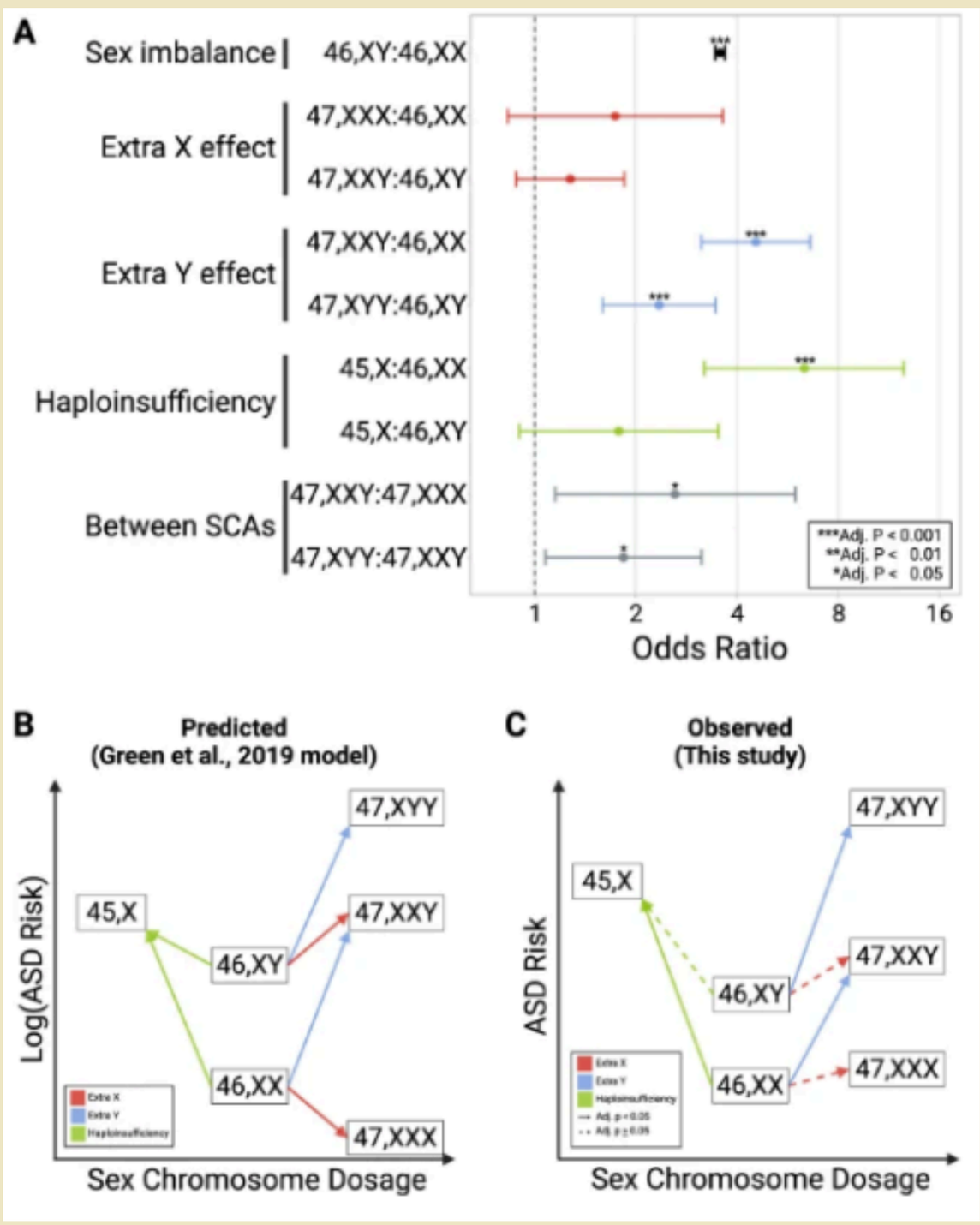


Y染色体的自闭症风险

该团队分析了 177,416 名参与者的遗传数据与 ASD 诊断结果。研究发现，拥有额外 X 染色体的个体ASD发生率的风险没有显著变化。无论是XXX，XXXX与正常女性XX自闭症比率接近；同样地，XXY与正常男性XY相比，自闭症比例也没有显著差异。然而。拥有额外 Y 染色体的个体，ASD发生率的可能性是其两倍，即XYY与XY对比，自闭症比例大幅增高。这揭示了一种与Y染色体相关的风险因素，而并非一种与X染色体相关的保护性因素。额外 Y染色体对ASD的显著影响表明，Y 染色体上的一个或多个剂量敏感基因导致男性 ASD 易感性增加。

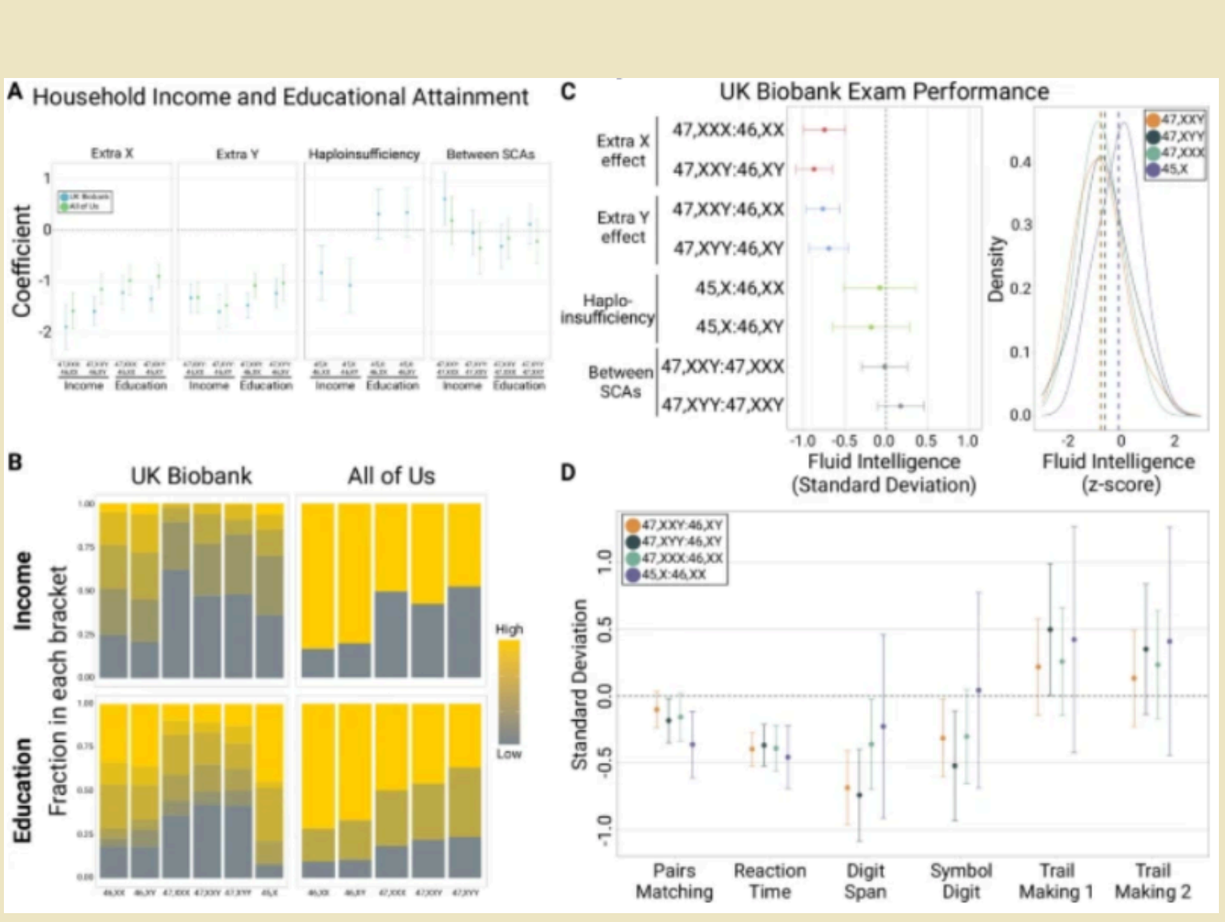
Y 染色体是最小的染色体，包含大约 23 Mb 的独特序列，称为男性特异性区域 （MSY）。大约 2 亿年前 X 和 Y 染色体分化以来，MSY 上的 18 个基因与哺乳动物物种中的 X 染色体对应物保持着高度的同源性。这些基因称为配子同源物，在包括大脑在内的成体组织中具有不同的表达模式。与文献中报道的许多 ASD 基因类似，配子谱具有纯化选择和剂量敏感性的有力证据，这被认为强调了它们对人类健康和发育的重要性。配子同源物 NLGN4Y 和 USP9Y 已被提议作为候选 ASD 位点。

对 ASD 风险的额外 Y 影响可能是多余 Y 染色体对整体基因表达影响的结果。例如，X和Y染色体上的一对配子同源基因ZFX和ZFY（均为转录因子）被发现调控了数百个基因的表达。这些基因在性染色体异常（SCA）个体中呈现异常表达。。研究还发现，ZFY 的作用对 Y 剂量的变化高度敏感。有趣的是，ZFX 中的变异最近被确定为 X 连锁 ID 综合征的原因，这表明该基因对神经发育的重要性。虽然其 Y 连锁配子学 ZFY 中变异的表型后果尚未报道，但该基因是额外 Y 效应的候选介质。



染色体与认知能力

由于认知和 ASD 具有许多遗传基础，研究人员假设在 SCA 和 ASD 之间观察到的关联模式在认知表现和健康的社会决定因素的测量中是相似的，包括基于学术和职业成就的测量。然而，如果该模式发生偏离，则表明性染色体剂量与 ASD 之间的关联至少部分独立于对认知的有害影响。研究发现 47XXY， 47XYY 和 47XXX 的认知表现显著低于 46XX 和 46XY个体。编外 SCA 之间的效应量彼此之间没有显着差异，并且不支持额外 X 或额外 Y 效应对这些指标的差异。相比之下，45X 与 46XX 或 46XY 的流体智力测试成绩或教育程度没有显着差异，尽管在 SPARKMC-SCA 和 iPSYCH-SCA 研究中观察到它对 ASD 风险有很大影响。结果表明，性染色体剂量与认知能力与健康的社会决定因素之间的影响模式与 ASD 不同。



男性 ASD 发病率的增加不能用性别之间的认知差异来解释。额外的 X 和 Y 染色体对认知表现具有相似的影响。这表明一种与性别、ASD 和认知能力之间的关系一致的模式：X 和 Y 染色体剂量增加对 ASD 风险的影响之间的差异不能用它们与认知能力的关系来解释。

研究局限：

1. 来自病例和对照的不同队列可能具有不同的确定偏倚。
2. 对照参与者仅由电子健康记录或自我或父母报告中缺乏 ASD 诊断来定义
3. 无法检验与 SCA 和 ASD 风险相关的荷尔蒙差异之间的关联。荷尔蒙差异不太可能解释 ASD 与 Y 染色体剂量之间的关联。
4. 种族或族裔群体对确定 ASD 队列的遗传祖先群体的影响没有得到很好的描述，也无法在统计建模中解释。

前景展望

本研究结果鼓励在Y染色体上将重点放在自闭症风险因素，而不仅仅将研究局限于在X染色体上寻找保护性因素。随后，研究人员还需要进一步研究识别出与Y染色体相关的特殊风险因素。该研究分析还证实了此前的研究结果，即称为特纳综合征（Turner syndrome）的X或Y染色体缺失疾病或许与机体自闭症风险大幅增加有关，即45条染色体X携带者比正常XX或XY的自闭症发生率都要高。研究人员还需要深入研究确定是否与性染色体非整倍性相关的自闭症风险因素能解释两性之间自闭症发病率的差异。

综上，本研究为理解X和Y染色体剂量对自闭症发病风险影响之间的关联提供了一个研究框架，或许能为未来科学家们进一步研究观察到的性别差异的基因组因素共享提供新的线索和研究基础。需要注意的是，即使真的如研究结论指出的，Y染色体增加了孩子的自闭症风险，那么也不能因为担心生一个自闭症的孩子而进行性别选择。

参考文献

[1]Berry, A.S.F., Finucane, B.M., Myers, S.M. et al. A genome-first study of sex chromosome aneuploidies provides evidence of Y chromosome dosage effects on autism risk. Nat Commun 15, 8897 (2024).doi： 10.1038/s41467-024-53211-7

[2]https://www.geisinger.org/about-geisinger/news-and-media/news-releases/2024/10/17/17/42/increased-autism-risk-linked-to-y-chromosome-geisinger-study-finds

1.

SMART MAGAZINE AUTHOR: Zeke EDITOR: Amanda

体内筛选平台可鉴定针对肺纤维化中的 p16INK4a 成纤维细胞的 senolytic 化合物

关键词：p16INK4a，衰老细胞，senolytic，HSP90抑制剂

摘要

衰老细胞在多种年龄相关疾病中发挥重要作用，其特征包括细胞周期永久停滞和分泌“衰老相关分泌表型”(SASP)。本研究开发了一种高通量体内筛选平台，利用荧光标记报告系统（INKBRITE）直接分离纤维化组织中的p16^INK4a^阳性成纤维细胞，筛选出具有清除衰老细胞能力的senolytic化合物。研究通过单细胞RNA测序和免疫组织化学分析，证实p16INK4a阳性成纤维细胞具有促纤维化特性。在体外和体内实验中，p16INK4a过表达或敲除分别加剧或减轻了纤维化反应。通过筛选发现，HSP90抑制剂XL888能够显著减少纤维化模型中p16INK4a阳性细胞及其相关病理重塑。此外，XL888在特发性肺纤维化患者样本中的疗效也得到了验证。本研究提供了一种精准的senolytic筛选平台，为治疗纤维化等衰老相关疾病提供了新思路。

研究背景

衰老细胞是指经历了细胞周期永久性停滞、失去增殖能力但仍然存活的细胞。它们通常表现为细胞大小增大、基因组不稳定性增加，以及表达特定的生物标志物，如p16INK4a和p21。衰老细胞的累积不仅是正常衰老过程的一部分，还在许多与年龄相关的疾病（如神经退行性疾病、心血管疾病、骨关节炎及纤维化）中起到关键作用。 这些细胞通过“衰老相关分泌表型”(SASP）分泌多种细胞因子、炎症因子、蛋白酶，导致组织微环境改变，进一步促进慢性炎症和组织退化。消除这些细胞可以减少这些负面效应，从而改善组织功能和整体健康。

Senolytic 是一类专门针对衰老细胞（senescent cells）的化合物，能够选择性清除衰老细胞。其作用机制基于衰老细胞特有的抗凋亡信号网络，Senolytic通过干扰这些网络，使衰老细胞更容易受到凋亡的影响而被清除。这些细胞无法继续分裂但依然存活，通过分泌多种炎性因子、细胞因子和蛋白酶形成“衰老相关分泌表型”（ senescence-associated secretory phenotype, SASP），对组织微环境和器官功能产生不利影响。因此在组织老化和许多年龄相关疾病中，衰老细胞的积累被认为是重要的病理机制。

在本研究中，研究团队开发了一种以疾病组织中的衰老细胞为靶点的高通量筛选平台，克服了传统筛选策略的不足。该平台采用了一种荧光报告系统（INKBRITE），可以在活体中标记和分离p16INK4a阳性细胞，并结合体外、离体组织切片（PCLS）以及活体模型验证化合物的功效。这一平台的建立，为在疾病相关背景下发现有效的senolytic提供了更可靠的工具。

p16INK4a是细胞衰老的关键标志物，由CDKN2A基因编码，其主要功能是通过抑制细胞周期蛋白依赖性激酶4/6（CDK4/6）阻止Rb蛋白的磷酸化，从而引发细胞周期永久停滞。在衰老相关疾病中，p16INK4a的表达上调与衰老细胞的积累密切相关。因此，作为靶标，p16INK4a可用于识别和清除衰老细胞，例如通过senolytic化合物精准作用于p16INK4a阳性细胞，有助于减缓组织损伤和疾病进展。

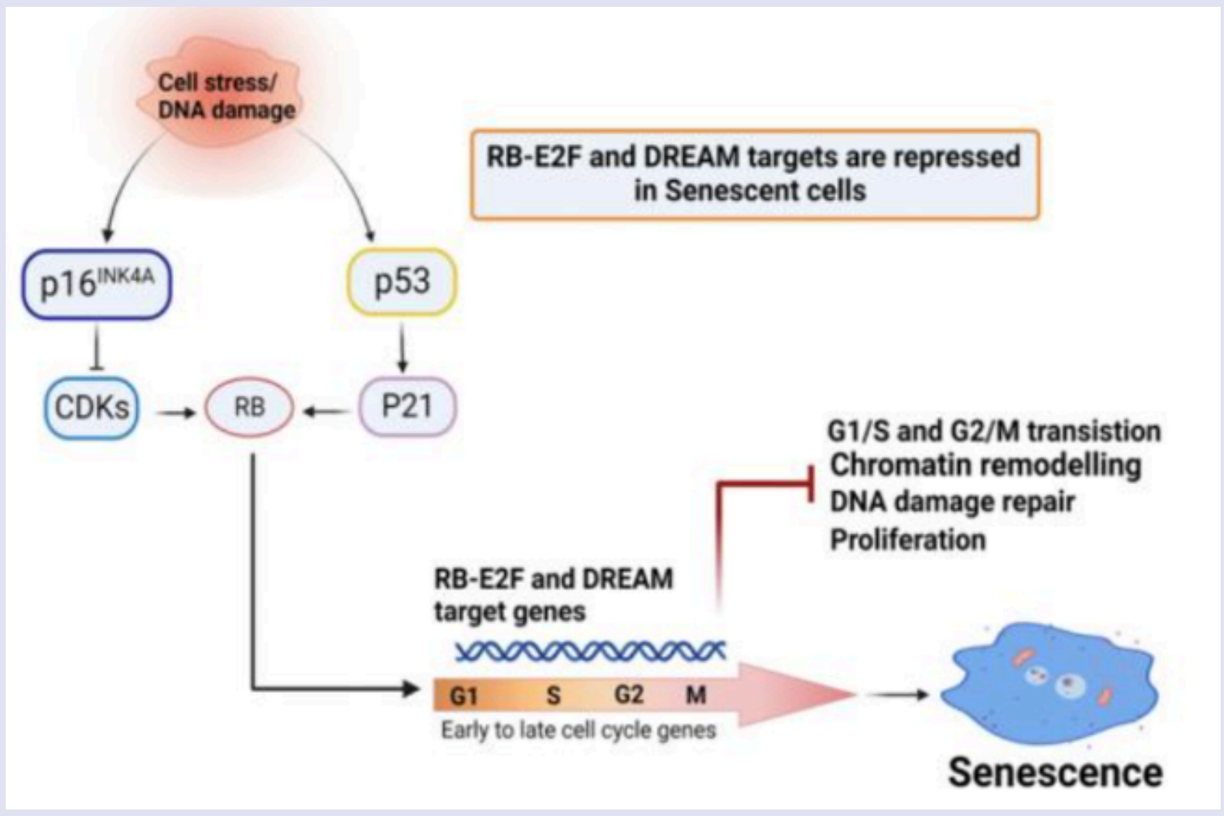


Fig1.p16INK4a作用机理

胞，多个亚群，包括已知的间质亚群如基底膜成纤维细胞和气道周围成纤维细胞，以及纤维化特异的新兴亚群，如促纤维化（profibrotic）成纤维细胞。进一步分析显示，促纤维化成纤维细胞显著上调了多种促纤维化基因（如ACTA2、COL1A1、TAGLN和CTHRC1）。此外，IHC进一步验证了这些亚型细胞的存在，显示在纤维化病变区域，p16INK4a阳性细胞与纤维化标志物（如ACTA2和COL1A1）共定位，尤其是在高密度胶原沉积区域。以上结果表明，这些p16INK4a阳性成纤维细胞不仅参与了纤维化反应，还具有显著的致病潜力，为其作为治疗靶标提供了有力的支持。

研究结果

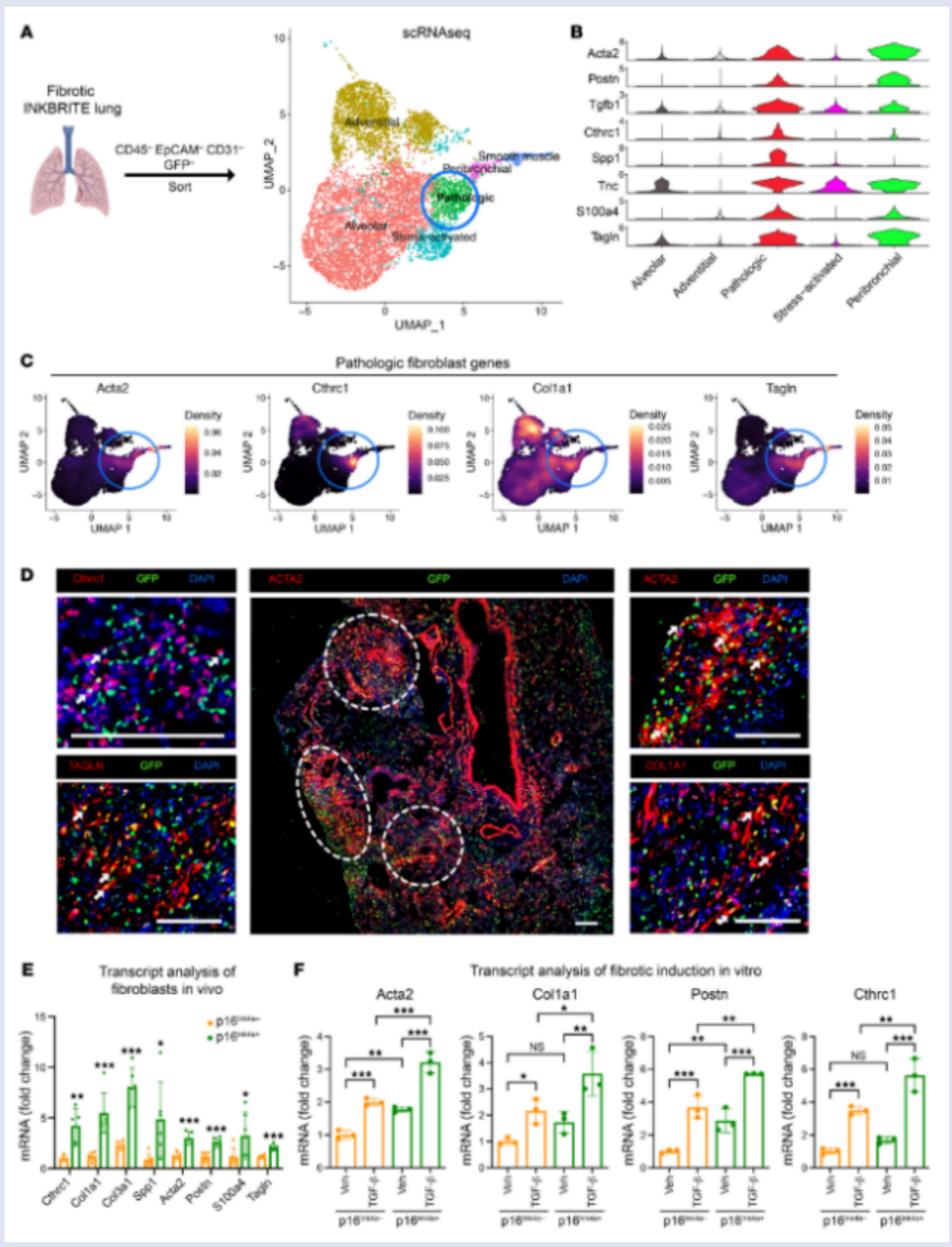


Fig2. p16Ink4a 成纤维细胞有助于小鼠肺纤维化模型中的病理性成纤维细胞

通过单细胞RNA测序（scRNA-Seq）和免疫组织化学（IHC）实验，研究详细表征了纤维化肺组织中表达p16INK4a的成纤维细胞亚型的特性。scRNA-Seq分析从Bleomycin诱导的纤维化小鼠模型中分离了GFP标记的p16INK4a阳性成纤维细

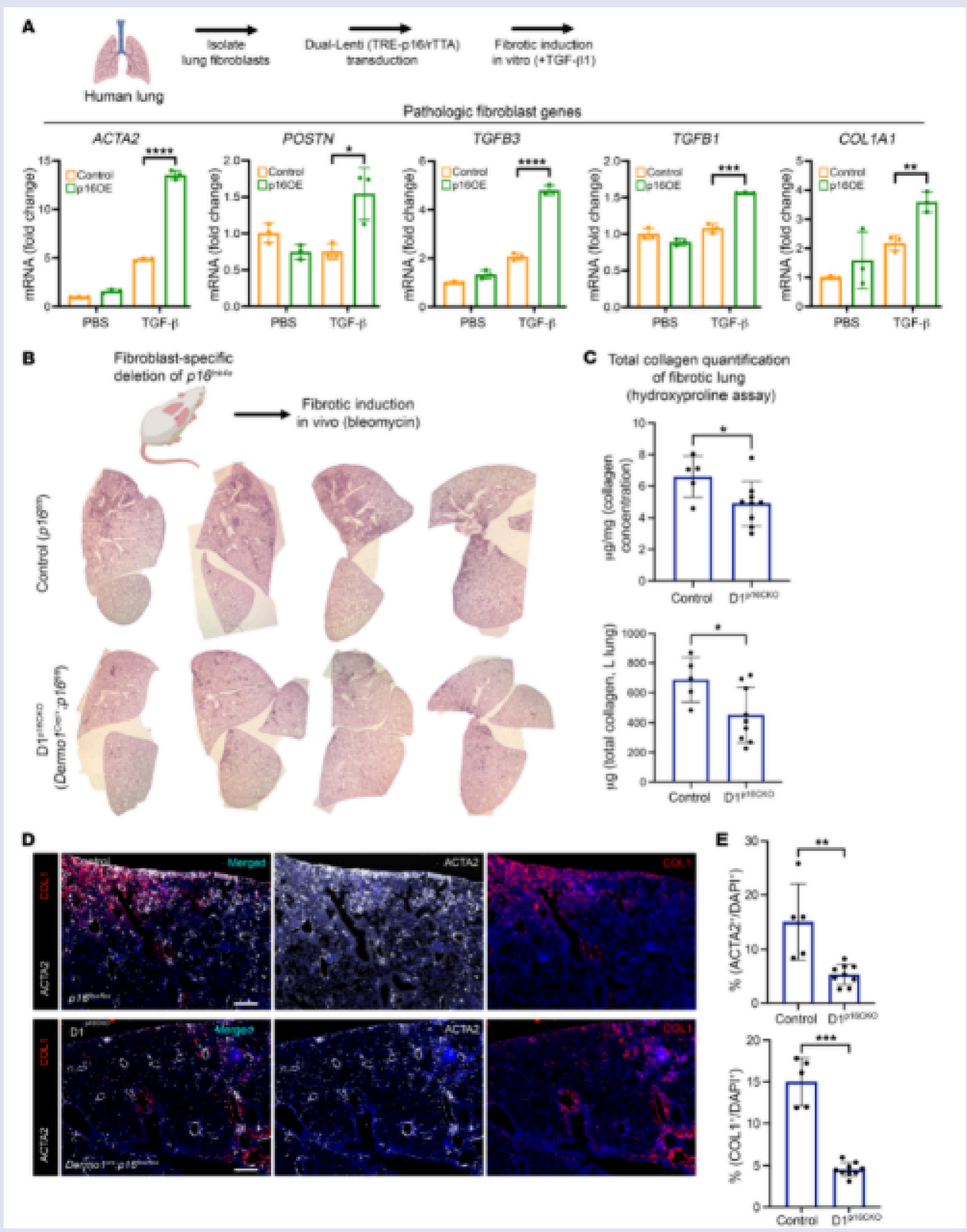


Fig3. p16INK4a 表达激发肺成纤维细胞增强纤维化反应

在体外实验中，研究人员通过构建诱导型p16INK4a过表达系统，以探讨其对成纤维细胞促纤维化反应的具体影响。具体而言，他们利用一种双组分的转基因系统在人肺成纤维细胞中实现了p16INK4a的可控过表达，并通过添加TGF-β1模拟纤维化诱导环境。结果显示，与对照组相比，

p16INK4a过表达的成纤维细胞在TGF-β1刺激下显著上调了多种促纤维化基因，包括COL1A1、ACTA2和TAGLN，而在没有TGF-β1刺激的情况下，促纤维化基因表达没有明显变化。这表明p16^Ink4a^的作用并非直接驱动纤维化，而是通过“增敏”机制增强了细胞对促纤维化信号的响应。

在体内实验中，研究利用纤维细胞特异性p16INK4a基因敲除小鼠验证了p16^Ink4a^在纤维化反应中的作用。在未受损的肺组织中，敲除p16INK4a并未引起显著的组织形态学改变。然而，在Bleomycin诱导的肺纤维化模型中，与对照组相比，D1p16CKO小鼠表现出纤维化显著减轻的特征，包括组织学观察中胶原沉积减少，以及通过羟脯氨酸定量分析验证的肺胶原含量下降。此外，免疫组织化学（IHC）显示，D1p16CKO小鼠的肺中促纤维化标志物（如ACTA2和COL1A1）阳性成纤维细胞数量明显减少。以上研究结果强有力地证明了p16INK4a在纤维化反应中的关键促进作用，并表明其可能通过增强纤维细胞对TGF-β1等促纤维化刺激的敏感性，推动纤维化的进展。

研究团队利用GFP标记的p16Ink4a+成纤维细胞对2000种化合物进行筛选，识别出几种选择性靶向p16Ink4a+成纤维细胞的化合物，同时不影响p16Ink4a-细胞。最终筛选出HSP90和HDAC抑制剂等具有强大潜力的化合物。

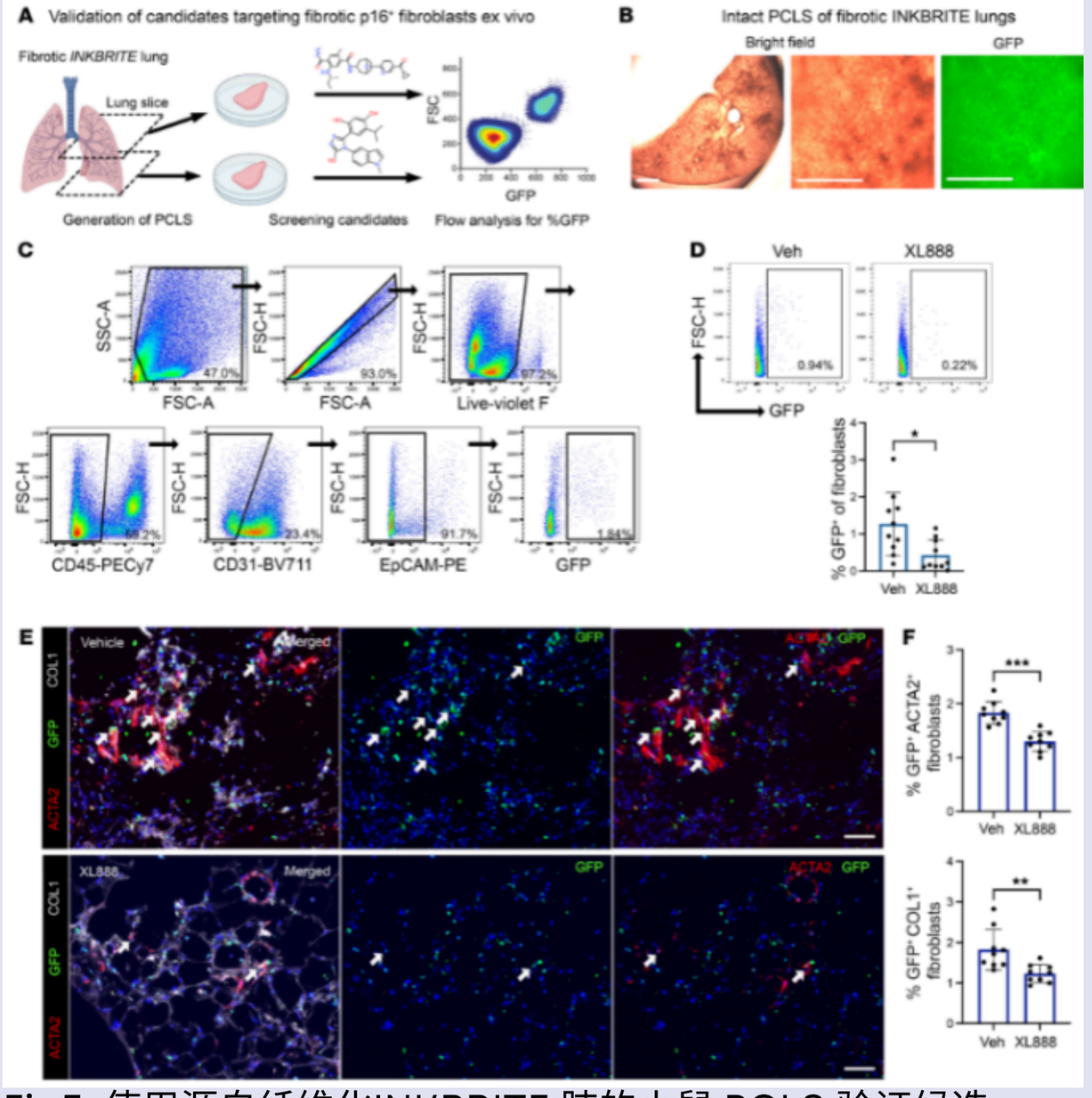


Fig5. 使用源自纤维化INKBRITE 肺的小鼠 PCLS 验证候选 senolytic 化合物

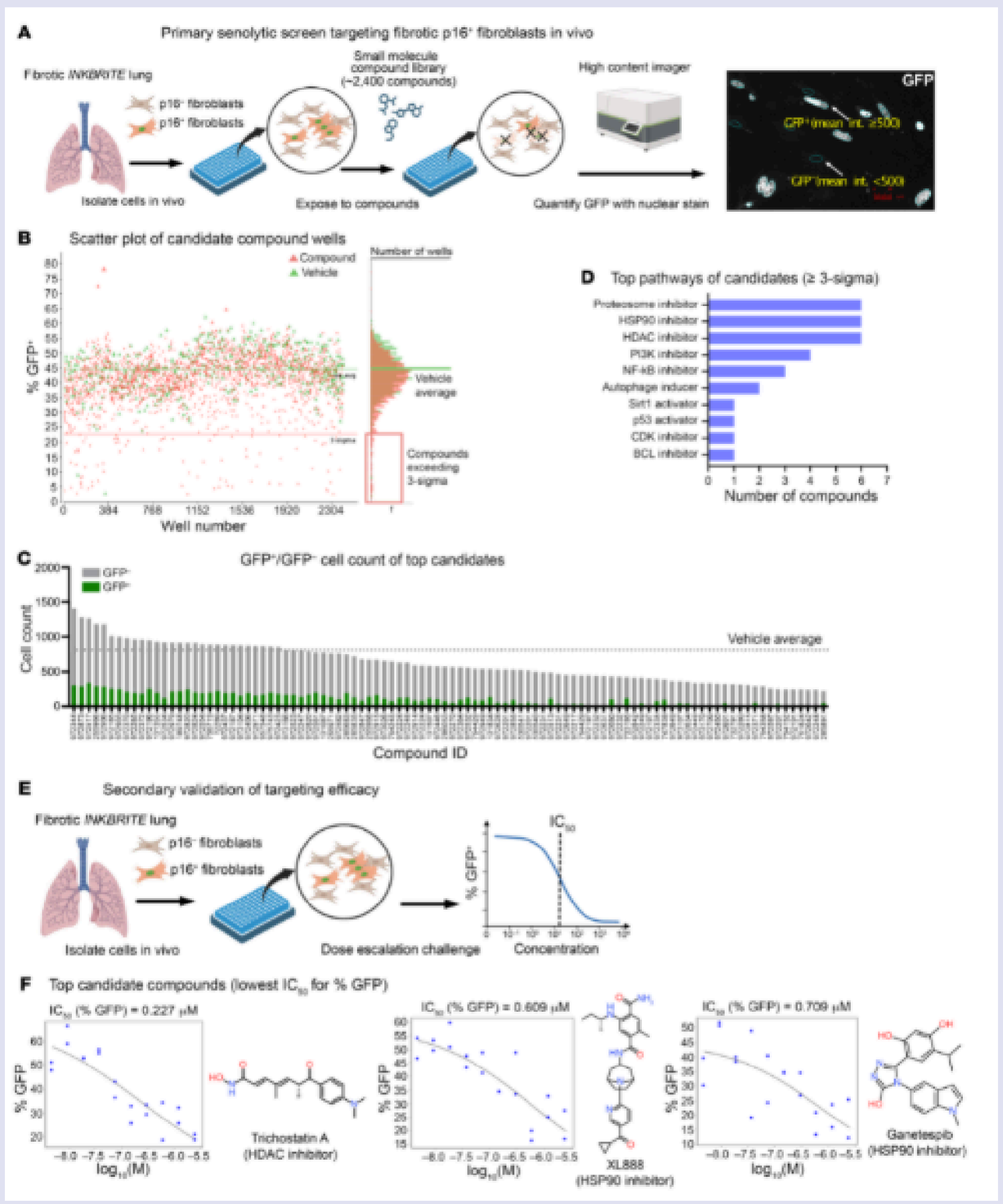


Fig4. HTS 靶向从纤维化 INKBRITE 肺中分离出的 p16Ink4a 成纤维细胞

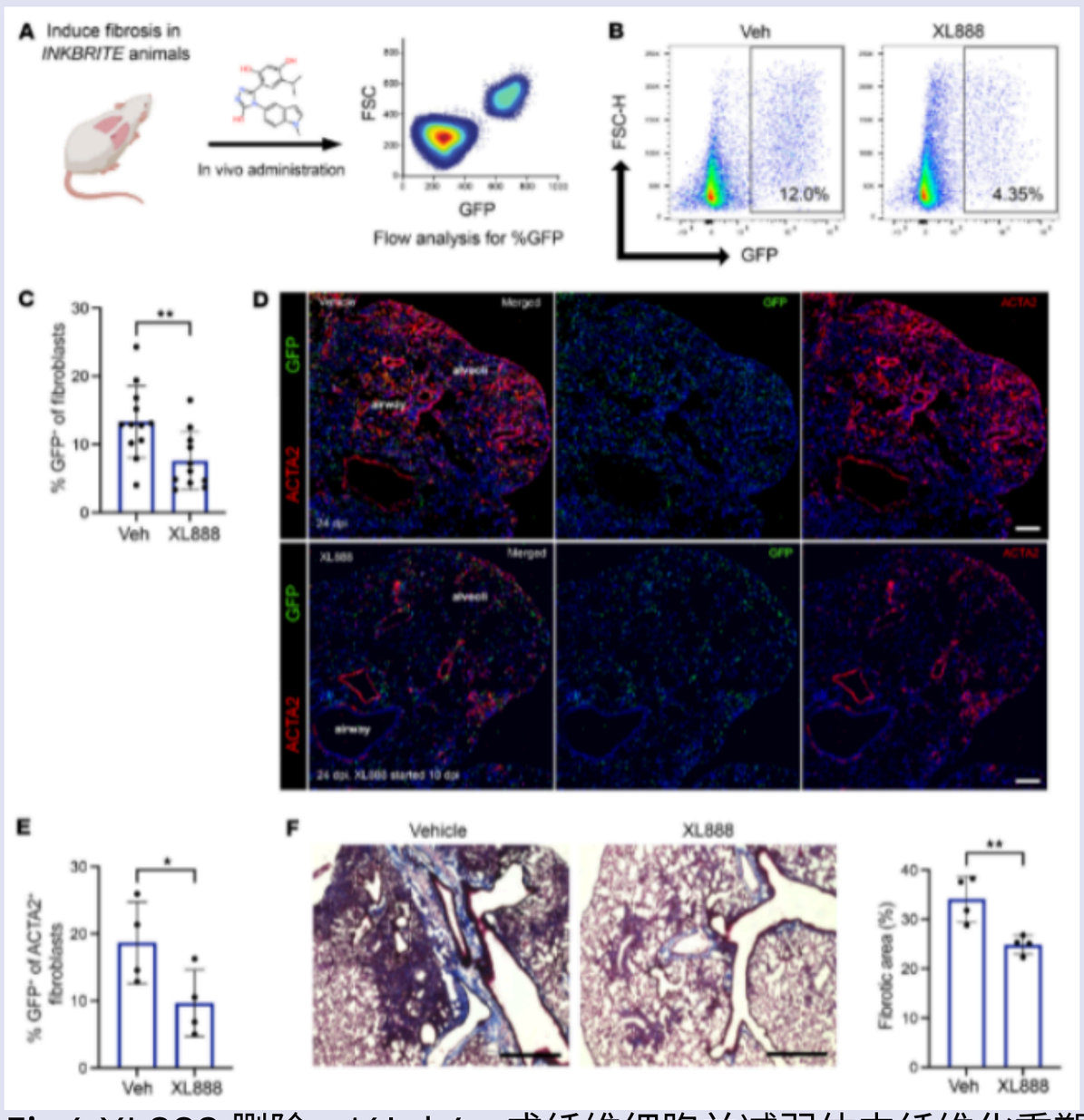


Fig6.XL888 删除 p16Ink4a 成纤维细胞并减弱体内纤维化重塑

在纤维化肺切片中测试化合物，以确认其在生理环境中的有效性。研究发现HSP90抑制剂XL888效果最佳，显著减少了肺切片中的p16Ink4a+成纤维细胞。

最终，研究在小鼠肺纤维化模型中验证了XL888的有效性。XL888治疗显著减少了p16Ink4a+成纤维细胞和纤维化重塑程度，通过流式细胞术、IHC及胶原含量分析得到了验证。

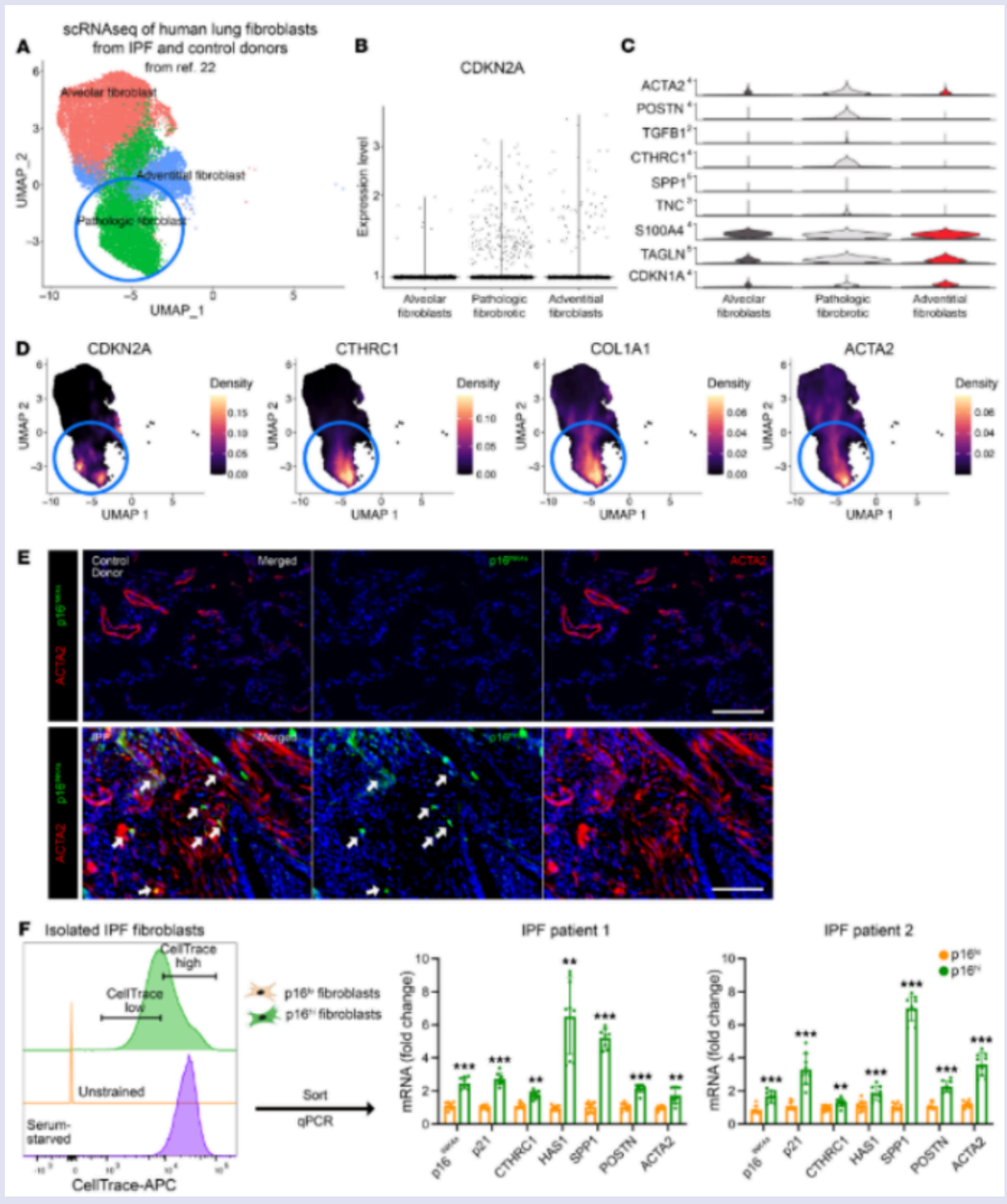


Fig7.人 p16INK4a 成纤维细胞有助于 IPF 中的病理成纤维细胞

研究进一步在从特发性肺纤维化（IPF）患者中提取的人肺成纤维细胞和PCLS模型上测试了XL888，证实了该化合物对人类p16INK4a+成纤维细胞的选择性衰老细胞清除作用，显示出其在人类纤维化治疗中的潜力。

总结

本研究聚焦于衰老细胞在肺纤维化中的致病作用，开发了一种高效精准的体内筛选平台，用于发现针对p16^INK4a^阳性衰老细胞的senolytic化合物。通过结合荧光报告系统（INKBRITE），单细胞RNA测序（scRNA-Seq）和免疫组织化学（IHC）系统表征了纤维化肺中p16^INK4a^阳性成纤维细胞的异质性，确认这些细胞在纤维化反应中的关键致病潜力。体外实验中，p16^INK4a^过表达的成纤维细胞在TGF-β1刺激下显著上调促纤维化基因，体内研究则表明敲除p16^INK4a^基因显著减轻了纤维化程度，验证了其在纤维化中的关键作用。

利用高通量筛选平台，研究从2000种候选化合物中鉴定出HSP90抑制剂XL888，并通过离体组织切片（PCLS）和小鼠模型验证其有效性。结果显示，XL888能够选择性清除p16^INK4a^阳性成纤维细胞并减轻纤维化病理重塑。此外，该化合物在人类特发性肺纤维化（IPF）样本中的疗效也得到验证。

本研究具有清晰的思路，和突出的技术创新性，提出了一种从疾病模型到临床相关验证的整合策略，为纤维化及其他衰老相关疾病的治疗提供了新思路。通过系统评估senolytic化合物在体内外的有效性和选择性，本研究为药物开发领域树立了技术典范，同时为进一步的临床应用奠定了基础。

参考文献

[1] Lee, J. Y., Reyes, N. S., Ravishankar, S., Zhou, M., Krasilnikov, M., Ringler, C., Pohan, G., Wilson, C., Ang, K. K., Wolters, P. J., Tsukui, T., Sheppard, D., Arkin, M. R., & Peng, T. (2024). An in vivo screening platform identifies senolytic compounds that target p16INK4a+ fibroblasts in lung fibrosis. The Journal of clinical investigation, 134(9), e173371. https://doi.org/10.1172/JCI173371

[2] Burd CE, et al. Monitoring tumorigenesis and senescence in vivo with a p16(INK4a)-luciferase model. Cell. 2013;152(1-2):340-351.

[3] Cai, Y., Song, W., Li, J., Jing, Y., Liang, C., Zhang, L., Zhang, X., Zhang, W., Liu, B., An, Y., Li, J., Tang, B., Pei, S., Wu, X., Liu, Y., Zhuang, C. L., Ying, Y., Dou, X., Chen, Y., Xiao, F. H., ... Liu, G. H. (2022). The landscape of aging. Science China. Life sciences, 65(12), 2354-2454. https://doi.org/10.1007/s11427-022-2161-3

SMART MAGAZINE AUTHOR: Seraphina TRANSLATOR: Anaya EDITOR: Zeke

失语症

简介：

失语症是由于大脑损伤引起的获得性沟通交流障碍，表现为语言理解、语言表达、阅读、书写、复述、命名等能力不同程度的受损。

病因

失语症的病因包括脑卒中、外伤、肿瘤、脑部神经退行性病变等等，其中脑卒中是引发失语症的主要原因。有报道显示50%～70%的脑卒中后患者遗留有瘫痪、失语等严重残疾，其中21%～38%患者患有失语症，主要表现为各种语言功能的障碍，严重影响患者的情绪和生活质量。我国目前脑卒中患者达 1242 万,且发病人群呈年轻化趋势，45 岁以下患者比例已经超过 10%，每年新增脑卒中 300 多万例，其中约有38%的脑卒中患者会出现失语症。

学说

现在对于失语症相关的研究主要分为三种学说：“雅克布逊回归假说”（Jakobson Regression Hypothesis, Jakobson, 1941)、“句法树裁剪假说”（Tree Pruning Hypothesis, Friedmann, 2001; Friedmann & Grodzinsky, 1997)和“论元结构复杂性假说”（Argument Structure Complexity Hypothesis, Thompson, 2003)。其中，“雅克布逊回归假说”认为失语症患者的失语是语言习得的镜像，即对于失语症患者来说，儿童时期先习得的后失去、后习得的先失去，儿童语言习得与失语症的失语呈现回归性特征。“句法树裁剪假说”认为，句法损伤实质上是屈折分裂树的裁剪。也就是说，受损的节点越高，则受损的功能语类数量越多,句法受损就越严重。“论元结构复杂性假说”认为，动词所对应的论元结构越复杂，失语症患者相应动词的理解和产出就越困难。

特性

汉语失语症患者的超音段音位损伤情况亦受到学者关注。汉语作为一种声调语言，语调只能在音节声调的基础上得以体现,即在不改变音节声调的前提下体现语调的升降。汉语失语症在超音段层面上的研究主要集中于声调和语调的探讨，研究表明，声调具有独立表征，且上声错误居多，汉语声调和声母在发音受损的严重程度、错误类型和错误语音特征分析(区别性特征)等方面表现相同。

治疗方法

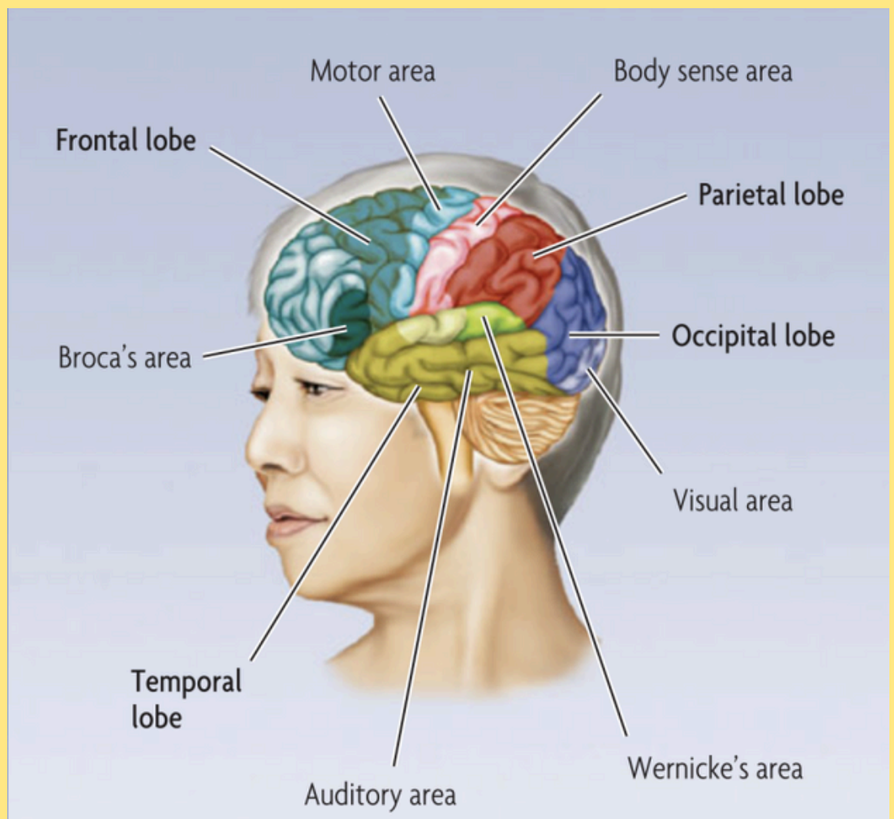
1 有研究发现药物治疗(回语丹、回言胶囊等)和针灸对中风失语症患者的言语功能具有改善作作用。其中，电针(electroacupuncture) 可激活脑卒中后运动性失语患者与语言加工相关的大脑区域，有助于治疗汉语失语症。针灸疗法具有一定疗效，但是目前还没有长期治疗成功的临床案例。经颅磁刺激亦可用于治疗汉语失语症。2021年报告了一例纯词聋失语症患者在经过重复经2颅磁刺激(rTMS)治疗后，听力理解能力中除环境音识别外均有较大提升，复述能力和听写改善明显。 有研究表明，tTMS 与计算机辅助治疗或同步言语治疗相结合比单独使用具有更好的疗效。

以上是针对汉语失语症患者的相关治疗方案以及展望。对于普遍的失语症患者，目前主要有三种方法：强制性诱导失语症治疗（constraint induced aphasia therapy，CIAT)、多模式失语 症 治 疗 （multimodality aphasia therapy，M-MAT）和音乐疗法。

3CIAT 是一种仅使用语言进行交流，并依赖于患者正确言语反应的语言游戏训练。CIAT 通过禁止非言语交流模式，增强刺激的渐进难度、 反应逐渐形成更复杂的话语进行治疗。该疗法后被修改为强化语言行动疗法 （ intensive language action therapy，ILAT ） 的新版本。研究表明，CIAT 可以显著改善生活质量，并可以在任何阶段改善患者的失语症状。M-MAT 是一种高强度的，涉及患者可使用的所有语言和非语言策略，以提高效率多模式联合治疗。M-MAT 主要用于治疗重度布洛卡失语症的患者。与常规社区护理相比，M-MAT 在单词检索、功能性交流和生活质量方面具有更好的治疗效果。
音乐疗法是一门集音乐学、 医学和心理学为一体
的新兴的交叉学科。音乐疗法能上调中脑边缘系统多巴胺，刺激受损的大脑语言区，调节语言网络内的神经可塑性，促进言语功能的恢复。神经影像学研究发现， 音乐和语言共享大脑网络， 都能激活大脑的布洛卡区，因此强化的音乐训练有助于语言功能的恢复，对 失语症患者的语言功能等具有一定的改善作用。
布洛卡失语症与韦尼克失语症是两种不同的失语症种类。布洛卡失语症一般指运动性失语症，以口语表达障碍为最突出。主要表现为说话费力、不流利、语量稀少、呈电报式（主要是实质词)，可表达基本意思。韦尼克失语症一般指感觉性失语症，其特点为口语流利、语量较多，但错语和赘语多。患者所说人们往往难以理解。患者对口语的理解也有严重障碍，常答非所问，并且复述、命名、阅读和书写等均不正常。相对来说，韦尼克失语症症状较为复杂，治疗也比较困难。

结论：

In daily life, aphasia patients endure more suffering than we might imagine. In clinical practice, therapists should base their approach on the individual's functional impairments, considering the patient's specific needs to choose the most suitable treatment method to aid in their recovery. In everyday life, society should show more understanding and care for aphasia patients, offering timely assistance when needed to help them overcome difficulties.



引用：

[1] 邱乐思,妥玉婷,汪洋,等.脑卒中后失语症治疗的研究进展[J].中国当代医药,2024,31(14):182-185.
[2] 王瑜元,孙长慧,白玉龙.卒中后失语症患者失语症类型及严重程度影响因素的回顾性分析[J].中国康复,2024,39(06):323-328.
[3] 常辉,王海燕.失语症研究的语言学转向[J].山东外语教学,2024,45(03):34-44.
[4] 刘佳,范琳.汉语失语症研究：回顾与展望[J].山东外语教学,2024,45(03):23-33.
[5] p1原AP Psychology and life教材
[6] p2原北京十一学校AP Psychology课程教案

SMART MAGAZINE AUTHOR: Kita EDITOR: Yates

抗性淀粉

摘要：

抗性淀粉（Resistant starch,RS）是指在120 min内不能被健康人体小肠消化和吸收、但在大肠中能够被发酵的淀粉及其淀粉降解物的总称。抗性淀粉具有多种保健作用，如预防糖尿病、改善肠道微环境、降血糖、降血脂和减肥等，这引起了农业、食品和医药等领域学者的极大兴趣。

关键词：抗性淀粉；碳水

引言

一提到“碳水”，很多人都避之不及，担心吃多了会发胖、升血糖，甚至将它视为自己健康路上的“绊脚石”。不过有一类“碳水”，不仅不会导致肥胖，甚至还有减轻脂肪肝的作用，它就是我们今天的主角--抗性淀粉！

1 什么是抗性淀粉?

抗性淀粉 （resistant starch） 又称抗酶解淀粉、难消化淀粉，在小肠中不能被酶解，但在人的肠胃道结肠中可以与挥发性脂肪酸起发酵反应。 简单来说，抗性淀粉从化学结构上看确实是货真价实的淀粉，只是不能被人体分解成葡萄糖，作为能量来源。 当然，小肠没办法消化它，它便会顺利地进入大肠，大肠菌群中那些喜欢淀粉的品种会非常欢迎它，并因为“食物充足”而繁荣起来，成为优势较强的菌群。这些菌群所产生的短链脂肪酸对维持健康的肠道环境、预防高血脂和肠癌等都是有益的。 [1]

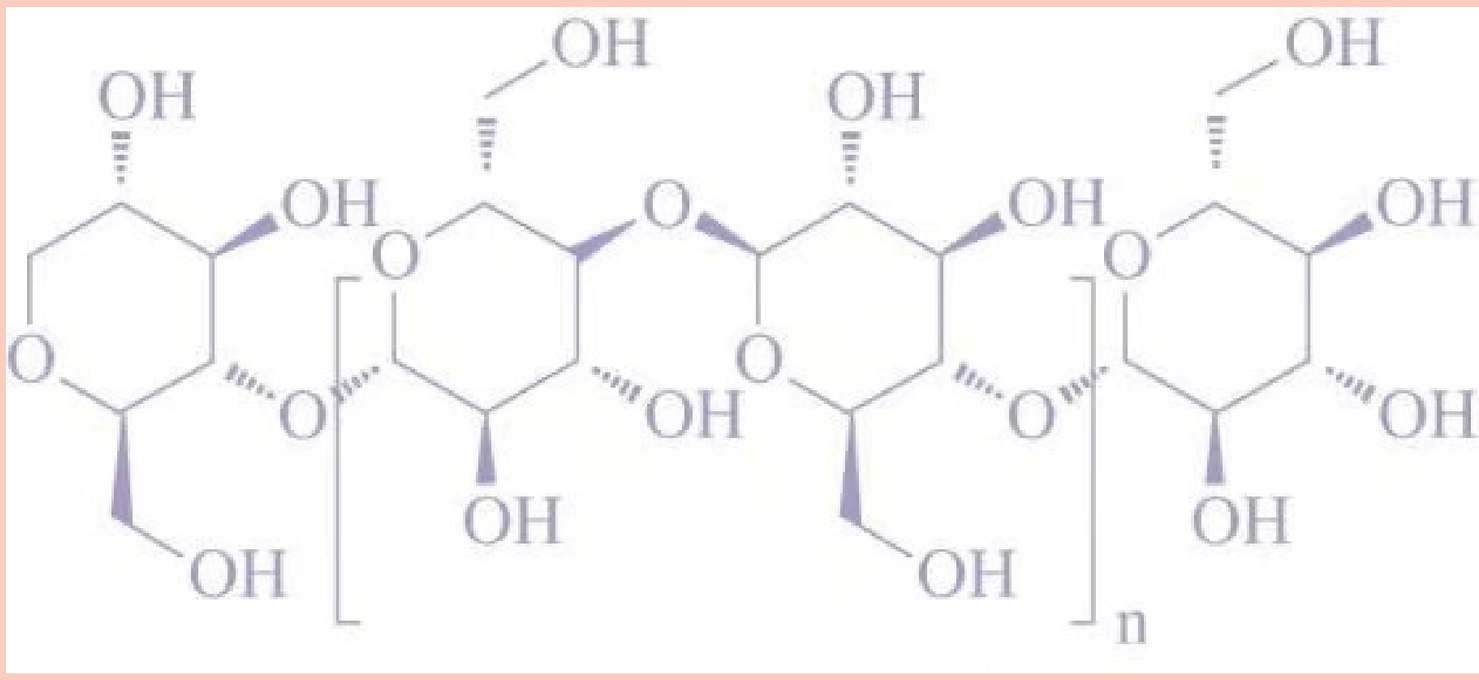


图 1 .抗性淀粉的化学结构

2 抗性淀粉对人体的益处

2023 年， Cell Metabolism 上刊登的一项研究表明，富含抗性淀粉的饮食，可以改变肠道菌群组成，降低与肝损伤、炎症相关的甘油三酯以及肝酶水平，减轻脂肪肝。 [2]

抗性淀粉含量	食品种类
≤1.0%	熟马铃薯、热米饭、高谷糖早餐麦片、小麦粉
1.0%～2.5%	普通早餐麦片、饼干、面包、冷米饭、冷稀饭
2.5%～5.0%	玉米片、大米碎片、油炸土豆片、爆豌豆
5.0%～15.0%	煮扁豆、煮蚕豆、生大米、玉米粉、豌豆
>15.0%	生马铃薯、生豆子、高直链玉米淀粉、青香蕉

图2.常见食物中抗性淀粉的含量

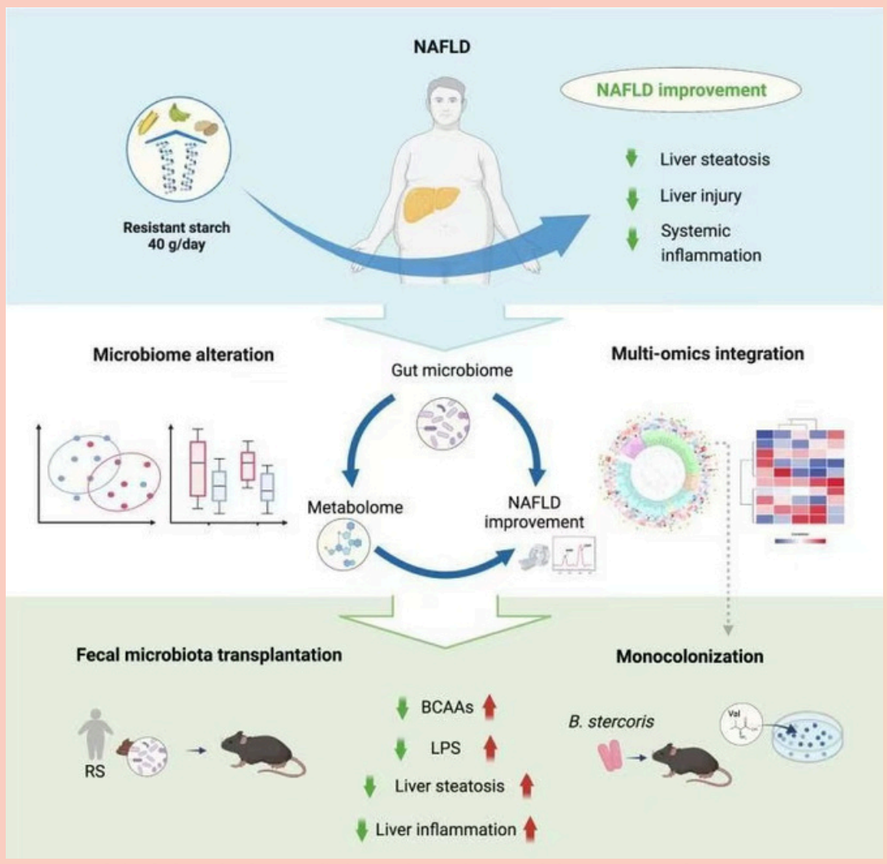


图3.抗性淀粉减轻脂肪肝的作用机理

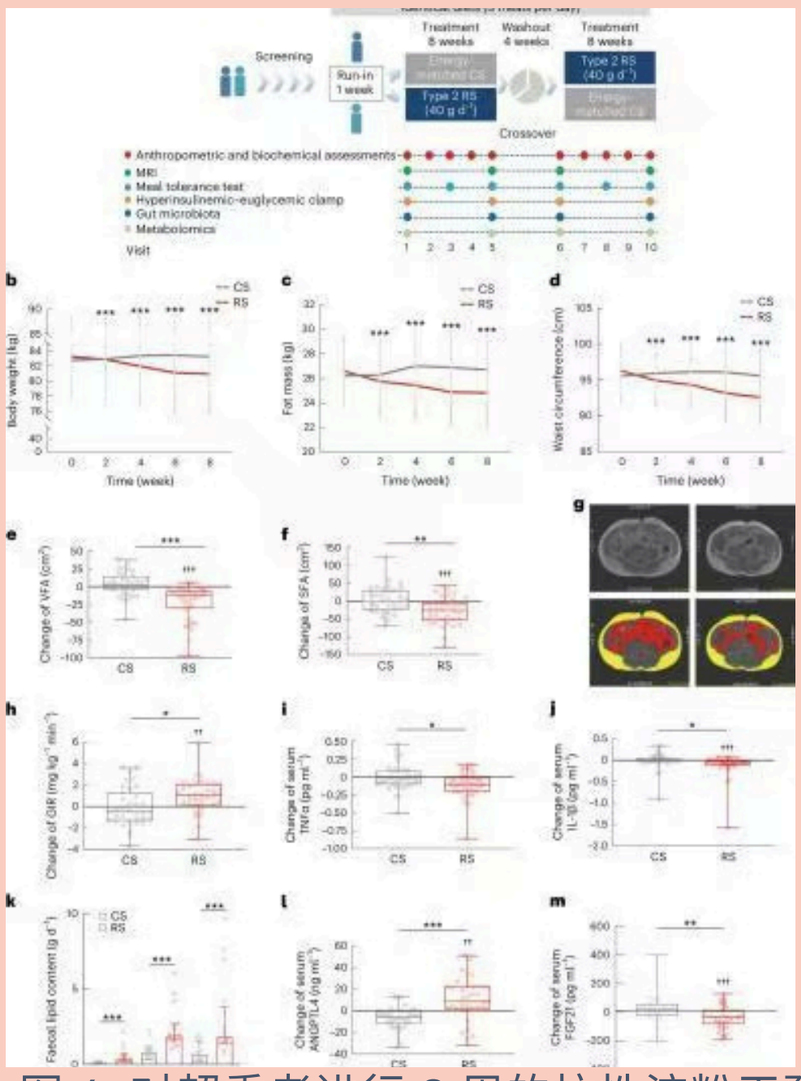


图 4 .对超重者进行 8 周的抗性淀粉干预后减轻肥胖

在为期四个月的临床实验结束后，研究人员发现，与对照组相比，抗性淀粉显著降低了参与者肝内甘油三酯含量（绝对降幅9.08%，相对降低39.42%），并且参与者的体重、BMI、脂肪含量等也有显著降低。

不仅如此，抗性淀粉实验组参与者的肝损伤也得到了一定程度上的改善，参与者的总胆固醇、低密度脂蛋白和高密度脂蛋白均有所改善，缓解了血脂异常。

2024年2月，另一项在Nature Metabolism上刊登的研究显示，仅8周的抗性淀粉补充，不仅有助于减肥，还可以改善超重个体的胰岛素抵抗水平。[3] 研究发现，补充 8 周抗性淀粉的参与者，平均体重减轻了 2.8 千克，脂肪含量和腰围明显下降。此外，参与者的葡萄糖耐量和胰岛素敏感性也得到了相应改善。

3 如何提高食物中的抗性淀粉含量?

1 主食冷却后再加热

米饭、馒头、土豆等淀粉含量高的食物煮熟后冷藏，抗性淀粉含量会显著增加，升糖指数也会明显下降。

再加热后，抗性淀粉依旧会部分保留，冷藏后的冷米饭重新加热后，血糖反应仍比新鲜热米饭更低。

高温状态下，淀粉会吸水糊化，抗性淀粉含量会降低，食物更容易消化吸收，但相应的，血糖反应也会变高。

2 选择水少的烹饪方式

选择烘烤、微波加热等水少的烹饪方式，能有效减少淀粉糊化，烤土豆的抗性淀粉含量就高于煮土豆。

结论:

通过本文的介绍，想必大家也对抗性淀粉有了简单的了解，不过也奉劝大家不要盲目增加抗性淀粉的摄入，只需在日常生活中通过适当的食物选择来均衡抗性淀粉的摄入，就能让我们的饮食结构变得更加健康、合理。

参考文献

[1]Englyst, H. N. & Cummings, J. H. Digestion of the polysaccharides of some cereal foods in the human small intestine. Am. J. Clin. Nutr. 42, 778–787 (1985).

[2]Resistant starch decreases intrahepatic triglycerides in patients with NAFLD via gut microbiome alterations.Cell Metabolism.SEPTEMBER 05, 2023.doi.org/10.1016/j.cmet.2023.08.002

[3]Resistant starch intake facilitates weight loss in humans by reshaping the gut microbiota.Nature Metabolism.26 February 2024.doi.org/10.1038/s42255-024-00988-y

SMART MAGAZINE AUTHOR:Molly Meng EDITOR: Hecate

新兴癌症突变位点——SWI/SNF家族

关键词：SWI/SNF复合体，基因突变，靶向药物

摘要:

癌症基因组的系统测序显示，编码染色质调节蛋白基因的高突变率是癌症生物学中最引人注目的论题之一。在这些畸变中，SWI / SNF染色质重塑复合物亚基编码基因的突变是最常见的，集中发生在所有癌症中的近25 %。目前已经明确，至少有9个编码SWI / SNF复合物亚基的基因在癌症中反复发生突变。因此，越来越多的研究倾向于了解预后，尤其是治疗编码SWI / SNF亚基的基因突变的潜在意义。在本篇文章中，研究人员回顾了影响SWI / SNF复合物的突变促进癌症的机制的新兴数据，并描述了这些突变所呈现的靶向治疗，包括新兴的针对免疫检查点抑制剂的免疫治疗。研究人员还关注了专门针对某些SWI / SNF基因突变的癌症患者进行的临床试验，并对相关药物展开了一定的研究。

SWI/SNF重塑染色质

在细胞内，人类基因组的~ 30亿个碱基对与组蛋白和其他蛋白质紧密相关，这种结构被称为染色质。在染色质中，人类基因组的组织化和致密化是通过将146个碱基对的DNA包裹在组蛋白八聚体周围，形成称为核小体的结构，从而使~ 3米的DNA被包裹在一个平均直径只有5 μm的细胞核内。此外，核小体通常会阻止负责激活或失活特定基因表达的转录因子的结合。细胞机制与转录因子协同作用，动员核小体以控制基因表达，这一过程被称为染色质重塑。染色质重塑复合物SWI / SNF家族，也称为BRG1 / BRM相关因子(BRM-associated factor，BAF)复合物(BOX 1)，是核小体定位的关键调节因子。目前已知SWI/SNF包含3个亚家族：经典BAF (c BAF)；多溴联苯BAF (PBAF)；非经典BAF (ncBAF)，也称为GLTSCR1或GLTSCR1L - containing and BRD9 containing (GBAF)复合物。这三个复合物都包含核心亚基，如SMARCC1，SMARCC2和ATP酶SMARCA4或SMARCA2，但也包含许多可变亚基，形成成百上千中不同的SWI/SNF复合物。

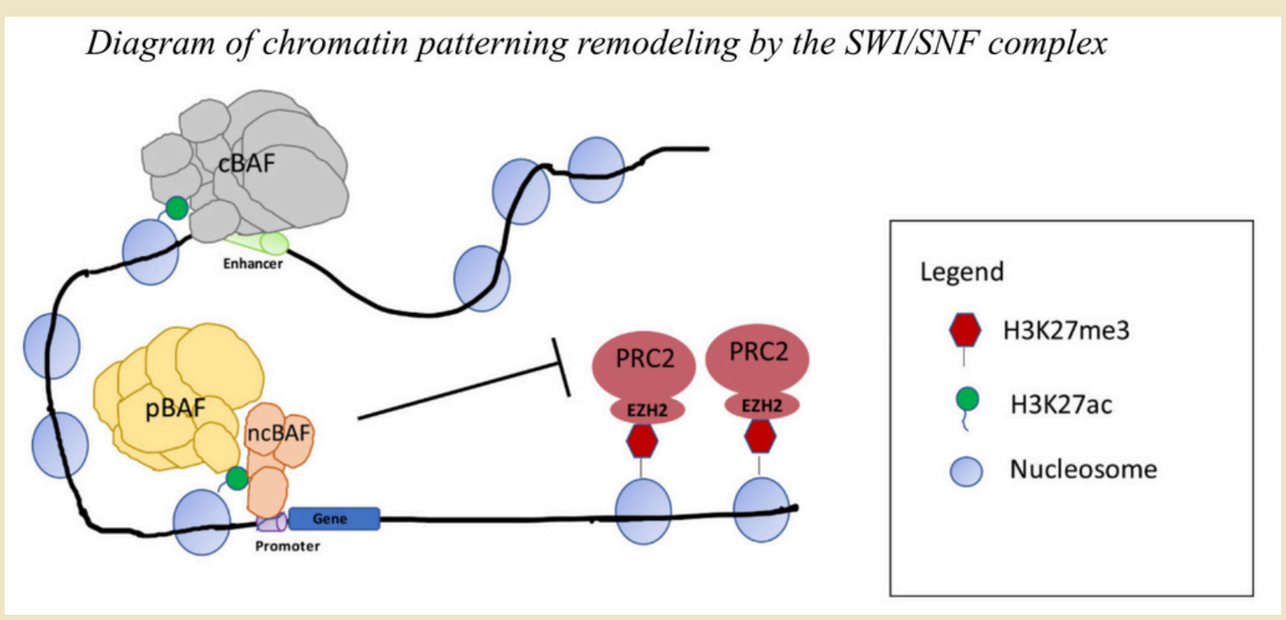


图1
SWI/SNF复合体重塑染色质模式图

复合物含有一个明确作用的基因组区域，称为增强子。这些增强子是短的非蛋白编码DNA元件，可形成转录因子的结合位点，从而调节相邻基因的转录活性。增强子只占基因组的一小部分，但SWI / SNF复合物在这些位点高度富集，并在调节转录因子激活基因表达所需的增强子可及性方面发挥重要作用。

SWI/SNF在肿瘤中的突变及机制

总体而言，至少有9种不同的SWI / SNF亚基在多种癌症中被鉴定为复发性突变(图2)，并且这些突变在所有癌症中的总和占比接近25 % 。

SWI / SNF亚基编码基因的突变，包括无义突变、移码突变和缺失突变，常提示功能缺失表型。然而，后续研究证实，SMARCB1突变的癌症不是由SMARCB1蛋白本身的缺失驱动的可能性，是由残余的SWI / SNF复合物的异常功能驱动的。例如，在滑膜肉瘤中发现的SS18 - SSX融合，使SWI / SNF复合物具有增加的核小体动员活性。

一般的致癌因素如放射线会引起多种类的癌症，但SWI/SNF亚基突变常与特定显著癌症表型有关，如SMARCB1的失活在很大程度上仅限于上述罕见的儿童横纹肌样肿瘤和少数其他类型的癌症。

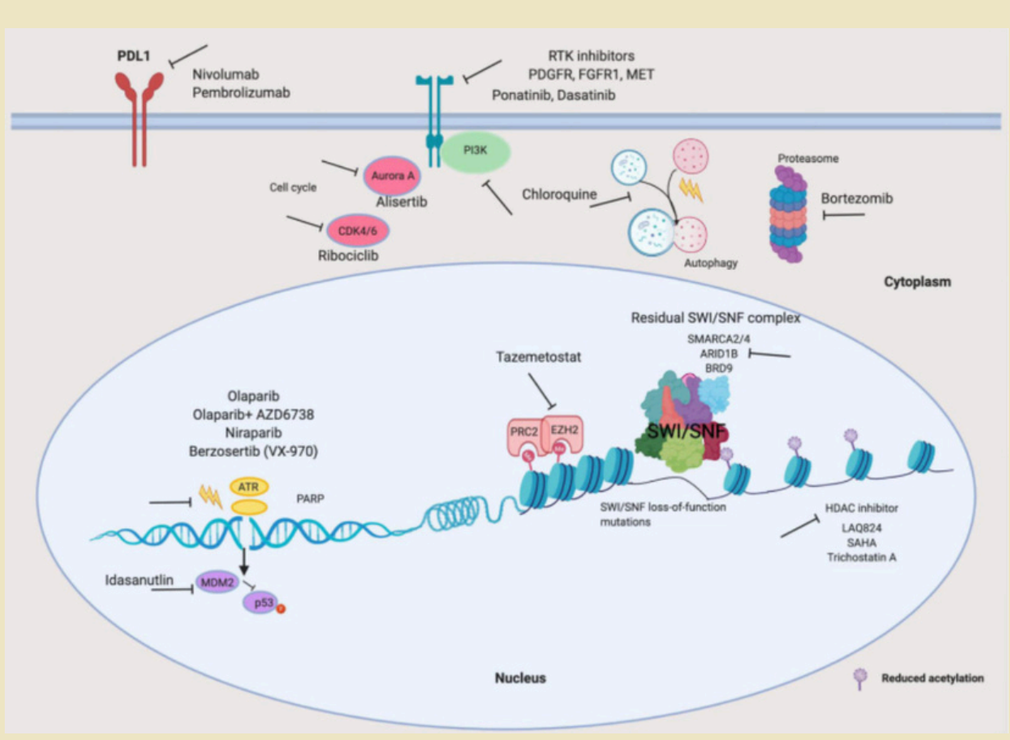
图二
SWI/SNF亚基在人类肿瘤中的突变频率

SWI/SNF缺陷型肿瘤的预后

SWI / SNF对预后的影响具有亚基特异性和/或情境特异性。值得注意的是，不仅突变，SWI / SNF特定亚基表达的整体变化也被认为是生存的预后标志物，其表达水平与预后的关系随肿瘤类型改变而改变。如，在乳腺癌和膀胱癌患者中，SMARCA4和ARID1A蛋白的低表达均与良好的预后相关，然而在肝细胞癌或宫颈癌患者中，SMARCA2和ARID1A的表达缺失与不良的总生存期相关。

研究人员发现，编码SWI / SNF亚基的某些基因的突变通常会对编码其他SWI / SNF亚基的基因产生特定的依赖性，表明亚基突变不会完全灭活SWI/SNF功能，而是使SWI / SNF亚基的损失部分由一个对等体来补偿。目前可以通过口服变构抑制剂或蛋白裂解靶向嵌合体抑制SWI/SNF ATP酶活性。蛋白裂解靶向嵌合体是双功能分子，利用泛素连接酶，共价连接到靶标结合配体上，直接靶向降解的目的蛋白，目前已进入临床试验。

PRC2的酶亚基EZH2是否抑制影响选择SWI / SNF亚基突变导致的癌症一直是大量研究的对象。早期在果蝇中的遗传学研究表明SWI / SNF复合物和Polycomb抑制复合物具有相反的基因调控功能，且后续研究发现哺乳动物在该方面进化保守。现已表明，SMARCB1突变导致Polycomb抑制复合物在局部的过度沉积，但因为细胞试图恢复平衡的基因表达谱可能导致这些复合物的整体活性下调。部分基于临床实验数据，FDA加速批准了年龄≥16岁的转移性或不可切除的上皮样肉瘤患者使用EZH2抑制剂Tazemetostat。



图三
SWI/SNF复合体缺陷型肿瘤的翻译机制

总结

与经典癌基因和抑癌基因的突变相比，在癌症中发现广泛的SWI / SNF基因突变只有10年，因此我们对其机制和相应的治疗意义的理解仍处于起步阶段。虽然现在已经明确，影响单个SWI / SNF亚基的失活突变可以赋予其他基因或通路的特定依赖性，但任何广泛的依赖性是否延伸到所有SWI / SNF癌症仍然是一个关键问题。

SWI / SNF亚基的突变通常会增加对剩余SWI/SNF复合物其他成分的依赖性，因此越来越多研究正在围绕着治疗靶向SWI/SNF复合物本身开展。但值得警惕的一点是，抑制某些亚基是否真的可以促进癌症的发展和/或生长仍然有待确定。

参考文献

Mittal, P., & Roberts, C. W. M. (2020). The SWI/SNF complex in cancer - biology, biomarkers and therapy. Nature reviews. Clinical oncology, 17(7), 435–448. https://doi.org/10.1038/s41571-020-0357-3IF: 81.1 Q1

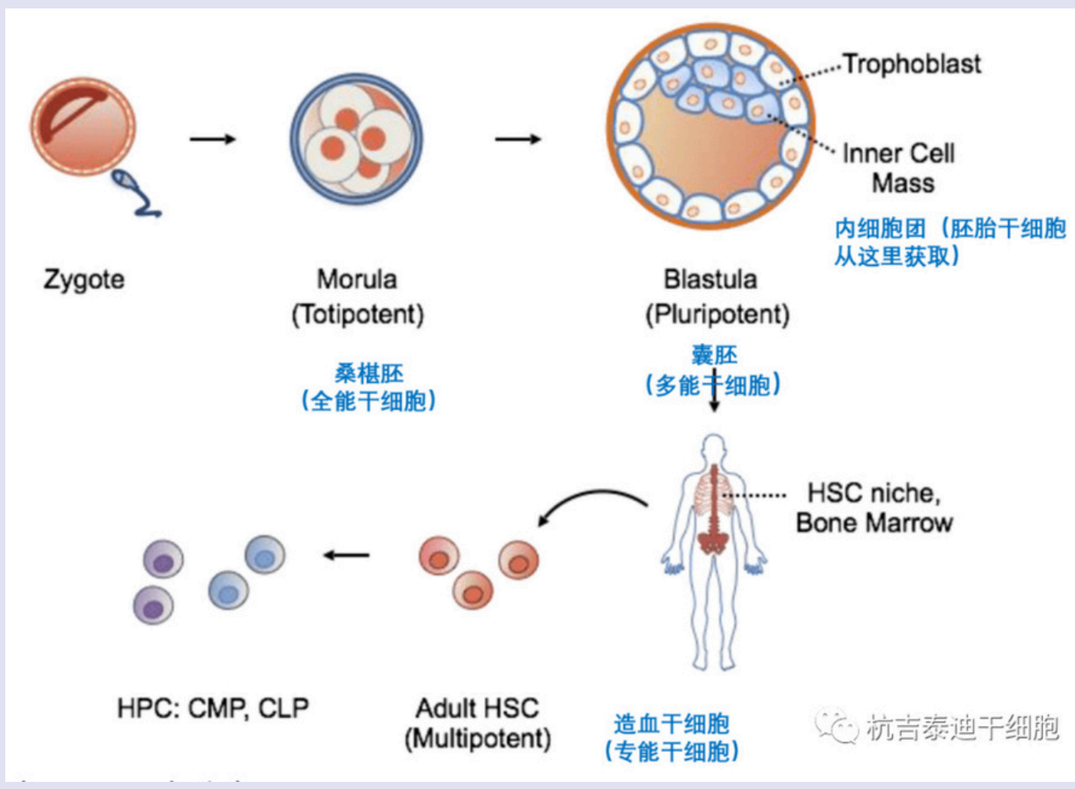
SMART MAGAZINE AUTHOR: Nox EDITOR: Hecate

回到生命本初——体外培养动物全能干细胞的理论基础与现有方法

关键词：全能干细胞；多能干细胞；体外培养

引言：

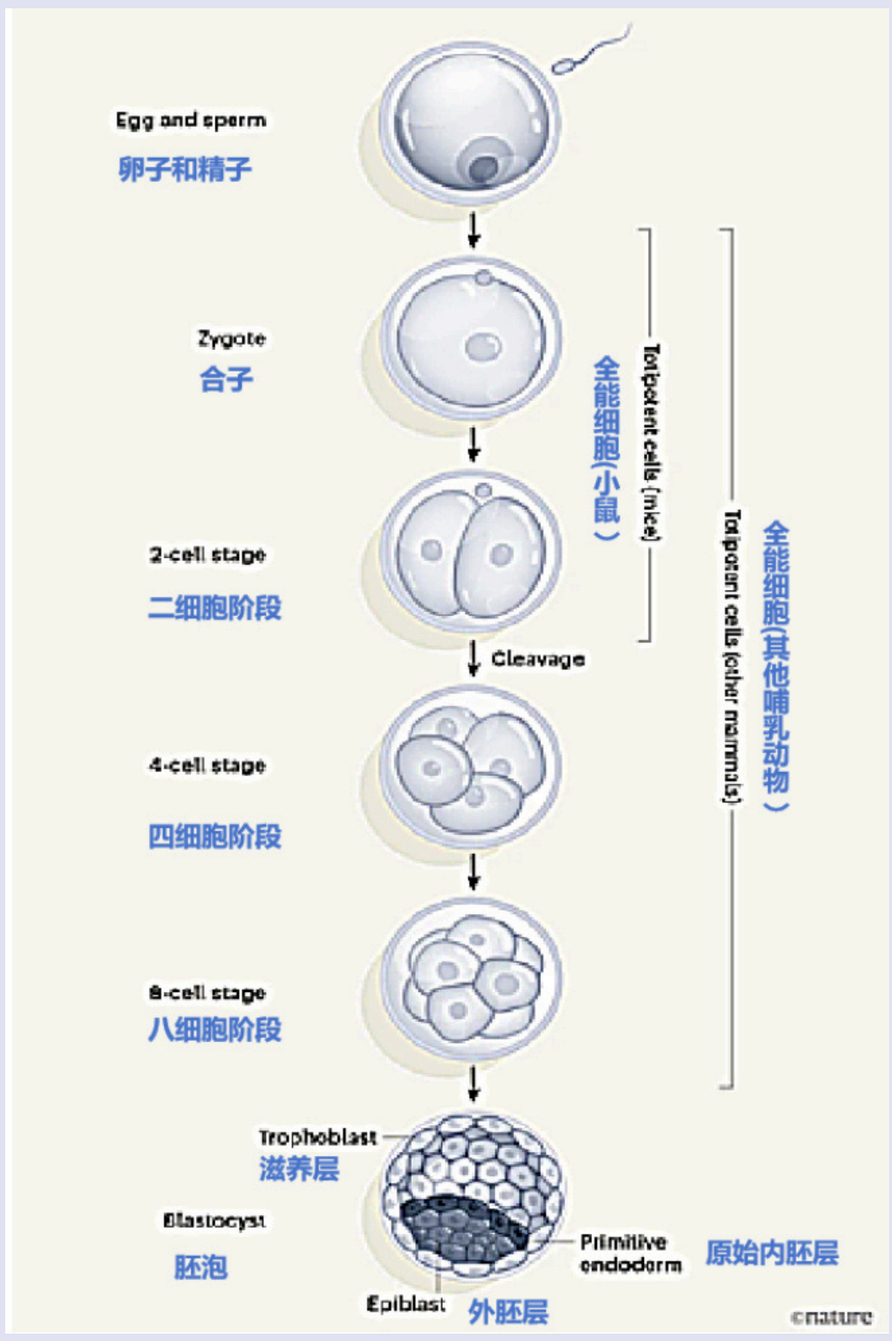
随着对细胞生命周期研究的逐渐深入，人们已经可以通过一个细胞诱导出各种不同的组织--比如人工诱导多能干细胞（Induced pluripotent stem cell，iPSC）技术已在再生医学和疾病模型研究等领域被广泛应用，并在2012年获得了诺贝尔生理学奖。虽然iPSC已经帮助人类实现了多向分化的目标，但它还未具备全能性，不能分化成为一个生物体所有类型的细胞，所以在早期胚胎发育的研究领域，全能干细胞的体外培养成为了一大技术难点。 全能干细胞（totipotent stem cells ，TCSs ）是具有分化成任何类型细胞的能力的细胞，它们存在于受精卵形成后的早期阶段，通常 只存在于 胚胎发育的头几天内。 与iPSC相比，TCSs可以 生成具有胚外结构支持的类器官或复杂组织 ， 这种能力可以弥补iPSCs生成复杂组织时的限制 。不仅如此，由于TCSs能生成胎盘样细胞，所以其能作为研究胎盘相关疾病（如妊娠期高血压、胎盘功能异常）提供独特工具，而这种分化为胚外组织的能力恰恰是iPSC所没有的。



（图源见水印）

TSCs的培养难点

过去在实验室中发现多能干细胞培养物中存在少数具有类似小鼠2C阶段全能性的细胞，这提示了体外培养全能干细胞的可能性[6]。 但获取全能干细胞的难度要远远大于多能干细胞，因为它在动物生命周期中存在时间极短。 在小鼠体内，全能细胞仅局限于受精卵及2C （2-cell） 胚胎阶段，而在人类及其他哺乳动物中，这一全能性状态的范围会扩展至4-8细胞（4-8 C ell ）胚胎阶段。之后，全能干细胞就开始迅速分化，形成外滋养层（outer trophectoderm, TE）、原始内胚层（primitive endoderm, PrE ）（ 之后发育成胎盘和卵黄囊用于母体与子代间物质交换 ） ，以及 外 胚层（epiblast, EPI） （ 之后发育成多个胚胎器官 ） 。尽管多能干细胞的体外培养技术已相对成熟，但全能干细胞的体外培养直到最近几年才有所突破 。由于全能干细胞(TSCs)存在时间极短，故科学家们首先从多能干细胞(PSCs)入手，通过发掘二者的区别与转换机制，从而实现全能干细胞的体外捕获与维持。



胚胎早期发育图（图源nature，翻译Nox）

SMART MAGAZINE AUTHOR: Nox EDITOR: Hecate

TSCs与PSCs之间的区别

研究全能干细胞与多能干细胞之间的区别是探索二者间转换机制的基础。首先全能干细胞的分子标记紧密与早期胚胎发育相关，表达如Zscan4、Zfp352、DUX4、Dux和Dppa2/4等基因，这些基因反映了全能干细胞与早期卵裂球阶段的高度相似性；而多能干细胞的分子标记则主要与胚胎植入前内细胞团的状态相关，核心多能性转录因子如Oct4、Sox2、Nanog和Klf4/5在多能干细胞中表达，维持其多能性。在表观遗传学特征上，全能干细胞具有低水平的DNA甲基化和特定的组蛋白修饰，与早期卵裂球的状态相似，而多能干细胞的DNA甲基化程度较高，且表观遗传修饰更加复杂，反映了其处于发育的中间状态。总体而言，全能干细胞在转录组水平上与2-/4-细胞卵裂球非常接近，具有更接近胚胎发育最早期阶段的特性，因此它们能够分化为所有类型的胚胎和非胚胎组织，表现出比多能干细胞更广泛的发育潜力。[1]

TSCs与PSCs间转换的调控机制

在了解全能干细胞与多能干细胞区别的基础上，二者之间转换的调控机制一直是干细胞研究的热点问题。2020年，同济大学高绍荣教授课题组与美国西奈山医学院（现哥伦比亚大学欧文医学中心）王建龙教授课题组在《Cell Stem Cell》杂志上发表的研揭示了DUX-miR-344-ZMYM2介导的MERVL激活在全能性样细胞产生过程中的作用[2]。该研究确立了miR-344是2CLC扩展多能性和植入前发育的第一个非编码正向调控因子，通过DUX→miR-344-|Zmym2/Lsd1-|MERVL通路来调控2C样细胞（2CLC）的全能性。2021年，浙江大学沈立团队通过三维基因组测序和一系列表观基因组学研究，揭示了染色质高级结构在多能性胚胎干细胞（ESCs）向全能样干细胞转变过程中的动态变化和调控功能[3]。该团队发现，胚胎干细胞向全能样转变时，染色质高级结构变松散，表现为A/B区室界限模糊、TAD结构减弱及染色质环减少。此变化导致增强子与基因启动子间联系减弱，降低ESCs特异增强子活性，下调多能性基因（如Oct4、Sox2、Nanog）转录，促使细胞退出多能性。同时，形成大量DUX结合、H3K27Ac修饰的2C特异性增强子，与邻近2C基因启动子频繁接触，可能促进2C基因表达，激活全能样转录程序。2023年8月，东南大学林承棋和罗卓娟团队研究发现，小鼠胚胎干细胞中，年轻LINE-1子集L1Md_Ts被ELL3标记并作为增强子。LINE-1虽具遗传毒性，但在早期胚胎中活跃[4]。ELL3不仅标记L1Md_Ts，还影响其附近基因表达，通过调节相关酶和蛋白的富集来影响5hmC和H3K27ac水平，进而调控基因上调和多能性关闭。这表明ELL3在调节小鼠早期胚胎发育的增强子功能中起关键作用。2023年12月， 南开大学帅领团队发现了Dyrk1a和Catip两个基因对小鼠胚胎干细胞（ESCs）命运调控的关键作用[5]。敲除这两个基因的小鼠胚胎干细胞能高效转化为诱导性滋养层干细胞（iTSCs），这些iTSCs与野生型TSCs相似。特别是Dyrk1a敲除的ESCs展现出类似全能性的性质，能贡献到胎儿、胎盘和卵黄囊，激活2-细胞相关基因，诱发类全能性状态，并能在体外自组装成囊胚样结构，为研究小鼠细胞命运决定和类全能性干细胞提供了新途径。

PSCs诱导TSCs的方法

1.阻断二者转换的信号通路

科学家首先从信号通路入手，成功诱导出全能性干细胞。2017年，英国Sanger研究院刘澎涛团队通过使用特定的小分子抑制剂阻断MAPKs、Src和Wnt/Hippo/TNKS1/2等信号通路抑制细胞分化，成功把ESCs和iPSCs诱导为具有全能性的扩展潜能干细胞（Expanded Potential Stem Cells，EPSCs），EPSCs在转录组和表观遗传学上与四细胞到八细胞阶段的胚胎相似，并且能够在嵌合体中分化成胚胎、胎盘和羊膜中的细胞类型[7]。2021年美国西南医学中心吴军及深圳华大生命科学研究院为主的科学家团队通过同时激活FGF/Erk、TGF-β/Smad、WNT/β-Catenin三条信号通路，首次在多个物种中建立了具有“Formative”特征的稳定干细胞系XPSCs[8]。2022年三月，中国科学院和深圳华大生命科学研究院利用，MEK抑制剂和腺苷半胱氨酸水解酶抑制剂DZNep成功从人类多能干细胞诱导产生8细胞类似细胞8C-like cells (8CLCs)，这一过程无需转基因且快速可控[9]。同年五月，北京大学邓宏魁和李程团队通过化学小分子组合CD1530，VPA，EPZ004777，CHIR 99021 (CPEC组合)，抑制HDAC1/2和Dot1L的活性、激活RARγ通路，成功诱导获得了全能潜能干细胞（totipotent potential stem cells, TPS细胞）[10]。同年六月，清华大学丁胜团队通过3种小分子药物组合形成的“鸡尾酒”(TAW组合)，诱导出当于二细胞胚胎阶段的化学诱导全能干细胞（ciTotiSCs)。TAW组合中的三种小分子分别是TTNPB（维甲酸受体激动剂)、1-Azakenpaullone（抑制剂，促进全能干细胞的自我更新)、WS6（维持全能干细胞稳定的作用）[11]。

2.抑制全能性向多能性发展其它思路

除了阻断或激活相关信号通路，现有研究还通过阻断翻译后修饰、改变染色质结构等方法实现了多能向全能干细胞的转变。2021年，北京大学杜鹏团队利用剪接体抑制剂Pladienolide B，成功在体外捕获并长期维持了具有高分化潜能的小鼠全能干细胞，这些细胞被称为全能囊胚样细胞（TBLCs），它们在分子和功能上与体内2细胞和4细胞囊胚相似，展现出强大的双向发育潜力[12]。2022年二月，中山大学王继厂团队通过化学诱导染色质重塑的方法，将小鼠胚胎干细胞（mESC）重编程为全能样干细胞（TLSC）[13]。

结语

通过研究全能干细胞，科学家可以更好地揭示生命起源、细胞命运决定机制以及早期发育过程中各种基因调控的复杂网络。在再生医学领域，全能干细胞的研究也有巨大的潜力。由于它们可以生成所有的细胞类型，全能干细胞为器官再生和细胞替代疗法提供了理论基础和实践可能性。例如，如果能够有效控制和维持全能干细胞的状态，便有望利用它们开发更先进的组织修复和器官移植技术，从根本上解决组织损伤和器官短缺问题。此外，全能干细胞的低表观遗传修饰状态可以为研究细胞命运转变和重编程机制提供重要线索，进而推动个性化医学、抗衰老疗法和遗传疾病治疗的发展。[14]

参考文献：

[1] Du, P., & Wu, J. (2024). Hallmarks of totipotent and pluripotent stem cell states. Cell Stem Cell, 31(3), 312-333.

[2] Yang, F., Huang, X., Zang, R., Chen, J., Fidalgo, M., Sanchez-Priego, C., ... & Wang, J. (2020). DUX-miR-344-ZMYM2-mediated activation of MERVL LTRs induces a totipotent 2C-like state. Cell stem cell, 26(2), 234-250.

[3] Zhu, Y., Yu, J., Gu, J., Xue, C., Zhang, L., Chen, J., & Shen, L. (2021). Relaxed 3D genome conformation facilitates the pluripotent to totipotent-like state transition in embryonic stem cells. Nucleic acids research, 49(21), 12167-12177.

[4] Meng, S., Liu, X., Zhu, S., Xie, P., Fang, H., Pan, Q., ... & Lin, C. (2023). Young LINE-1 transposon 5′ UTRs marked by elongation factor ELL3 function as enhancers to regulate naïve pluripotency in embryonic stem cells. Nature cell biology, 25(9), 1319-1331

[5] Zhang, W., Sun, S., Wang, Q., Li, X., Xu, M., Li, Q., ... & Shuai, L. (2023). Haploid-genetic screening of trophectoderm specification identifies Dyrk1a as a repressor of totipotent-like status. Science Advances, 9(51), eadi5683. .

[6] Baker, C. L., & Pera, M. F. (2018). Capturing totipotent stem cells. Cell stem cell, 22(1), 25-34.

[7] Yang, J., Ryan, D. J., Wang, W., Tsang, J. C. H., Lan, G., Masaki, H., ... & Liu, P. (2017). Establishment of mouse expanded potential stem cells. Nature, 550(7676), 393-397.

[8] Yu, L., Wei, Y., Sun, H. X., Mahdi, A. K., Arteaga, C. A. P., Sakurai, M., ... & Wu, J. (2021). Derivation of intermediate pluripotent stem cells amenable to primordial germ cell specification. Cell stem cell, 28(3), 550-567.

[9] Mazid, M. A., Ward, C., Luo, Z., Liu, C., Li, Y., Lai, Y., ... & Esteban, M. A. (2022). Rolling back human pluripotent stem cells to an eight-cell embryo-like stage. Nature, 605(7909), 315-324.

[10] Xu, Y., Zhao, J., Ren, Y., Wang, X., Lyu, Y., Xie, B., ... & Deng, H. (2022). Derivation of totipotent-like stem cells with blastocyst-like structure forming potential. Cell Research, 32(6), 513-529.

[11] Hu, Y., Yang, Y., Tan, P., Zhang, Y., Han, M., Yu, J., ... & Ding, S. (2023). Induction of mouse totipotent stem cells by a defined chemical cocktail. Nature, 617(7962), 792-797.

[12] Shen, H., Yang, M., Li, S., Zhang, J., Peng, B., Wang, C., ... & Du, P. (2021). Mouse totipotent stem cells captured and maintained through spliceosomal repression. Cell, 184(11), 2843-2859.

[13] Yang, M., Yu, H., Yu, X., Liang, S., Hu, Y., Luo, Y., ... & Wang, J. (2022). Chemical-induced chromatin remodeling reprograms mouse ESCs to totipotent-like stem cells. Cell Stem Cell, 29(3), 400-418.

[14] Strelez, C., Perez, R., Chlystek, J. S., Cherry, C., Yoon, A. Y., Haliday, B., ... & Mumenthaler, S. M. (2023). Integration of patient-derived organoids and organ-on-chip systems: Investigating colorectal cancer invasion within the mechanical and GABAergic tumor microenvironment. bioRxiv.