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Editorial

Epigenetics and traditional Chinese medicine: A noteworthy research area

Accumulated evidence indicates that most human chronic diseases and aging are closely associated with epigenetic changes that occur after birth, with the exception of genetic and infectious diseases. In recent years, research into the role of epigenetics in disease and aging has surged, and the development of related drugs has become increasingly active. According to incomplete statistics, the number of articles published on epigenetics has increased dramatically from just 3 in 1958 to 14 938 in 2024. The number of drugs targeting epigenetic mechanisms is also rising rapidly. To date, over 10 epigenetic-targeting drugs have been introduced into clinical practice, such as azacitidine, decitabine, and vorinostat, with more than 100 additional drugs currently in the clinical trial stage. These drugs are not only effective in treating tumors but also show significant potential in managing common chronic diseases in clinical practice.

However, compared to the extensive research on epigenetics and the development of chemically synthesized drugs, studies on traditional Chinese medicine (TCM) related to epigenetics are relatively limited, which is not in line with the current status of epigenetics research. Based on the fundamental understanding of TCM regarding disease occurrence, prevention, and treatment, we believe that elucidating the mechanisms of TCM from an epigenetic perspective holds great significance for further revealing the principles of TCM in disease prevention and treatment, as well as anti-aging. It also provides important research directions for the development of TCM.

1. Relationship between epigenetics and diseases/aging

Epigenetics is the study of heritable changes in gene expression that occur without altering the DNA sequence. The main processes involved in epigenetics include DNA methylation, RNA methylation, histone post-translational modifications, and chromatin remodeling. Various enzymes are involved in regulating these epigenetic changes, such as DNA methyltransferase (DNMT), histone methyltransferase (HMT), histone acetyltransferase (HAT), histone deacetylase (HDAC), and histone ubiquitinase. As research on epigenetics deepens, more molecules and enzymes related to epigenetic changes are constantly being discovered, and their roles in physiological and pathological processes are being evaluated. For example, abnormal DNA methylation, histone methylation, and histone deacetylation have been recognized as related to tumorigenesis. Abnormal DNA methylation is also associated with obesity and type 2 diabetes. Histone acetylation is involved in cell cycle regulation, proliferation, and apoptosis. In addition to tumors, many common chronic diseases and aging in humans are closely related to epigenetics, such as the significant impact of sirtuin protein regulation on aging processes.

2. Drug research related to epigenetics

With the continuous progress of epigenetic research, our understanding of the mechanisms underlying diseases and aging has become more profound, providing research directions and therapeutic targets for the prevention and treatment of diseases and the delay of aging processes. For example, DNA methylation has been approved as a tumor marker for the early detection of colon cancer. Decitabine, a DNMT3A inhibitor, is used for tumor treatment. Tazemetostat, an EZH2 inhibitor, is used to treat epithelioid sarcoma. Cediranib and Tibsovo are HDAC and IDH inhibitors, respectively, both of which have demonstrated definite therapeutic effects on tumors in clinical practice. Although previous research on epigenetic drugs has primarily focused on tumor treatment, in recent years, research on epigenetic drugs for non-tumor or chronic diseases has also garnered significant attention. For example, Givinostat, an HDAC inhibitor, has shown positive results in a Phase III trial for the treatment of Duchenne muscular dystrophy. Pyrazole derivatives have demonstrated benefits in acute liver injury by selectively inhibiting and degrading HDAC6. HAT activators are used to treat chronic experimental spinal cord injury, among other applications.

3. Great potential of epigenetics for TCM research

Epigenetics plays a crucial role throughout all stages of life, and its abnormal changes are one of the important factors contributing to various diseases and aging. Epigenetic research has shown that the living environment and lifestyle can affect the body's epigenetics, thereby influencing the occurrence and development of diseases. Studies have indicated that cancer is the result of the accumulation of genetic and epigenetic alterations. However, epigenetic changes are reversible, which provides the possibility for disease treatment through drugs. Although the aforementioned epigenetic drug research has garnered attention and some drugs have been introduced into clinical practice, these anti-tumor drugs are rarely used alone as first-line anti-tumor drugs in clinical practice, highlighting the complexity of the epigenetic regulatory mechanism.

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TCM is a medical system that has been clinically validated for thousands of years. Guided by the philosophy that "humans are an integral part of nature," it emphasizes the important role of the living environment, lifestyle, and emotions in the pathogenesis and treatment of diseases. This aligns with the theory of epigenetics in disease occurrence and development. Therefore, the application of epigenetic theories and methods in TCM research holds great potential for elucidating the mechanisms of TCM in disease prevention and treatment, as well as health preservation and anti-aging. For example, numerous studies have shown that polyphenols such as resveratrol and quercetin, terpenoids such as tanshinone IIA, alkaloids such as leonurine, and glycosides such as astragaloside IV have significant regulatory effects on sirtuins. Curcumin and gallic acid can regulate HAT, and curcumin can alleviate cardiac hypertrophy, fibrosis, and inflammatory reactions by disrupting p300-HAT. The research indicates that Xiaochaihutang, a classic formula for resolving Shaoyang syndrome in the *Treatise on Febrile Diseases*, exerts antidepressant effects by increasing hippocampal histone acetylation and promoting BDNF expression. This is one of the few cases in China where epigenetics has been applied to study TCM formulas. It has also been reported that epigallocatechin gallate inhibits the progression of breast cancer by reducing the expression of DNMTs and activating the expression of SCUBE2 by reducing the methylation state. It is extremely interesting that some anti-aging natural substances recognized based on the free radical theory of aging can be consistent with the theory and research results on epigenetics of TCM health preservation and anti-aging drugs.

With the application of big data and artificial intelligence, the complex and diverse mechanisms of epigenetics will be further elucidated. Similarly, the mechanisms of TCM, whether as single herbs or complex formulas, will also be deeply elucidated with the support of these modern technological platforms. The key is how to effectively integrate big data and artificial intelligence with epigenetics to clarify the mechanisms of action of TCM and promote its role in disease prevention and treatment.

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