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Research progress on the mechanism of RPE destroying blood-retinal barrier in diabetic retinopathy

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Abstract: Diabetes mellitus (DM) is a globally prevalent chronic disease, and diabetic retinopathy (DR), one of its complications, is a leading cause of vision impairment and blindness in the adult working population. The disruption of the blood-retinal barrier (BRB) serves as the key pathological basis for DR, with retinal pigment epithelium (RPE) cells and their tight junctions constituting the outer barrier of BRB and playing a pivotal role in the repair process. This review explores the structure and function of BRB and RPE cells, elucidates the mechanisms underlying pathological changes in BRB and RPE associated with diabetes mellitus, and highlights the significance of RPE in treating various diseases. By summarizing the actions undertaken by RPE in DR, this review underscores its crucial role in clinical management while offering novel insights into potential treatments for DR.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized primarily by hyperglycemia. It is highly prevalent worldwide, and its incidence is rising rapidly. Over the past few decades, the global number of people with diabetes has continued to climb, and it is projected that by 2045, the global diabetic population will reach 629 million [1]. In China, approximately 30% of diabetic patients suffer from diabetic retinopathy (DR) [2], and the overall prevalence of DR among all diabetic patients is approximately 35% [3]. Studies have shown that DR has become a major disease leading to visual impairment and blindness [4]. The traditional view holds that DR results from retinal microvascular damage caused by chronic hyperglycemia, accompanied by pathological changes in the retinal neuroglial network [5]. However, with deeper investigation into retinal pathology, it has been found that retinal neurodegeneration often precedes clinically detectable microvascular injury, which may lead to reduced visual contrast sensitivity and impaired dark adaptation. Disruption of the blood-retinal barrier (BRB) is a primary pathological basis of DR [6-7]. Retinal pigment epithelium cells (RPE) and their tight junctions constitute the outer BRB and play a critical role in BRB repair. Therefore, studying diabetic retinopathy from the perspective of structural and functional impairment of RPE is of great significance. Although the pathogenesis of diabetic retinopathy is complex, numerous studies have demonstrated that RPE injury is one of the key factors in diabetic

microangiopathy [7]. Thus, thoroughly exploring the mechanisms of RPE injury in DR, identifying effective therapeutic approaches, and elucidating their underlying therapeutic principles are of critical importance for the clinical treatment of DR. Although the pathogenesis of diabetic retinopathy is complex, numerous studies have demonstrated that RPE injury is one of the key factors in diabetic microangiopathy [7].

2. BRB and RPE cells: structure and main functions

2.1 Blood-retinal barrier (BRB)

The BRB is composed of retinal vascular endothelial cells, basement membrane, and tight junctions between RPE. It is divided into inner and outer layers, possesses selective permeability, and maintains retinal homeostasis. The continuous capillaries within the retina consist of endothelial cells, pericytes, and basement membrane. Endothelial cells form a seal through non-fenestrated tight junctions and have unidirectional active transport functions, while pericytes support vascular stability [8-9]. The BRB has a delicate structure and specialized functions, and its integrity is essential for normal retinal function. BRB dysfunction is associated with a variety of retinal and choroidal diseases involving the vasculature and pigment epithelium. In diabetic retinopathy, in particular, metabolic disturbances and microcirculatory impairment induced by hyperglycemia cause significant BRB damage, aggravating the progression of retinal vascular lesions [8]. BRB injury not only plays an important role in DR, but is also considered a key pathological factor in age-related macular degeneration (AMD), mainly involving RPE dysfunction. When the BRB is damaged, vascular permeability increases and inflammatory mediators are upregulated, leading to retinal cell apoptosis and neovascularization, thereby exacerbating disease progression [9]. In addition, retinal pericytes, neurons, glial cells, and vascular endothelial cells together constitute the BRB, providing an intact neural regulatory environment for the generation and transmission of visual signals [8]. In early DM, death of retinal endothelial cells leads to BRB disruption, and subsequent apoptosis of neural cells and pericytes further promotes retinal neurodegenerative changes, manifested as cell apoptosis and alterations in glial cells, especially loss of retinal ganglion cells, which impedes effective transmission of visual information to the brain [10-12]. Clinically [12,13], DR has two distinct stages. The first stage is non-proliferative diabetic retinopathy (NPDR), characterized by microaneurysms, increased permeability, and vascular occlusion and degeneration. Subsequently, some patients progress to proliferative diabetic retinopathy (PDR), whose hallmark is abnormal neovascularization in the retinal vasculature. These new vessels may extend from the retina into the vitreous cavity, where they impair vision secondary to leakage from abnormal new vessels and fibrosis. In the late stage of DR, patients may develop diabetic macular edema (DME), a condition in which fluid accumulates in the macular retina due to vascular leakage, causing retinal thickening. It is one of the main causes of vision loss in diabetic patients [14]. BRB disruption marks the transition of DR from the non-proliferative to the proliferative stage, representing a critical turning point. As DR progresses, retinal hypoxia and ischemia gradually worsen, further aggravating BRB damage. This triggers a series of pathological changes, including increased permeability of capillary endothelial cells, thickening of the basement membrane, capillary occlusion, and neovascularization [13-15].

2.2 Retinal pigment epithelium cells (RPE)

RPE are composed of approximately 4.2 to 6.1 million monolayer polygonal cells arranged in an orderly manner, and are divided into three parts: the apical portion, the main body, and the basal portion. One side of these cells lies adjacent to Bruch's membrane and the choroid, while the other side contacts the outer segments of photoreceptors. Their outer layer possesses specialized basal

membrane infoldings that increase surface area and facilitate substance exchange [15-17]. RPE lack regenerative capacity, and after cell death, neighboring cells fill the defect through lateral migration [18]. RPE play multiple critical roles in visual function [19-23]: first, by secreting various growth factors such as pigment epithelium-derived factor (PEDF) and vascular endothelial growth factor (VEGF), they regulate the physiological state of themselves and neural retinal cells, maintain retinal structural integrity, and influence the occurrence of various ocular diseases; second, they secrete erythropoietin (EPO) and employ antioxidant mechanisms to neutralize reactive oxygen species (ROS), protecting the retina from oxidative damage; third, they possess phagocytic function, clearing shed debris from photoreceptor outer segments to maintain retinal homeostasis, and their dysfunction is closely related to diabetic retinopathy; in addition [24-26], RPE are responsible for extracting nutrients such as glucose and retinol from the blood and transporting them to photoreceptors. In patients with high myopia, degenerative changes and pigment loss in RPE are associated with abnormal expression of subretinal vascular growth factors (such as decreased VEGF and PEDF), and abnormal expression of the ZNF644 gene in RPE may be involved in regulating related genes, suggesting its involvement in the pathogenesis of high myopia [27,28], although further studies are still needed for verification. Together, these functions support the critical role of RPE in maintaining retinal health and the visual cycle.

3. Possible mechanisms underlying diabetes-induced pathological changes in the BRB

The mechanisms by which DM induces BRB alterations mainly include the following [29]: first, hyperglycemia induces oxidative stress, impairing retinal microvascular endothelial cell function and disrupting BRB integrity; second, hyperglycemia activates the polyol pathway and the hexosamine pathway, leading to intracellular osmotic disturbance and cell damage, and increasing vascular permeability; third, advanced glycation end products (AGEs) cross-link with BRB proteins, altering protein structure and function and promoting vascular leakage; in addition, protein kinase C (PKC) is activated, further impairing endothelial function and enhancing permeability; fourth, in the diabetic state, the renin-angiotensin system (RAS) is activated, increasing vascular permeability and promoting inflammatory responses, thereby weakening BRB stability; fifth, levels of inflammatory factors such as tumor necrosis factor (TNF), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interleukin-8 (IL-8), and C-C motif ligand 2 (CCL2) are elevated, disrupting barrier structure; sixth, hyperglycemia promotes enhanced VEGF expression, increasing capillary permeability and endothelial cell proliferation, leading to BRB damage; seventh, the neurovascular unit (NVU) is impaired, disrupting coordination among retinal vascular cells, neurons, glial cells, and microglia, and affecting BRB maintenance and retinal blood flow regulation; finally, glutamate excitotoxicity promotes neural injury and imbalance of neuroprotective factors, indirectly disrupting the BRB. These factors act in an intertwined manner, collectively leading to BRB dysfunction and structural damage in diabetic retinopathy and endangering retinal health.

4. Possible mechanisms underlying diabetes-induced pathological changes in RPE

Under diabetic conditions, hyperglycemia damages RPE through multiple pathways, mainly manifested as increased oxidative stress, elevated expression of pro-inflammatory genes, impaired cell proliferation, and induction of endothelial-to-mesenchymal transition (EndMT), thereby weakening tight junctions and promoting various forms of cell death, including apoptosis, ferroptosis, and pyroptosis. A clinical study by Giovanni Sartore et al. found [30] that the occurrence of DR is not only related to chronic hyperglycemia but also closely associated with acute blood glucose fluctuations. A study by Irini P. Chatziralli et al. further demonstrated [31] that although hemoglobin A1c (HbA1c) level is an indicator of hyperglycemia, it does not fully correlate with the course of DR, whereas increased amplitude of blood glucose fluctuation is positively correlated with DR

progression [31], suggesting that blood glucose fluctuation plays an important role in the development of DR. RPE injury has been observed in diabetic animal models, where high glucose levels induce oxidative stress and increased expression of pro-inflammatory genes, leading to RPE dysfunction and further promoting the pathophysiological changes of DR [13,14,32-34]. Classical pathological pathways, including the polyol pathway, the hexosamine pathway, activation of the PKC pathway, and accumulation of AGEs, all induce excessive ROS production, forming a unified disease-promoting mechanism [35,36]. Excessive ROS generation not only causes retinal oxidative damage but also promotes retinal neovascularization. Meanwhile, the retinal antioxidant defense system is impaired under diabetic conditions, with decreased levels of glutathione (GSH), the major intracellular antioxidant, leading to free radical accumulation and exacerbation of oxidative stress injury [37]. Various plant extracts (such as tangeretin and hesperidin) and hypoglycemic drugs (including sodium-glucose cotransporter 2 inhibitors, metformin, and glucagon-like peptide 1 receptor agonists) have shown protective effects on RPE, potentially delaying DR progression by regulating RPE function and promoting cell survival [38]. RPE injury disrupts the retinal immune barrier, affects the choroidal blood supply to the retina, aggravates the hypoxic environment, and subsequently induces upregulation of VEGF expression, promoting choroidal neovascularization (CNV) and ultimately causing vision loss [39]. Unlike neovascular AMD, vision loss caused by non-neovascular AMD is usually progressive and may develop into geographic atrophy (GA), whose pathogenesis is closely related to RPE dysfunction, persistent oxidative stress, chronic inflammation, and abnormal lipid deposition [40]. The above mechanisms act in an intertwined manner, collectively causing RPE dysfunction, affecting retinal health, and driving DR progression [41]. Therefore, therapeutic strategies targeting these pathological processes are particularly important, including improving retinal microcirculation, strictly controlling blood glucose levels, and applying antioxidant therapy, with the aim of alleviating RPE injury, restoring retinal function, and thereby providing active intervention approaches for the treatment of diabetic retinopathy [41].

5. Mechanisms of RPE in the treatment of various diseases

RPE are essential for maintaining normal vision and function to reduce ultraviolet damage to the retina and internal neurons. They possess a complex metabolic system that effectively reduces excessive ROS accumulation and oxidative damage, thereby protecting the health and function of retinal cells. RPE dysfunction can cause a variety of retinal diseases, including retinitis pigmentosa (RP), AMD, and Stargardt disease (STGD) [42]. Recent studies have shown that mitochondrial damage and oxidative stress in RPE play a key role in the pathogenesis of AMD [42,43]. Chronic inflammatory responses are also important factors driving AMD progression. Drusen, formed by the accumulation of metabolic products between RPE and Bruch's membrane, is an important substance for complement system activation. This accumulation, together with oxidative stress, causes RPE damage and even death, which in turn triggers persistent inflammatory responses and promotes AMD progression [44]. Therefore, antioxidants and RPE protective agents have become key directions in AMD treatment, protecting RPE function by reducing oxidative stress levels. Notably, although RPE originate from the neuroectoderm, they still possess certain differentiation and proliferation capabilities under specific conditions, which brings new hope for using RPE to treat retinal degenerative diseases and inherited retinal disorders [45]. The mechanisms of exogenous RPE transplantation for treating AMD mainly include the following: first, through paracrine effects, the transplanted RPE secrete multiple cytokines to protect the host's remaining photoreceptor cells; second, reconstruction of physiological structures, promoting the integration of transplanted RPE with host RPE and photoreceptor cells, and restoring the retinol-retinal cycle and synaptic connections; third, inhibition of microglial activation, gliosis, and production of inflammatory factors

in the diseased microenvironment, alleviating retinal inflammation and damage. Stem cell-based therapies have shown promising prospects in the treatment of retinal degenerative diseases such as AMD, with the goal of restoring retinal structure and function by reestablishing the interaction between the retina and photoreceptors.

In summary, RPE play a central role in maintaining retinal health, visual function, and the pathological mechanisms of retinal diseases. Related therapeutic strategies focus on protecting, repairing, and regenerating RPE, providing multiple potential approaches for the future clinical treatment of retinal diseases.

6. Possible mechanisms of RPE in the treatment of DR

In DR, RPE exert key protective effects through multiple mechanisms. RPE secrete PEDF, which has anti-angiogenic, antioxidant, anti-inflammatory, and neurotrophic functions, inhibiting the formation of pathological neovascularization and alleviating inflammatory responses. At the same time, RPE possess strong antioxidant capacity and contain SOD, catalase (CAT), and antioxidant substances such as carotenoids and glutathione, which can effectively scavenge ROS and protect retinal cells from oxidative damage [45,46]. Their phagocytic function is responsible for clearing cellular debris shed from photoreceptor outer segments and maintaining retinal structural stability, but this function is susceptible to impairment under diabetic conditions, promoting the development of DR. In addition, RPE participate in retinol metabolism and visual pigment regeneration; defects in related genes such as RPE65 and LRAT can cause retinal lesions. PEDF also protects RPE from damage by inhibiting inflammatory responses and reducing complement activation and persistent inflammation caused by drusen formed from metabolic waste accumulation. The pathogenesis of DR also involves mitochondrial dysfunction and AGE accumulation, and PEDF may regulate these pathological processes. Meanwhile, RPE further prevent the occurrence and progression of DR by influencing the Wnt/β-catenin signaling pathway, mitochondrial uncoupling proteins (UCPs), the nuclear factor kappa-B (NF-κB) pathway, and peroxisome proliferator-activated receptor γ (PPARγ) [46,47]. In summary, RPE play an important role in the pathophysiology of DR through the secretion of PEDF, multiple antioxidant and anti-inflammatory mechanisms, maintenance of phagocytic and metabolic functions, and regulation of signaling pathways, providing a theoretical basis for the development of novel therapeutic strategies.

7. Conclusions

The development of DR is closely related to BRB injury. Although the specific mechanisms of this injury have not been fully elucidated, they involve complex interactions among multiple factors. In-depth investigation of these factors and their mechanisms of action is of great significance for developing more effective therapeutic strategies. Because RPE injury is often irreversible, the treatment of DR requires not only strict control of systemic medical indicators such as blood glucose, blood pressure, and blood lipids, but also greater emphasis on repairing damaged RPE to restore retinal function. As understanding of the mechanisms of RPE in the pathology and treatment of DR continues to deepen, more innovative therapies are expected to emerge in the future. These therapies will more effectively protect and repair RPE, thereby improving visual outcomes and quality of life in patients with DR.

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