· Review article ·

Research progress on cell signal transduction pathway mediating age-related cataract

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细胞信号转导通路介导年龄相关性白内障发生的研究进展

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摘要

年龄相关性白内障是一种由于晶状体混浊而影响视力的致盲眼病,居世界首位。氧化应激下晶状体上皮细胞凋亡相关信号转导通路的激活是介导年龄相关性白内障的主要机制。细胞凋亡有许多相关的信号转导通路,是一个复杂的网络系统。本文总结介导年龄相关性白内障不同的凋亡细胞信号转导通路,为进一步研究奠定基础。

关键词:年龄相关性白内障;凋亡;信号转导

Abstract

• Age-related cataract is a blinding eye disease that affects vision due to opacity of intraocular lens, ranking first in the world. Under oxidative stress, the activation of apoptosis related signal transduction pathways in lens epithelial cells is the main mechanism mediating age-related cataract. There are many related signaling pathways for apoptosis, and it is a complex network system. The purpose of this literature review is to summarize different apoptotic cell signal transduction pathways that mediate age-related cataract, laying the foundation for further researching.

• KEYWORDS: age-related cataract; apoptosis; signal transduction

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INTRODUCTION

Age-related cataract is a blinding eye disease that affects vision due to intraocular lens opacity, ranking first in the world. At present, surgery is still the main treatment. The exact cause has not been fully investigated, but oxidative stress damage in the lens has been considered to be the most closely related factor for the occurrence of age-related cataract. It has been reported that the oxidative stress process mainly involves a variety of stress-sensitive signaling pathways inside and outside the cell. Under oxidative stress, the lens epithelial cells initiate apoptosis-related signal transduction pathways, which mediate apoptosis of lens epithelial cells and promote the development of cataracts. Therefore, by further studying the signal transduction pathway mediating age-related cataract and specifically blocking the regulatory targets of major genes in the transduction pathway, we can block the

apoptotic signal transduction pathway of age-related cataract, thereby reducing the occurrence and development of age-related cataract. In this literature, the research progress of cell signaling pathways that mediate age-related cataract are reviewed.

Cell Signal Transduction Pathway Cell signal transduction refers to the process by which extracellular factors bind to the receptor, thereby triggering a series of biochemical reactions and interactions between proteins, until the physiological response of the cells begins to express the desired genes and form various biological effects. Through cell signal transduction, part of the metabolic process in the cell can be changed, the cell migration can be changed, and the rate of cell growth can be affected. And even in some cases, cells can be induced by external signals into the programmed death process (apoptosis)[1-2]. It is known that there are many signal transduction pathways in cells, and there are multiple levels of cross regulation between various pathways, which is an extremely complex network system. There are many cell signal transduction pathways, including TGF-β/Smad, MAPK, Nrf2/Keap1, pi3k-akt, microRNA, *etc*. The study of signal transduction pathway is of great significance to cell growth, development, differentiation, proliferation and apoptosis.

Age-related Cataracts Cataract is a blinding eye disease that affects vision due to intraocular lens opacity, ranking first in the world, and at least 42% of blind patients are caused by it. According to the World Health Organization, by 2020, more than 40 million people worldwide are blinded by cataracts[3], and the number of people who have newly added cataracts in China is about 40 to 1.2 million. As the society ages, the incidence of age-related cataract (ARC) will increase further. Surgery is currently the only effective treatment for cataracts. However, the patient population is huge, and the cost of surgery and consumables is a heavy economic burden for both individuals and society. Therefore, deep research and clarify the specific molecular mechanism in the development of ARC, find the cause of the disease, conduct early intervention, prevent, delay or even reverse the opacity of the lens, to maximize the protection of patients' visual function, improve the quality of life, reduce patients and the burden of society has important theoretical and practical significance.

At present, the exact cause of ARC has not been fully studied. It is generally considered that age, gender, occupation, radiation (visible light, ultraviolet light, X-ray, *etc*.), oxidation, physical damage, diet and medication are all risk factors, among which oxidative stress of lens injury is considered to be most closely related to the occurrence of cataract[4-5]. Under oxidative stress, the production of reactive oxygen species (ROS) in cells is excessive. As functional molecular signals, ROS [including superoxide anion (O^2-), hydrogen peroxide (H_2O_2) and hydroxyl radical (-OH) *etc*.] can activate a variety of stress-sensitive signaling pathways in cells and initiate apoptosis procedures[6]. In this process, it mainly involves signal transduction pathways such as TGF-β/Smad, MAPK, Nrf2/Keap1, PI3K-AKT, and microRNA.

Signaling Pathway Mediating Age-related Cataract

TGF-β/Smad signaling pathway The TGF-β/Smad signal transduction pathway is involved in the apoptosis process of various cellular tissues. Studies have shown that transforming growth factor β (TGF-β) is an important cell proliferation inhibitor[7], which can induce apoptosis in a variety of cells. TGF-β mainly exists three different subtypes in human body: TGF-β1, TGF-β2 and TGF-β3. These three different subtypes are in human aqueous humor, ciliary body, lens, vitreous, retina, *etc*. And it can be detected in the ocular tissues. Among them, the content and activity of TGF-β2 in the vitreous and intraocular anterior chamber are significantly higher than other subtypes, and have the closest relationship with ocular tissues[8]. Li *et al*[9] and others found that the expression of TGF-β2 mRNA in lens epithelial cells (HLECs) of ARC patients was significantly higher than that of the control group, suggesting that it may mediate apoptosis of HLECs in ARC. And more and more studies have confirmed that TGF-β can cause apoptosis of HLECs and induce the formation of ARC[10-11]. The TGF-β signal is transduced by the Smad pathway and the non-Smad pathway (mainly including MARK, p38, SPARC, wnt, *etc*.), and the Smad pathway is the major TGF-β target gene inhibition or activated signaling pathway[12]. Wei *et al*[13] successfully established the HLECs photodamage model and found that the TGF-β2/Smad3 signal transduction pathway is involved in the process of apoptosis, and blocking its signal transduction has a certain inhibitory effect on apoptosis.

MAPK signaling pathway Mitogen activated protein kinases (MAPKs) are a kind of serine/threonine protein kinases present in cells. The MAPKs signal transduction pathway exists widely in most cells, and its main function is to transduce extracellular stimulation signals into cells and their nucleus, and cause corresponding cellular biological reactions. So far, there are four distinct MAPK signaling pathways in mammalian cells: extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), P38 mitogen-activated protein kinase (p38) and ERK5/mega MAP kinase (BMK1) signaling pathway. Studies have confirmed[14] that the MAPK/ERK1/2 signaling pathway is involved in the regulation of HLECs function and promotes the development of ARC. Upadhya *et al*[15] found that in the lens of developing mice, the lack of ERK2 conditions leads to the destruction of cell proliferation and the increase of apoptosis. The result of culturing HLECs with UVB irradiation is that CALML3 is down-regulated, which induces apoptosis of HLECs by mediating JNK1/2 and ERK1/2 signaling pathways, and participates in the development of ARC[16]. In addition, the MAPK-P38 signaling pathway also plays an important role in ARC. Yan *et al*[17] demonstrated in experiments that activation of MAPK-P38 signaling pathway can promote the

development of ARC. Ji *et al*[18] studied the role of CRTAC1 gene in ARC and concluded that this gene may mediate the occurrence and development of ARC by inhibiting p38 and JNK signaling pathways in inducing apoptosis of HLECs. Other studies[19] pointed out that inhibition of phosphorylation of p38 in the MAPK pathway can prevent apoptosis of HLECs, thereby reducing the occurrence and development of ARC. In addition, Peng *et al*[20] found that p-Coumaric Acid (p-CA) inhibited H_2O_2-induced phosphorylation of p38, ERK and JNK in HLECs, and further demonstrated that it inhibits HLECs cell development by regulating MAPK signaling pathway, suggesting that p-CA has a potential role in the prevention and treatment of ARC.

Nrf2/Keap1 signal pathway The Nrf2-Keap1 system is considered as one of the major cellular defense mechanisms against oxidative stress. Nrf2 belongs to the cap-ncollar (CNC) leucine zipper transcriptional activator family, which consists of six member sincluding NF-F2, Nrf1, Nrf2, Nrf3, Bach1 and Bach2. Keap1 is a cysteine-rich protein that acts as a substrate regulatory protein for Cullin 3 (Cul3)-dependent E3 ubiquitin ligase. Keap1 binds to the Neh2 domain of Nrf2 through its DGR domain, and negatively regulates the activity of Nrf2[21]. Normally, Nrf2 is anchored in the cytosol by Keap1 and undergoes ubiquitination and proteasomal degradation, but when stimulated by oxidative stress, phosphorylation or electrophile, Nrf2 dissociates from Keap1, then Nrf2 is transferred into the nucleus through the nucleus, first forming a heterodimer with the small Maf protein, which in turn binds to the antioxidant response element (ARE), activates the downstream target gene, and enhances cell resistance oxidation capacity through signal transduction[22].

The structural or functional anomalies of the Nrf2/Keap1 system are inseparable from the development of ARC. Studies have shown that oxidative stress in HLECs of ARC patients leads to increased ROS content, demethylation of Keap1 DNA promoter, and increased expression of Keap1 protein, which in turn reduces the content of negatively regulated Nrf2, while proteases degrade Nrf2, antioxidant enzymes. Gene transcription is also inhibited, and the function of the Nrf2/Keap1 antioxidant system is greatly impaired, which in turn promotes the development of ARC[23-26]. Recent studies[27] have found that trimetazidine can inhibit the demethylation of the Keap1 DNA promoter by regulating the expression level of Nrf2 and reduce the production of ROS, thereby delaying the formation of ARC. The data provided by Whitson[28] demonstrate that glutathione (GSH)-deficient lenses are dependent on activation of the Nrf2 signaling pathway to initiate oxidative stress. In addition, Liu *et al*[29] found that Nrf2 inhibitor may increase lens oxidative stress, and Nrf2 inducer may reduce oxidative stress to prevent cataract formation, confirming that Nrf2/Keap1/ARE signaling pathway exists in cataract, and suggesting that it can be used as a target for the prevention and treatment of ARC against oxidative stress.

MicroRNA signaling pathway MicroRNAs are small, non-coding RNAs composed of 21-25 nucleotides. It binds to the complementary pairing of the 3' untranslated regions (UTR) bases of the target gene, and regulates the expression of the target gene protein at the post-transcriptional level. The results show that microRNA plays an important role in cell apoptosis, differentiation and proliferation. And more and more researchers continue to find differential expression of microRNAs in ARC.

Recent studies have found that microRNA-378a participates in the development of ARC by regulating reactive oxygen species (ROS)/phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathways in human HLECs and cataracts[30]. The expression of beta-2-microcrystalline protein (CRYBB2) is predicted to delay the progression of ARC. In addition, MicroRNA-133b promotes apoptosis of HLECs in ARC by up-regulating the BCL2L2 gene[31]. In the study[32], miR-24 expression was significantly increased in the anterior lens capsule of ARC patients and in oxidative stress HLECs, and its overexpression directly induced p53 expression and promoted apoptosis of HLECs. In addition, miR-125b can also participate in the formation of ARC by directly targeting p53 to regulate apoptosis of HLECs[33]. Some scholars[34-35] have found that microRNA-34a is expressed in the lens of ARC patients, which triggers mitochondria-mediated apoptosis and oxidative stress by inhibiting Notch2. At the same time, MicroRNA-34a was also shown to promote apoptosis of HLECs by down-regulating Bcl-2 and SIRT1.In addition, Jin *et al*[36] confirmed that the KCNQ1OT1-miR-214-caspase-1 signal transduction pathway is a novel mechanism for promoting ARC formation.

Other signal pathways The study found that other signal transduction pathways can also mediate the development of ARC. Studies have found that histidine has a strong antioxidant effect in HLECs, which may be achieved by inactivating the NF-kB signaling pathway[37]. Zhou *et al*[38] demonstrated that the NF-kB/p65 signaling pathway is involved in the oxidative stress process of ARC. Peng *et al*[39] also studied Eaf2 and found that it inhibits oxidative stress-induced apoptosis in human HLECs by activating Wnt3 signaling pathway, and thus participates in the development of ARC.

Posterior Capsular Opacification Posterior capsular opacification (PCO) is the most common complication of postoperative cataract extraction and blindness, which is also called posterior capsule opacity. Since cataract surgery can destroy the blood-aqueous humor barrier, the lens epithelial cells remaining in the anterior subcapsular and equatorial regions proliferate excessively and migrate to the posterior capsule, transforming into fibroblasts and secreting a large amount of collagen to accumulate in the posterior capsule of the lens, resulting in opacity of the posterior capsule[40]. It occurs as a result of the interaction between lens epithelial cell proliferation, migration, epithelial-mesenehymal transition

(EMT) and extracellular matrix (ECM). Studies have shown that signal transduction pathways in lens epithelial cells also play a crucial role in the development of posterior cataract.

TGF-β/Smad Signaling Pathway Existing studies have shown that the TGF-β/Smad signaling pathway is a well-defined major regulatory signal transduction pathway during PCO formation[41-43]. Li *et al*[44] and others confirmed by experiments that Smad2 and Smad3 are critical in the TGF-β2 signaling pathway. At the same time, Li *et al*[45] also found that Smad2 and Smad3 play a role in the process of PCO and prove its biological effects of cells are different. Smad2 plays an important role in mediating the occurrence of EMT and increasing cell migration ability, while Smad3 is mainly involved in the accumulation of extracellular matrix and induce apoptosis. In addition, Smad4 also mediates the signaling pathway of EMT in PCO. In a study of cataracts, Nahomi *et al*[46] found that during the treatment of HLECs cells, the markers Smad4 and EMT were up-regulated. In addition, by studying the KCNQ1OT1 gene, researchers[47] found that it is the upstream target of Smad, and its influence on cell proliferation and EMT is also achieved through the Smad4 signaling pathway.

PI3K-AKT Signal Pathway The phosphatidylinositol-3-kinase /protein kinase B (PI3K/Akt) signaling pathway exists widely in various cells, PI3K catalyzes the phosphorylation of phosphatidylinositol D3 hydroxyl, then the phosphadydylinositol-4,5-bisphosphate (PIP2) is converted to 3, 4, 5-triphosphate phosphatidylinositol-3, 4, 5-triphosphate (PIP3), PIP3 will acted as a second messenger to activate AKT, and then fully activated AKT is separated from the plasma membrane, which initiates signal transduction by acting on downstream molecules, thereby regulating gene expression, cell cycle, and apoptosis[48].

The PI3K/AKT signaling pathway plays an important role in the process of lens epithelial cell proliferation. It has been found that PI3K inhibitors can block a variety of cytokines and have a proliferative effect on HLECs. Li *et al*[49-50] pointed out that PI3K/AKT signaling pathway blockers can inhibit the proliferation of lens epithelial cells by regulating the expression of downstream target molecules in the PI3K/AKT signaling pathway and by blocking the cell cycle. At the same time, this pathway also plays an important role in the migration of lens epithelial cells. Jiang *et al*[51] observed that epidermal growth factor (EGF) binds to its receptor to phosphorylate AKT in HLECs, thereby initiating PI3K-AKT signaling pathways. Then it promote matrix metalloproteinases (MMP)-2 expression and migration of HLECs. Other studies have confirmed that migration of HLECs can be reduced though the PI3K/AKT signaling pathway[52]. In EMT regulation of HLECs, Yao *et al*[53] concluded that PI3K/AKT signaling pathway is involved in the induction of human lens epithelial EMT by mediating gap junction protein 43 (Cx43). Guo *et al*[54] also confirmed that PI3K/AKT signaling pathway

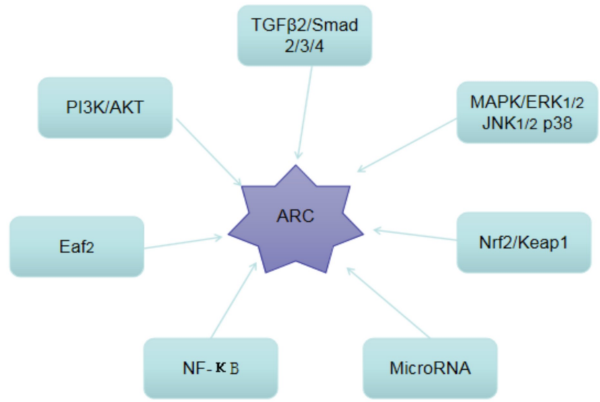

Figure 1 Different cell signal transduction pathways mediate age-related cataract.

can induce transdifferentiation of human HLECs and mediate the development of PCO.

MicroRNA Signaling Pathway The researchers[55-57] found that miR-204-5p, miR-26 and miRNA-181a can directly regulate EMT by participating in TGF-β/Smad4 or cyclooxygenase-2 (COX2) signaling pathway, becoming a new target for PCO therapeutic intervention. Recent studies have shown that microRNA-23b-3p can promote the proliferation, migration and EMT of HLECs by regulating the Sprouty2 (SPRY2) gene, and predict that inhibition of microRNA-23b-3p may have the potential to treat PCO[58]. Han *et al*[59] found that in EMT of HLECs, the expression level of miR-34a was down-regulated, while Notch1 was up-regulated by TGF-β2, and it was confirmed that Notch1 gene is a direct target gene of miR-34a. In addition, the researchers found through analysis[60] that miR-184 and miR-204 play important roles in the regulation of PCO formation after cataract surgery in mice. Dong *et al*[61] confirmed by studies that epidermal growth factor (EGF) and EGF receptor (EGFR) signal transduction can induce Myc overexpression in HLECs, and Myc overexpression inhibits miR-26b by recruiting HDAC3, thereby inducing zeste homologous protein 2 (EZH2) expression enhancer that promotes the progression of EMT in HLECs.

Concluding Remarks The occurrence and development of age-related cataract is the result of multi-factor and multi-channel synergy. The oxidative stress damage of the lens is considered to be the most closely related factor for the occurrence and development of age-related cataract. The process of oxidative stress mainly involves a variety of stress-sensitive signaling pathways in the cell, which promotes the apoptosis of lens epithelial cells by initiating the signal transduction pathway of lens epithelial cells, thereby promoting the development of cataract (Figure 1). By studying the signal transduction pathway of age-related cataract, we can block the apoptosis signal transduction pathway by interfering with the regulatory targets of major genes on the signal transduction pathway, thereby reducing the incidence of age-related cataract. This not only provides a theoretical basis for the pathogenesis of cataract, but we can

develop more effective drugs and methods for the treatment of age-related cataracts according to the signal transduction pathways, providing new ways and ideas for the prevention and treatment of age-related cataracts.

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