

Research Progress of Traditional Chinese Medicine in the Treatment of Steroid-induced Femoral Head Necrosis Based on PI3K/Akt Signaling Pathway

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Abstract: Steroid-induced osteonecrosis of the femoral head (SONFH) is a common bone and joint disease, mainly due to long-term or high-dose use of glucocorticoids leading to femoral head blood supply disorders and bone tissue necrosis. At present, the most effective treatment for SONFH is hip replacement, but there are some limitations and complications. As a traditional medical system, traditional Chinese medicine has the characteristics of multi-target, multi-channel and multi-component, which may provide a new treatment strategy for SONFH. In recent years, more and more studies have shown that traditional Chinese medicine can act on the PI3K/Akt signaling pathway, affect the angiogenesis, osteogenic differentiation, apoptosis and other processes in the necrotic area of the femoral head, thereby promoting angiogenesis and bone repair, and achieving the purpose of protecting the femoral head. This article reviews the research results of traditional Chinese medicine in the treatment of SONFH based on PI3K/Akt signaling pathway, and further provides a reference for the clinical application of traditional Chinese medicine in the treatment of SONFH.

1. Introduction

Osteonecrosis of the Femoral Head (ONFH) is a chronic progressive disease with complex etiology and unknown pathogenesis [1]. The progression of the disease often leads to severe hip pain, limited mobility and dysfunction in the later stage. According to statistics, in China, there are about 150,000-200,000 people suffering from this disease every year. The disease occurs mostly in the young and middle-aged group aged 30-50 years old, and tends to develop more young, and the incidence of Asians is much higher than that of Europeans [2,3]. Steroid-induced osteonecrosis of the femoral head (SONFH) is caused by the reduction or interruption of the blood supply to the femoral head due to the death of bone marrow components and bone cells due to the long-term and heavy use of glucocorticoids. A metabolic disease in which the morphological and structural changes and collapse of the femoral head occur, causing pain and dysfunction of the hip joint [4]. At present, the most effective treatment method recognized at home and abroad is hip arthroplasty, which can restore the walking function of patients with osteonecrosis of the femoral head and improve their quality of

life. However, the operation is not only traumatic and expensive, but also has obvious complications. The incidence of hip dislocation after hip arthroplasty is high in elderly patients, and young and middle-aged patients may face the disadvantages of hip revision, which greatly reduces the long-term prognosis. Therefore, hip preservation therapy is often preferred in clinical practice [5].

Finding a more effective, safe and low-trauma treatment method is still one of the hotspots of current research. In recent years, with the rapid development of traditional Chinese medicine, the prevention and treatment of SONFH with traditional Chinese medicine has become an important topic in the current society. Traditional Chinese medicine in the treatment of SONFH has the advantages of less trauma, low price, less toxic and side effects, and obvious curative effect, which is well received by patients. It not only greatly reduces the economic burden of patients and society, but also reduces surgical trauma and postoperative complications, and improves the quality of life of patients [6]. This article will mainly focus on the regulation of PI3K/Akt signaling pathway by traditional Chinese medicine in the prevention and treatment of SONFH, and clarify the relationship between the treatment of SONFH and PI3K/Akt signaling pathway, in order to provide reference for the clinical application of traditional Chinese medicine in the treatment of SONFH.

In traditional Chinese medicine (TCM), there is no clear name to describe osteonecrosis of the femoral head, but according to the specific situation and clinical manifestations of the patient, it can be summarized into different categories of TCM symptoms, such as: "bone paralysis", "paralysis", "bone hemorrhoids", "bone erosion" and so on. Some doctors call it "hip palsy" depending on the site of its onset. "The Theory of Suwen Paralysis" says: "The five internal organs are combined,....., so the bones are paralyzed, the feeling is in evil, and the inside is in the kidney." "Suwen Treatise on Hemorrhoids" said: "If the kidney qi is hot, the lumbar spine will not lift, the bones will wither and the pulp will decrease, and it will become bone hemorrhoids." "Lingshu Thorn Festival True Evil" said: "If heat beats cold, rotten flesh and rotten muscle will be pus, internal wounded bones, and internal wounded bones will be bone erosion." [7,8]. The pathogenesis of the disease is mainly caused by liver and kidney deficiency caused by external evil taking advantage of the deficiency, causing poor flow of qi and blood, and eventually leading to qi stasis and blood stasis, meridian blockage, bone loss of nourishment, and its disease is the basis of false standards, so it should be the focus of treatment to activate blood and remove stasis, nourish blood and improve qi [9].

2. PI3K/Akt signaling pathway

The PI3K (phosphatidylinositol 3-kinase) /Akt (protein kinase B) signaling pathway is a signal transduction pathway that regulates cell survival, growth, metabolism, proliferation and plays an important role in the formation of blood vessels [10-12]. PI3K is an important intracellular kinase composed of regulatory subunit p85 and catalytic subunit p110. According to its structural characteristics and substrate specificity, it can be divided into three types: type I, type II and type III [13,14]. Akt is an important downstream target protein kinase in the PI3K signaling pathway, which is mainly expressed in the cytoplasm. It belongs to a class of serine/threonine protein kinases with a molecular expression of 57 kD, including AKt1/ α , AKt2/ β , and AKt3/ γ isoforms [8,13]. PI3K recruits and activates Akt by phosphorylating phosphatidylinositol-4,5-diphosphate (PIP2) to phosphatidylinositol-3,4, 5-triphosphate (PIP3) on the cell membrane, Activated Akt regulates cell survival, growth, proliferation, metabolism and other functions through the phosphorylation of downstream effector molecules such as mTOR, FOXO, GSK-3 β . In recent years, more and more studies have found that PI3K/AKT signaling pathway can regulate cell growth, proliferation, differentiation, apoptosis, metabolism, promote angiogenesis and repair, improve the blood supply around the femoral head, and prevent and delay osteonecrosis of the femoral head by regulating other signaling pathways that affect the proliferation and differentiation of osteoblasts and osteoclasts and

angiogenesis [13-15].

3. PI3K/Akt signaling pathway and SONFH

Long-term and large use of glucocorticoids can lead to decreased osteogenic differentiation and increased adipogenic differentiation, which can damage or interrupt the blood circulation of the femoral head, cause local tissue ischemia and hypoxia, and lead to the collapse of the femoral head structure and local bone tissue necrosis. The study by Lu Feifan et al. showed that glucocorticoids can lead to apoptosis and necrosis of human femoral head bone microvascular endothelial cells by inhibiting the expression level of key proteins in the PI3K-Akt-mTOR signaling pathway, thereby affecting the blood supply around the femoral head [16]. Therefore, the important conservative treatment of femoral head necrosis is to promote the repair and regeneration of blood vessels around the femoral head, and restore the blood circulation supply around the femoral head. PI3K/Akt signaling pathway is a key signal transduction pathway involved in cell generation, differentiation, proliferation and metabolism, and can mediate vascular repair and regeneration by regulating related factors [12].

Osteoblasts play a key role in the completion of bone formation and homeostasis. The occurrence and development of SONFH are affected by the degree of osteoblast differentiation. If the osteogenic differentiation and adipogenic differentiation are unbalanced, it will lead to bone loss and bone deterioration, which will reduce bone activity and form osteonecrosis. Therefore, the key link in the prevention and treatment of SONFH is the mineralization of osteoblasts, which plays an important role in promoting osteogenesis and preventing osteonecrosis [8]. The occurrence and development of SONFH is closely related to the abnormal expression of PI3K/AKT signaling pathway [17]. PI3K and AKT, as the key regulators of this process, play an important regulatory role in the formation and differentiation of osteocytes. PI3K plays a positive regulatory role in promoting the proliferation and differentiation of osteoblasts and inhibiting the proliferation and differentiation of osteoclasts. Each of its isoforms is active and plays a role in the expression of osteocytes. AKT and its target genes can enhance the differentiation ability of osteoblasts by up-regulating their expression and phosphorylation after activation [12].

4. Chinese medicine is based on PI3K/Akt signaling pathway to treat SONFH

4.1 Traditional Chinese medicine monomer

The occurrence of SONFH is mainly due to the deficiency of liver and kidney, qi stagnation and blood stasis, and its essence is the deficiency of the essence and the excess of the standard. The traditional Chinese medicine treatment often uses the methods of reinforcing liver and kidney, strengthening muscles and bones, promoting blood circulation and removing blood stasis. Shi Wei et al. [18,19] explored the mechanism of icariin regulating PI3K/AKT signaling pathway in the intervention of steroid-induced osteonecrosis of the femoral head in rats and found that the expression of PI3K and p-Akt protein was decreased in the model group, and the expression of PI3K and p-Akt protein was increased in the icariin group. In conclusion, icariin can improve the pathological changes of subchondral bone tissue, trabecular bone and cortical bone parameters of SONFH rat model, increase the expression of Pi3k, Akt and p-Akt proteins, effectively alleviate the pathological progress of SONFH rat model, and promote the repair and regeneration of osteonecrosis. Zeng Suolin et al. [20] found in the study on the effect of puerarin on PI3K/AKT signaling pathway in SONFH model rats: Compared with the model group, the serum levels of VEGF and NO in the puerarin treatment group were improved, and the expression of p-Akt protein in the femoral head was increased, indicating that puerarin could improve the pathological process of steroid-induced osteonecrosis of

the femoral head in rats. The mechanism may be that puerarin can increase the serum vasoactive factors, thereby promoting the repair and regeneration of blood vessels and promoting the formation of new bone at the necrotic site. To reconstruct its blood supply and circulation. Cao et al. [21] found in their study on ginkgo biloba extract preventing steroid-induced femoral head necrosis through PI3K/AKT/eNOS pathway that ginkgo biloba extract increased the expression levels of p-PI3K, p-AKT and p-eNOS, inhibited cell apoptosis and restored cell function. Mice receiving ginkgo biloba extract had fewer cavities and normally arranged trabeculae. These results indicate that Ginkgo biloba extract can improve SONFH-induced vascular injury in mice and is essential for the prevention of SONFH. Xue et al. [22] used salidroside to activate PI3K/AKT signaling pathway, reduce the content of caspase-3 in osteoblasts, increase the expression of AKT after phosphorylation, and reduce the cavitation ratio in SONFH rat model, so as to reduce the apoptosis of osteoblasts caused by dexamethasone and prevent the occurrence of femoral head necrosis in rats. Zhan et al. [23] used allicin to activate PI3K/AKT signaling pathway to inhibit the abnormal expression of cytochrome C, Bcl-2, Bax, c-caspase3 and c-caspase9 induced by dexamethasone, reduce the number of cavities, and inhibit the apoptosis of osteoblasts. Allicin can effectively delay the progression of SONFH and may be a potential drug for the treatment of SONFH. Lv et al. [24] found that the total flavonoids of *Drachlor* could improve the steroid-induced osteonecrosis of the femoral head in rats through PI3K/AKT pathway, significantly alleviate the pathological degree of SONFH model rats, and inhibit cell apoptosis, up-regulate VEGF, RUNX2, OPG, OCN, and down-regulate RANKL. Activation of PI3K/AKT pathway in osteoblasts promotes their proliferation, inhibits apoptosis and reduces ROS levels. These results indicate that *Drynaria* total flavonoids can promote the differentiation of osteoblasts and protect osteoblasts from steroid hormone damage. Xiao Zhen et al. [25] found through cell experiments that resveratrol can activate PI3K/AKT/VEGF signaling pathway to improve the activity of BMECs and promote cell migration, increase the relative expression of VEGF, PI3K and Akt proteins in cells, and increase the rate of cell scratch healing. These results indicate that resveratrol can repair the damage of bone microvascular endothelial cells. LEUNG et al. [26] found that ginsenoside Rg1 could increase the expression of PI3K/Akt and β -catenin. Finally, β -catenin entered the nucleus and gradually accumulated, and then activated VEGF to promote angiogenesis and reconstruct the blood supply in the femoral head, and finally achieve the therapeutic effect.

4.2 Chinese herbal compound

In the treatment of SONFH, traditional Chinese medicine compound usually adopts the treatment method of tonifying kidney and activating blood circulation, nourishing blood and benefiting qi, and has achieved good therapeutic effect. Xu Tengeng et al. [27], in studying the intervention effect of Jianpi-Huogu Decoction on glucocorticoid-induced vascular endothelial cell function damage, found that Jianpi-Huogu Decoction could play a protective role in glucocorticoid-induced vascular endothelial cell angiogenesis damage by activating PI3K/Akt and MAPK signal axis, which provided a theoretical basis for the treatment of SONFH. Liu Mengchu [8] found that Shenggu Zaogu pill increased the mRNA and protein expression of PI3K, AKT and mTOR in different degrees in the experiment on the effect of Xinggu Zaozao Pill on the osteogenic differentiation of SONFH rabbit BMSCs based on PI3K/AKT/mTOR pathway, which could promote the osteogenic differentiation of BMSCs. Wang Junxiao [28] found in the study of the regulation of autophagy by Gubi Tongxiao Recipe and the pathogenesis of steroid-induced osteonecrosis of the femoral head based on PI3K/Akt/mTOR signaling pathway: Hormone can inhibit the counterregulation of PI3K/Akt/mTOR signaling pathway and cause autophagy, and the expression of Akt and mTOR decreased. After the application of Gubi Tongxiao Decoction, the expression of microtubule-associated protein LC3-II, autophagy-related protein Beclin1, Akt and mTOR changed significantly, and inhibited cell

autophagy. The results suggested that Gubi Tongxiao Decoction could delay the pathological process of SONFH. Sun Shihui et al. [29] found that Yanghe decoction could affect the PI3K-Akt signaling pathway and regulate bone metabolism of hip joint, thus promoting the metabolism of necrotic bone and increasing new bone in the treatment of femoral head necrosis. Wang et al. [30] found that Buxue-Tongluo pills can down-regulate the expression of PI3K and Akt, have obvious inhibitory effect on osteoclasts, and induce their apoptosis, thus achieving the effect of treating SONFH.

5. Summary and prospect

In conclusion, SONFH, as a common bone and joint disease in orthopedics, has the characteristics of high disability rate and low cure rate [6]. Currently, the most effective treatment for SONFH is hip replacement, but it has certain limitations and complications. Therefore, it is of great clinical significance to find effective, safe and economical new treatment methods. As an important part of traditional Chinese medicine, TCM has the characteristics of multi-target, multi-pathway and multi-component, and has shown good effects in the prevention and treatment of SONFH. This article summarizes the related research results of the intervention of SONFH with traditional Chinese medicine monomers and compounds based on PI3K/Akt signaling pathway. In recent years, more and more studies have found that traditional Chinese medicine promotes vascular repair and regeneration, regulates osteoblast proliferation and differentiation, induces cell apoptosis and metabolism and other processes by regulating PI3K/Akt signaling pathway, so as to promote vascular repair and regeneration around the femoral head and delay femoral head necrosis [12]. Both the active components of traditional Chinese medicine monomer and traditional Chinese medicine compound can delay the occurrence and development of the disease, and provide new ideas for clinical treatment of SONFH. Although there are more and more related studies at present, the relationship between traditional Chinese medicine and these signaling pathways is complex and variable. It is particularly important to clarify the relationship between them to explain the specific pathogenesis of SNOFH. Traditional Chinese medicine has shown great research prospects in the treatment of SONFH based on PI3K/Akt signaling pathway. It is expected that in the future scientific research, more effective prevention and treatment measures and methods can be explored, which can provide a reference scheme for more accurate treatment of SONFH, and better play the advantages of traditional Chinese medicine in the treatment of SONFH.

References

- [1] Xu Y, Jiang Y, Xia C S, et al. *Stem cell therapy for osteonecrosis of femoral head: Opportunities and challenges*[J]. *Regenerative Therapy*, 2020, 15: 295-304.
- [2] Liu F, Wang W, Yang L, et al. *An epidemiological study of etiology and clinical characteristics in patients with nontraumatic osteonecrosis of the femoral head* [J]. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*, 2017, 22.
- [3] Kubo Y, Motomura G, Ikemura S, et al. *Effect of collapse on the deformity of the femoral head-neck junction in osteonecrosis of the femoral head* [J]. *Archives of Orthopaedic and Trauma Surgery*, 2017, 137: 933-938.
- [4] Wang A, Ren M, Wang J. *The pathogenesis of steroid-induced osteonecrosis of the femoral head: a systematic review of the literature* [J]. *Gene*, 2018, 671: 103-109.
- [5] Chen Haojie, Li Shaopeng, Yang Fan, etc. *The research progress of mesenchymal stem cell-derived exosomes in the treatment of non-traumatic osteonecrosis of the femoral head in the early and middle stages* [J]. *Chinese Clinical Research*, 2020, 33 (09): 1274-1277.
- [6] Shang Zhengya, Cao Linzhong, Yang Haodong, et al. *Research progress of Chinese medicine regulating Wnt / β -catenin signaling pathway in the treatment of steroid-induced osteonecrosis of the femoral head*[J/OL]. *Chinese Journal of Experimental Prescriptions: 1-10* [2023-03-13]. <http://kns.cnki.net/kcms/detail/11.3495.R.20220830.1040.006.html>.
- [7] Feng H B. *Exploring the molecular mechanism of Taohong Siwu decoction on angiogenesis in traumatic ANFH rats from exosome MiR-126-VEGF/Notch signal axis* [D]. *Hunan University of Chinese Medicine*, 2022.

- [8] Liu M C. Experimental study on the effect of Shenggu Zhaizao pills on osteogenic differentiation of BMSCs in SANFH rabbits based on PI3K/AKT/mTOR pathway [D]. Gansu University of Traditional Chinese Medicine, 2022.
- [9] Han Jie, Xie Xiaozhong, Jin Wanqing, et al. Research progress on conservative treatment of avascular necrosis of the femoral head [J]. *Journal of Liaoning University of Traditional Chinese Medicine*, 2012, 24(10):15-18.
- [10] Solinas G, Becattini B. PI3K and AKT at the Interface of Signaling and Metabolism [M]/PI3K and AKT Isoforms in Immunity: Mechanisms and Therapeutic Opportunities. Cham: Springer International Publishing, 2022: 311-336.
- [11] Zaxi Dawa. M2-macrophages-derived exosomes play a therapeutic role by inhibiting PI3K/AKT/mTOR pathway in rats with knee osteoarthritis [D]. Qinghai University, 2022.
- [12] Liu Mengchu, Cao Linzhong, Jiang Wei, et al. Expression and role of PI3K/AKT/mTOR signaling pathway in glucocorticoid-induced osteonecrosis of the femoral head [J]. *Chin J Osteoporosis and Bone Mineral Diseases*, 2021, 14(01): 87-93.
- [13] Liu L B. Effect of modified Duhuo parasitic mixture on PI3K/AKT signaling pathway in OVX osteoporotic mice [D]. Hunan University of Chinese Medicine, 2022.
- [14] Zheng Haotian, Wang Xiaoping, Liu Haiping, et al. Role of PI3K/AKT signaling pathway in non-traumatic femoral head necrosis [J]. *Chin J Orthopedics*, 2021, 30(17):1592-1596.
- [15] Song Shilei, Chen Yueping, Zhang Xiaoyun. Mechanism of PI3K/AKT signaling pathway regulating femoral head necrosis [J]. *Chinese Tissue Engineering Research*, 2020, 24(03):408-415.
- [16] Lu Fanfei, Wang Weiguo, Guo Wanshou, et al. Study on the effect of glucocorticoid on the apoptosis of femoral head bone microvascular endothelial cells through PI3K-Akt-mTOR signaling pathway [J]. *Chin J Osteoporosis*, 2021, 28(05): 631-636+669.
- [17] Xu Canhong, Chen Yueping, Zhang Xiaoyun. The role of osteogenic signaling pathway in non-traumatic osteonecrosis of the femoral head [J]. *Tissue Engineering Research*, 2020, 24(14):2235-2242.
- [18] Shi Wei, Jin Xin, Wang Jinfeng, et al. Effects of icariin on early steroid-induced osteonecrosis of the femoral head in rats by mediating PI3K/Akt signaling pathway [J]. *Modern Medicine & Clinic*, 2021, 37(12):2680-2686.
- [19] Shi W. Effects of icariin on steroid-induced osteonecrosis of the femoral head in rats through PI3K/AKT signaling pathway [D]. Anhui University of Traditional Chinese Medicine, 2022.
- [20] Zeng Suolin, Shi Nengbing, Liu Yi. Effect of puerarin on bone tissue and PI3K/Akt signal transduction pathway in rats with steroid-induced osteonecrosis of the femoral head [J]. *Journal of Bengbu Medical College*, 2019, 44(11):1441-1444.
- [21] Cao F, Qin K, Kang K, et al. Ginkgo biloba l. extract prevents steroid-induced necrosis of the femoral head by rescuing apoptosis and dysfunction in vascular endothelial cells via the PI3K/AKT/eNOS pathway[J]. *Journal of Ethnopharmacology*, 2022, 296: 115476.
- [22] Xue X H, Feng Z H, Li Z X, et al. Salidroside inhibits steroid-induced avascular necrosis of the femoral head via the PI3K/Akt signaling pathway: In vitro and in vivo studies[J]. *Molecular Medicine Reports*, 2018, 17(3): 3751-3757.
- [23] Zhan J, Yan Z, Zhao M, et al. Allicin inhibits osteoblast apoptosis and steroid-induced necrosis of femoral head progression by activating the PI3K/AKT pathway[J]. *Food & function*, 2020, 11(9): 7830-7841.
- [24] Lv W, Yu M, Yang Q, et al. Total flavonoids of *Rhizoma drynariae* ameliorate steroid-induced avascular necrosis of the femoral head via the PI3K/AKT pathway[J]. *Molecular Medicine Reports*, 2021, 23(5): 1-10.
- [25] Xiao Z, Li S H. Identification of angiogenesis related genes in steroid-induced osteonecrosis of the femoral head and screening and verification of targeted traditional Chinese medicine components [J]. *Chinese Herbal Medicine*, 2023, 54(05): 1526-1539.
- [26] Leung K W, Pon Y L, Wong R N S, et al. Ginsenoside-Rg1 induces vascular endothelial growth factor expression through the glucocorticoid receptor-related phosphatidylinositol 3-kinase/Akt and β -catenin/T-cell factor-dependent pathway in human endothelial cells[J]. *Journal of Biological Chemistry*, 2006, 281(47): 36280-36288.
- [27] Peng F L, Liu M J. Progress in genetic research into high-degree myopia and myopia[J]. *China Journal of Modern Medicine*, 2015.
- [28] Wang J X. Study on the regulation of cell autophagy and the pathogenesis of steroid-induced osteonecrosis of the femoral head by Gubi Tongxiao Decoction based on PI3K/Akt/mTOR signaling pathway [D]. Anhui University of Traditional Chinese Medicine, 2021.
- [29] Sun Shihui, Xu Heng, Zhang Jinmin, et al. To explore the core mechanism of Yanghe decoction in the treatment of osteonecrosis of the femoral head by network pharmacology and molecular docking [J]. *Medical Research and Education*, 2020, 37(05):36-49.
- [30] Wang D, Liu Y, Tang D, et al. Induction of PI3K/Akt-mediated apoptosis in osteoclasts is a key approach for Buxue Tongluo Pills to treat osteonecrosis of the femoral head [J]. *Frontiers in Pharmacology*, 2021, 12: 729909.