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Research Progress of SREBP in Ocular Disease

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Abstract: Sterol regulatory element-binding proteins (SREBP) is a class of transcription factor that regulate the metabolism of cholesterol, fatty acids and phospholipids and is widely expressed in body tissues. SREBP is known to play important roles in the physiological and pathological processes of metabolic diseases, cardiovascular diseases, tumors and other diseases. In recent years, the study of SREBP in ocular diseases has received extensive attention, and it has been shown that SREBP plays an important role in the development of diseases such as dry eye, diabetic retinopathy (DR), age-related macular degeneration (AMD), glaucoma, cataract, and retinoblastoma. SREBP affects the function of ocular tissues by regulating lipid metabolism, inflammation, oxidative stress, and apoptosis, and may be a novel therapeutic target for ocular diseases. This article summarizes the progress of SREBP in ocular diseases, focusing on its role in various ocular pathologies and its potential therapeutic value to provide new ideas for the prevention and treatment of related diseases.

Keywords: Sterol Regulatory Element Binding Protein; Ocular Disease; Lipid Metabolism; Inflammation.

1. Introduction

Sterol regulatory element-binding protein (SREBP) is a major regulator of lipid homeostasis and glucose metabolism and is classified mainly as SREBP-1 and SREBP-2, genes for those enzymes of the glycoheterotrophic and pentose phosphate pathways that it mediates (PKLR, PCK1, G6P and G6PD). As a trans-endoplasmic reticulum membrane protein, SREBP senses a variety of metabolic signals, and processed SREBP translocates to the nucleus to stimulate transcription of its target genes[1] . Currently, SREBP is not only involved in the development of abnormalities in glucose and lipid metabolism[2-4] , but also plays a key role in the pathogenesis of various diseases, such as oxidative stress, inflammation, apoptosis, and neovascularization, etc.[5-7] . SREBP is involved in the pathogenesis of a variety of diseases, but there is a lack of systematic integration of SREBP in ocular diseases, and the present review aims to summarize the preliminary results of SREBP. The purpose of this review is to summarize the preliminary findings of SREBP.

2. Overview of SREBP

SREBP is a class of transcription factors that mainly regulate cholesterol, fatty acid and phospholipid metabolism and belongs to the basic helix-loop-helix leucine zipper (bHLH-LZ) family whose N-terminal structural domain is a transcriptionally active region that binds to sterol regulatory elements (SREs) and enhancer boxes (E-boxes) in target genes to stimulate transcription of the target genes. The protein is encoded by sterol regulatory element-binding transcription factor (SREBF), which is divided into two genotypes, SREBF1 and SREBF2, and SREBP, which is divided into three isoforms (SREBP1a, SREBP1c and SREBP2)[8] . SREBF1 is mainly involved in fatty acid and triglyceride synthesis and is transcribed into SREBP1a and SREBP1c by binding to different promoters [9] . SREBP1a is increased in the early stages of adipogenesis, is predominantly expressed in highly proliferative cells, has strong transcriptional activity, is induced by the GSK3β-C/EBPβ pathway, and can stimulate fatty acid and cholesterol synthesis; whereas SREBP1c is a key factor in adipogenesis and fat accumulation, mainly regulates lipid metabolism, is mainly induced by C/EBP, and promotes adipocyte differentiation, transcription of triacylglycerol and fatty acid-related synthesis genes via PPARγ ligand or transactivation of PPARγ, and is also regulated by signals such as insulin[10] . SREBP2 is expressed in all tissues of the body, and unlike SREBP1, it is regulated by the transcriptional gene SREBF2, but they are closely related SREBP1a which is able to compensate for the lack of SREBP2 by binding to CREB1 SREBP2 is mainly responsible for cholesterol synthesis and the regulation of cholesterol homeostasis, and its activity is affected by cellular cholesterol levels and endoplasmic reticulum stress, among other factors[8]. SREBP is activated in cells mainly through the endoplasmic reticulum-Golgi apparatus-nucleus signaling pathway. At the endoplasmic reticulum membrane, SREBP binds to SREBP cleavage activating protein (SCAP) and is regulated by insulin-inducible gene 1 (INSIG-1/2). When cellular cholesterol levels decrease, the SCAP-SREBP complex translocates to the Golgi apparatus and is sheared by the Site 1 protease and Site 2 protease, releasing SREBP-active fragments that subsequently enter the nucleus, bind to sterol regulatory elements (SREs) on DNA, promote transcription of related genes, and ultimately regulate lipid synthesis, inflammatory responses, and cellular metabolism[11] . In tumors, SREBP is highly expressed in a variety of cancer cells and may be involved in the pathological process of hepatocellular carcinoma, rectal cancer and breast cancer, etc[12-14]. Abnormal activation or inhibition of SREBP has also been strongly implicated in a variety of metabolic disorders, including diabetes mellitus, non-alcoholic fatty liver disease, and cardiovascular disease[2, 15, 16] . In recent years, the role of SREBP in ocular diseases has received increasing attention, and studies have shown that SREBP is expressed in ocular tissues such as the retina, lens, and meibomian gland, and that abnormalities in its function can lead to a variety of pathological changes[17-19] .In recent years, a great number of studies have found that SREBP may play an important role in the development of a variety of ocular diseases, including dry eye, diabetic retinopathy, cataract, age-related macular

degeneration, glaucoma, and thyroid-related eye disease.

3. SREBP and Dry Eye Disease (DED)

Dry eye disease is a chronic ocular surface disease characterized by decreased tear production or excessive evaporation, resulting in tear film instability and inflammation. The tear film is a fluid film evenly distributed on the surface of the cornea and its main function is to maintain the wetness of the ocular surface, which is divided into three main layers from the inside to the outside, namely the mucin layer, the aqueous layer and the lipid layer. The lipid layer is a layer of tear film components secreted by the meibomian glands and its main function is to protect the plasma layer, reduce evaporation and keep the tear film in a stable state. Meibomian gland dysfunction (MGD) is a chronic meibomian gland dysfunction characterized by abnormal meibomian gland secretion or obstruction of the meibomian gland orifice, altered meibomian gland lipid quality, and ultimately atrophy of the lacrimal gland and glandular desquamation. MGD is the main cause of tear film lipid layer instability and one of the pathogenesis of evaporative hyperalimentation type of dry eye[20]. The expression of SREBP1 was significantly increased in the palpebral gland tissues of estrogen-deficient C57 mice, exacerbating the process of lipid deposition leading to blockage of the palpebral gland orifices, dilation of the gland ducts, and deterioration of tear film stability[21]. Studies have shown that SREBP1 is also expressed in both human meibomian gland and lacrimal gland epithelial cells, and when the lipid metabolism pathway PPAR-γ/SREBP1 is activated, it also exacerbates the accumulation of lipids in both types of cells, thus exacerbating the pathological process of MGD[19, 22] . Abnormal activation or inhibition of SREBP may lead to abnormal secretion of meibomian gland lipids, which affects the composition of the tear lipid layer, and the tear film will evaporate more easily, ultimately aggravating the pathology of DED. The tear film becomes prone to evaporation, ultimately exacerbating DED symptoms.[19, 23] .

Inflammation is critical to the chronic injury in DED, and inflammatory mediators and immune cell infiltration destabilize the tear film. Macrophage polarization plays an important role in inflammation and is divided into two major categories, M1 and M2, and in DED it is mainly mediated by M1 macrophages.SREBP1a expression is increased in macrophages and activates M1 macrophage polarization, which is closely associated with a number of inflammatory factors (TNF-α, IL-1β, and IL-6), with the production of IL-1β also relying on SREBP1a-mediated lipid polysaccharide increase[24]. C57 mice develop DED after high-fat feeding, with increased lipopolysaccharide expression leading to polarization of M1 macrophages, which may be related to changes in SREBP1a due to lipid abnormalities[25]. Melatonin was found to inhibit the overexpression profile of SREBP1 in human meibomian gland cells while reducing the expression of inflammation-related factors in DED, providing a new idea for the prevention of DED[25, 26]. SREBP overactivation also triggers lacrimal gland inflammation, which further exacerbates the dysfunction of tear secretion [22] . In the treatment of DED, modulation of SREBPs may become a new intervention strategy. For example, modulation of SREBP-1c-mediated lipid metabolism by PPAR-γ agonists is expected to improve lid lipid quality and enhance tear film stability[27] . In human meibomian gland cells, 13-cis-retinoic acid inhibits eyelid lipid secretion and exacerbates the progression of MGD through its negative regulatory effect on SREBP2[28] . In addition, the use of SREBP inhibitors may reduce the inflammatory response and have a potential therapeutic effect in patients with dry eye disease[29]. Thus, it is clear that SREBP as a key factor in lipid synthesis in meibomian gland function and blepharitis, and may provide a new aid to the principles of prevention and treatment of DED.

4. SREBP and Diabetic Retinopathy (DR)

DR is the leading cause of visual impairment in diabetic patients. Diabetic mellitus (DM) is a serious chronic metabolic disease that occurs when the body produces low levels of insulin or has impaired use of insulin. By 2021, approximately 540 million people worldwide will have diabetes, and the number is expected to increase by approximately 20% by 2030[30]. As one of the microvascular complications of diabetes mellitus, DR is mainly caused by hyperglycemia-induced retinal vascular damage, oxidative stress and inflammatory response[31-33]. Dihydroartemisinin (DHA), the active metabolite of the antimalarial drug artemisinin, has been shown to have antineovascular effects in a variety of diseases. Gu[34] and Zhang[35] et al. They found that DHA inhibited the expression of SREBP1 and ameliorated streptozotocin (STZ)-induced retinal damage in DR mice, retinal vascular dysfunction in DR mice, and high glucose-induced hyperproliferation, migration, and tube-forming ability of human retinal microvascular endothelial cells (HRMECs). This demonstrates the potential of DHA in DR anti-neovascularization. Diabetic retinal neurodegeneration is actually a retinal neurovascular element injury that may occur early in DR. Studies have shown that SREBP1 expression is significantly upregulated in the retina of diabetic mice and, when inhibited, attenuates retinal ganglion cell death[36]. This may provide new insights for the treatment of early DR.

The human circadian rhythm is a time program regulated by the biological clock system, and when the circadian rhythm is disturbed, it will aggravate the development of DM or even DR. As a key regulator of the biological clock system, clocks genes control metabolic rhythms by regulating protein synthesis and degradation. It therefore have an important impact on circadian rhythms. [37]. Brain and Muscle Arnt-Like Receptor Nuclear Transporter Protein 1 (BMAL1) is a core factor of biological clock genes, and BMAL1 regulates the metabolism of the organism through the regulation of SREBP[38, 39] . The retina has a unique set of circadian rhythms due to the regulation of photoreceptor cells, and its function and metabolism are also affected by this biological clock gene.Wang[40] found that there were significant differences in the daily rhythmicity of SREBP1c in the retinas of two groups of rats (normal Long Evans rats and DM rats). It is hypothesized that the dysregulated circadian rhythm of SREBP1c exacerbates the progression of DR by affecting lipid metabolism in the retina. In addition, overactivation of SREBP-2 may lead to abnormal cholesterol metabolism, exacerbating retinal vascular inflammation and neovascularization[41]. Taken together, modulation of SREBP expression may become a new target for the treatment of DR.

5. SREBP and Cataract

Cataract is a multifactorial disorder of lens metabolism that results in clouding of the lens due to protein denaturation and is the leading cause of blindness in the developing world. Metabolic syndrome is one of the risk factors for lens degeneration, with abnormal lipid metabolism being a key factor in cataract development[42]. SREBP is a key regulator of lipid metabolism, which plays an indispensable role in cataract. Lanosterol synthase (LSS), an intermediate molecule in the cholesterol biosynthetic pathway, catalyzes the conversion of 2,3-oxidized squalene to oxysterols, which, together with LSS, maintain lens clarity by inhibiting the formation of protein aggregates.The expression of LSS is increased in human lenses with age-related cataracts and positively correlates with the degree of lens opacification[43]. Studies have shown that overexpression of LSS upregulates SREBP1, thereby reducing epithelial-mesenchymal transition in lens epithelial cells (the major cause of lens fibrosis) and inhibiting cataract progression[44]. On the other hand, lanosterol can improve abnormal cholesterol metabolism in the lens and reverse amyloid accumulation in cataract cell models by inhibiting SREBP2[45].

Quaking (Qki) is a protein involved in mRNA metabolism in a tissue-specific manner and includes three selective splice isoforms, Qki-5, Qki-6 and Qki-7, of which Qki-5 is involved in lipid metabolism as a transcription factor for cholesterol synthesis Shin found that Qki is an obligatory gene for transcriptional cholesterol synthesis in the lens. Knocking down its expression in the mouse lens led to cataracts via a mechanism whereby Qki-5 knockdown decreased SREBP2 expression, resulting in subnormal cholesterol levels and reduced lens transparency. In addition, an abnormal mutation in the gene for SREBP1 was found in 2 patients with congenital cataract[18]. Based on these results, SREBP has a significant impact on lens lipid metabolism, and altering its abnormal expression may be a new idea for cataract treatment therapy.

6. Other

Age-related macular degeneration (AMD) is a leading cause of vision loss in the elderly and its pathogenesis involves retinal pigment epithelial (RPE) cell damage, lipid deposition and chronic inflammation. Abnormalities in retinal lipid metabolism lead to lipid deposition between the RPE basal lamina and Bruch's membrane to form drusen, a typical pathologic change in AMD[47] . In human ocular tissues, SREBP is predominantly distributed in the RPE layer, and SREBP2-mediated cholesterol production leading to abnormal RPE lipid metabolism may result in the formation of drusen, which may affect retinal function and exacerbate the progression of AMD[41, 48]. Modulation of SREBP2-mediated cholesterol metabolism may be important in the treatment of AMD. For example, the use of cholesterol-modulating drugs (e.g., statins) or SREBP2 inhibitors may reduce lipid deposition and ameliorate AMD-related retinal damage[41, 49].

Glaucoma is a chronic eye disease characterized by optic nerve damage and retinal ganglion cell (RGC) apoptosis. A high-fat diet has been shown to increase retinal cholesterol, leading to thinning of the peripheral retina, exacerbation of retinal neuropathy, and RGC damage[50]. Chronic or sustained elevation of intraocular pressure due to altered biological properties of the trabecular meshwork is one of the risk factors for glaucoma. In human and porcine trabecular meshwork cells, inhibition of SREBP expression reduces extracellular matrix production and deposition, while silencing SREBP in mouse trabecular meshwork reduces IOP and delays glaucoma progression through actin relaxation[51].

Graves' ophthalmopathy (GO) is an orbital inflammatory disease associated with autoimmune thyroid disease. Its main features include orbital tissue inflammation, extraocular muscle hypertrophy, adipose tissue hyperplasia, and globe protrusion, etc. SREBP, a central factor in lipid regulation, plays an important role in lipid accumulation and hyperplasia of orbital adipocytes[52]. Studies have shown that the expression of SREBP with its upstream factors C/EBP and PPAR-γ is upregulated in orbital fibroblasts from GO patients, leading to increased lipid synthesis, and that inhibiting their expression (especially SREBP1) significantly improves lipid deposition in the cells[53-55]. The release of inflammatory factors IL-6 and TNF-α play a dominant role in the pathogenesis of GO. They are not only involved in the inflammation of orbital tissues, but are also closely associated with SREBP-mediated abnormalities in lipid metabolism[24]. Studies have shown that there is cross-regulation between inflammatory signaling pathways (e.g., NF-κB) and SREBP, and that the release of inflammatory factors may promote lipid synthesis through activation of SREBP, which in turn exacerbates the pathological process of GO[56, 57] .

7. Summary and Outlook

In conclusion, SREBP is upregulated in a variety of ocular pathologies and is involved in the development and progression of ocular diseases such as DED, DR, cataract, AMD, glaucoma, GO, etc., through a variety of pathophysiological processes such as abnormalities in lipid metabolism, inflammation, circadian rhythm disruption, neoangiogenesis, and cell migration. Given the critical role of SREBP in the above-mentioned diseases, interventions targeting the SREBP pathway may become a new therapeutic strategy. For example, the use of SREBP inhibitors (e.g., fatostatin), PPAR-γ modulators, or AMPK activators may improve the pathological process of related diseases. In addition, gene editing or RNA interference technologies are also expected to be used to modulate SREBP expression, thereby optimizing treatment options for ocular diseases. Future studies could further explore the specific mechanisms of SREBP in ocular diseases and develop more precise SREBP regulation strategies to provide new directions for clinical diagnosis and treatment.

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