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The role of Wnt5a in aging-related diseases

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Abstract. Wnt is a family of glycoproteins that are essential signalling molecules during development, but its overexpression in adulthood leads to ageing of the organism, and in particular, the expression of Wnt5a is an important factor in the development of diseases such as atherosclerosis, osteoarthritis and tendon ageing. In atherosclerosis, patients serum levels of Wnt5a is elevated and Wnt5a is linked to β-catenin-independent signaling pathways which is related to the expression of inflammatory genes and the advancement of inflammation. Osteoarthritis' one character is the demolition of cartilage. In this disease, the expression model of Wnt5a will change from canonical to non-canonical, and this kind of model actives chondrocyte catabolism. Tendons can repair and regenerate themselves through tendon stem cells (TSPC). Tendon senescence is inextricably linked to the senescence of TSPC, overexpressing of Wnt5a affects tendon stem cells thus leads to tendon aging.The aim of this paper is to analyse the role of Wnt5a in the development of these diseases and suggest effective treatments for them.

Keywords: Wnt5a, atherosclerosis, osteoarthritis, tendon aging

1. Introduction

Ageing is a problem that people all face. As people grow older, the functions of various parts of the body gradually deteriorate, losing many of their normal physiological functions and complex anatomy. The human being, as an organic whole, is made up of a large number of cells. Each cell has a certain lifespan, ranging from 120 days for red blood cells, for example, to almost a lifetime for nerve cells. Each cell ages from the moment it is created until it dies, but the ageing of a single cell does not represent the ageing of a human being, it is the cumulative result of the ageing of a large number of cells. The ageing of cells first affects the tissues, then the organs and finally the whole person. Typical signs of ageing are cardiovascular disease, osteoarthritis and loss of muscle strength.

External environmental influences such as photodamage, radiation, dust and changes in the internal environment can all affect the ageing process. DNA is a major part of the cell and is essential for the cell to cope with oxidative damage, autophagy and division, therefore ensuring that DNA functions correctly is the key to ageing [1]. Under normal circumstances, DNA is correctly expressed and damage can be well repaired. However, as time goes on, DNA becomes abnormally expressed and the activity of enzymes associated with repair decreases so that the damaged DNA cannot be repaired properly. Therefore, correcting abnormal DNA expression, preventing DNA damage and promoting its effective recovery is one way to deal with ageing and related diseases. Preventing damage can be achieved by increasing the antioxidant pathway, which metabolises DNA-damaging substances such as free radicals

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in time to make them harmless, and by repairing damaged DNA through the use of enzymes that help to recover it as quickly as possible and minimise the impact on the cell. Another way is to improve the regenerative and resistance capacity of the cells themselves. Different signalling pathways have different effects in different tissues and organs, so the most effective pathway can be targeted to inhibit ageing. For example, athletes have more wear and tear on their articular cartilage than the general population, so the Prx II pathway can be selected to inhibit ageing [1].

The relationship between DNA and the typical signs of ageing mentioned above, namely cardiovascular disease, osteoarthritis and loss of muscle strength, is inextricably linked and will be described in detail below.

2. Atherosclerosis

Cardiovascular diseases are the main cause of disability and premature death worldwide. By 2015, cardiovascular diseases had affected approximately 422.7 million people and caused approximately 179 million deaths, accounting for 31% of the global total [2]. Atherosclerosis is the main factor leading to cardiovascular complications, which is a chronic inflammatory disease. The study found that about 28% of people aged 30-79 years around the world have early atherosclerosis, that is, carotid intima-media thickness is more than 1.0 mm; About 21% of people have carotid plaque and 1.5% have advanced manifestations of carotid stenosis [2]. The proportion of men and the elderly is higher among the affected population; The Western Pacific region has the most cases of increased carotid intima-media thickness and plaque, while Africa has the least cases of increased carotid intima-media thickness, and the Eastern Mediterranean region has the smallest proportion of cases of carotid plaque [2]. In China, among people aged 30-79, the prevalence of carotid atherosclerosis and carotid plaque was 24.93% and 18.41% respectively in 2000; 27.22% and 20.15% in 2010; The prevalence of these two diseases is expected to increase to 30.07% and 22.49% by 2020 [3]. Through data, it can be found that before 2010, the prevalence of carotid artery plaque in Chinese people was lower than at the international level, but it will further increase until exceeding, presumably related to population aging. In view of the large proportion of atherosclerosis patients in the world, how to reduce the harm of the disease to patients and find effective possible cure methods has become a research hotspot.

Wnt5a is a glycoprotein that is secreted and functions as a signaling pathway activator. It is linked to β-catenin-independent signaling pathways, which include the Ca2+ and PCP pathways. These two pathways can then trigger additional downstream signals, such as those that involve Jun N-terminal kinase (JNK), protein kinase C (PKC), and Ca2+/calmodulin-dependent kinase II (CaMKII) [4]. According to certain in vitro research, Wnt5a stimulates the production of inflammatory cytokines, chemokines, and matrix metalloproteinases. It also triggers the activation of nuclear factor-κB (NF-κB), which is linked to the expression of inflammatory genes and the advancement of inflammation [4]. The fact that elevated serum levels of Wnt5a have been reported in patients with atherosclerosis suggests that Wnt5a plays an active role in the pathogenesis of atherosclerosis.

A recombinant adenoviral vector specifically silencing Wnt5a expression was constructed by Lei Yang et al. to investigate the role of Wnt5a in atherosclerosis. The experimental animals were 8-week-old ApoE-deficient C57 male mice. 45 mice were randomly divided into three groups: the first group was injected with PBS, the second group was injected with a non-specific recombinant adenoviral vector, and the third group was injected with a specific recombinant adenoviral vector. Two weeks later, the mice were injected once more in the same way. Two weeks later, the mice were euthanized and heart blood was collected for observation, and paraffin sections of the hearts were stained for plaque area and lipid area. The results showed that the mice transfected with Ad-Wnt5a siRNA had reduced atherosclerotic lesions and decreased the lipid content of the plaques. The mRNA expression of MCP-1, COX-2, MMP-2 and MMP-9 in atherosclerotic lesions was significantly down-regulated by Ad-Wnt5a siRNA using RT-qPCR and western blot analysis of relevant inflammatory factors [4]. In addition, Ad-Wnt5a siRNA decreased the protein expression of MCP-1, COX-2, MMP-2 and MMP-9. These results suggest that silencing of Wnt5a inhibits the inflammatory response in atherosclerosis. activation of NF-κB and MAPK pathways can phosphorylate p65, JNK, ERK1/2 and p38 associated with them,

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and it is known that Ad-Wnt5a-siRNA attenuates the phosphorylation of the above enzymes by WB analysis, indicating that Ad-Wnt5a-siRNA can inhibit NF-κB and MAPK pathways [4]. Thus, silencing of Wnt5a could inhibit NF-κB and MAPK signaling, thereby regulating the level of inflammation under atherosclerotic conditions and preventing vascular injury in atherosclerosis. It could also serve as an effective molecular target for atherosclerosis gene therapy.

3. Osteoarthritis

Osteoarthritis (OA) is the most common joint disease in the world, especially among the elderly, with knee osteoarthritis accounting for almost four-fifths of global osteoarthritis [5]. The current treatment methods cannot cure knee osteoarthritis. Although knee replacement surgery can indirectly cure it, the surgical cost of knee replacement surgery is high, and it also faces difficulties in obtaining donors and immune rejection reactions, which cannot benefit most patients. Late-stage osteoarthritis can cause great inconvenience to the physical activities of the elderly, and in severe cases, it can also cause disability, not only causing harm to the body but also causing mental harm to the elderly. The study found that by 2020, the total incidence of knee osteoarthritis worldwide was 16.0%, and among people over 40 years old, it had risen to 22.9% [5]. That is to say, in 2020, among the global population aged 40 and above, at least 654.1 million people fell ill, which is a very large number. The study also found significant differences in the prevalence rate among different countries, with Germany only accounting for 2.5% and Thailand as high as 46.3% [5]. The reasons for this may be related to genetic and environmental factors. In terms of gender, the prevalence rate of women is almost twice that of men. Osteoarthritis, a chronic inflammatory disease, is inextricably linked to cellular ageing. Senescent chondrocytes have been found in the tissues of human OA patients and increase with age, OA's character is the loss of extracellular matrix (ECM) and demolition of cartilage. Inflammatory factors can make matrix metalloproteinases (MMP), disintegrants etc. more active [6]. Research confirms that the development of OA is associated with inflammatory factors. WNT5A is a kind of non-canonical Wnt protein. There is growing evidence that Wnt signaling is highly associated with the development of joints, like joint cavities and cartilage. WNT5A plays a role in both cartilage differentiation and cartilage degradation [6]. It stimulates chondrocyte proliferation and suppresses their differentiation in the early phases of cartilage production. In addition, WNT5A stimulates matrix metalloproteinases (MMPs), which reduce cartilage extracellular matrix formation and chondrogenesis in both mature chondrocytes and late chondrogenesis. WNT5A plays a critical role in the pathophysiology of OA by destroying and degrading cartilage. Huang and colleagues demonstrated that WNT5A stimulates chondrocyte catabolism in human OA cartilage activity by means of non-canonical Wnt signaling [6]. Furthermore, Ge demonstrated the critical function WNT5A plays in the NF-κB pathway-mediated cartilage degradation caused by interleukin (IL)-1β. According to research by Shi et al., WNT5A silencing suppressed the breakdown of type II collagen in rat chondrocytes caused by interleukin-1β. It also stopped WNT3A's catalytic activity and reduced the breakdown of cartilage. Utilized as a strong inhibitor of the Wnt pathway, the Wnt inhibitor M04690 has shown potential as a disease-modifying OA drug (DMOAD) [7]. Through the downregulation of WNT5A, exosomal miR-92a-3p was discovered to have a negative regulatory function in cartilage production and OA pathogenesis. One potential novel therapy and preventative strategy for OA is to regulate the expression of exosomal miR-92a-3p [6].

4. Tendon Ageing

The 19 Wnt family members identified have now been divided into two categories, typical and atypical, based on their signalling function [8]. Wnt1, wnt2, wnt3, wnt3a and wnt-8 activate the typical Wnt signalling pathway, enabling the stabilisation of β-catenin. the accumulation of β-catenin leads to its nuclear translocation and the activation of lymphatic enhancer factor/T-cell factor (Lef/Tcf) transcription factor activation. Wnt5a and Wnt11 are involved in the non-classical Wnt signalling pathway, a type that cannot signal through β-catenin or induce axial replication in Xenopus embryos. The tendon is generally defined as the dense connective tissue connecting bone and muscle and is one of the main components of the musculoskeletal system. Tendons transmit muscle contraction to bones and play a

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crucial role in exercise. The susceptibility to tendon disease increases with age, which is generally believed to be caused by damage to the mechanical function of the tendon. The maximum stress and stiffness of the tendon may be the main affected parameters. In vitro experiments on the ultimate stress of the human patellar tendon showed that compared to the 25-50-year-old group, the ultimate stress of the 64-93-year-old group decreased by 17% [9]. The testing of human Achilles tendon specimens also found that the ultimate stress decreases with age. Collagen is the main component in tendons that bears tension, so the decrease in ultimate stress with age may be due to a decrease in tendon collagen content. Research on the human patellar tendon and Achilles tendon has found that the stiffness of the patellar tendon is lower in the elderly group (60-69 years old) than in the young group (21-32 years old), but there is no difference in the Achilles tendon. Further research subsequently confirmed this conclusion. This suggests that there are differences in the effects of aging on different functional tendons. A systematic retrospective study found that the prevalence of rotator cuff disease was 9.7% among people aged ≤ 20 years old, while it increased to 62% among people aged ≥ 80 years old. Similarly, Achilles tendon disease is common in people aged 40-50, while rotator cuff tear and biceps tendon tear are common in the elderly [9]. Tendons can repair and regenerate themselves through tendon stem cells (TSPC). Tendon senescence is inextricably linked to the senescence of TSPC, which is due to a shift in Wnt signalling from classical to non-classical and enhanced expression of Wnt5a in TPSC. The study by Minhao Chen et al. proved that in aged TSPC, senescence, age-related cell polarity and senescence-associated secretory phenotype (SASP) expression will be attenuated after the inhibition of Wnt5a [8]. Mechanistically, it was shown that Wnt5a regulates TSPC senescence through the JAK-STAT signalling pathway, that Ror2 acts as a functional receptor for Wnt5a in TSPC senescence, and that Wnt5a enhances the JAK-TAT signalling pathway through Ror2. Thus, Wnt5a could be a very effective target in response to tendon senescence.

5. Conclusion

The treatment of these diseases utilises recombinant adenoviral vectors and exosomes to treat individual mice at birth, but adenovirus is potentially dangerous as a virus, whereas the crisper cas/9 system is a gene editing system that does not use a virus as a vector and is favoured for its high efficiency, targeting and low cost. Microinjection is also a well-established technique, so peoplemay combine the two and manipulate mouse-fertilised egg embryos to knock out the Wnt5a gene, thus allowing us to observe the pathophysiological changes that occur if the gene is absent from the developmental stage of the fertilised egg, to better understand the function of the gene. In the case of atherosclerosis, for example, if the edited embryos develop and are born successfully, they can be fed on a high-fat diet as described above to see if lesions develop or the magnitude of the lesions compared to the control group.

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