

Research Progress on Pathogenesis and Related Inflammatory Factors of Macular Edema Secondary to Retinal Vein Occlusion

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Abstract: Retinal vein occlusion (RVO) is a relatively common retinal vascular disease characterized by vascular obstruction due to thrombus from various causes, resulting in retinal hemorrhage, fluid exudation, and varying degrees of retinal hypoxia and ischemia, and its secondary macular edema (ME) is the main cause of patients' impaired vision. Retinal vein occlusion secondary to macular edema is a pathophysiological process involving multiple factors, with a complex pathogenesis and many cytokines involved, resulting in an imbalance of fluids entering and transferring out of the retina, which leads to the formation of ME^[1]. In recent years, with the development of molecular biology techniques, inflammatory factors associated with RVO-ME have become an important aspect in the study of RVO-ME. In this paper, we review the inflammatory factors associated with retinal vein occlusion secondary to macular edema and the pathogenesis of RVO-ME.

1. Introduction

Retinal vein occlusion can be divided into central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) according to the site of occlusion. Retinal vein occlusion is a retinal vascular disease in which the retinal veins are dilated and tortuous, leading to retinal hemorrhage, edema, and exudation as the main fundus manifestations, and its secondary macular edema is the most common complication of RVO, and it is also usually the most important cause of vision loss, and the long-term macular edema can cause irreversible damage to vision^[2-3]. The pathogenesis of RVO is complex, and it is currently believed that RVO is caused by impaired retinal blood circulation, ischemia and hypoxia in the retinal vein distribution area, elevated intraocular VEGF levels, and altered cell permeability, resulting in disruption of the blood-retinal barrier (BRB) and disruption of the balance of fluid in and out of the retina, and thus the formation of macular edema, and studies have shown that cytokines, such as inflammatory factors, are also involved in its development^[4].

Inflammatory processes play a crucial role in ME secondary to RVO, and a number of studies have shown elevated levels of some inflammatory factors in the atrial fluid and vitreous of patients with

ME secondary to RVO[5]. Intravitreal injections of steroidal hormone drugs are effective in the treatment of RVO-ME[6], and also indirectly demonstrate that inflammation is associated with the pathogenesis of macular edema secondary to RVO.

2. Inflammatory factors associated with RVO-ME

2.1 TNF- α

As an important pro-inflammatory factor, TNF- α can improve the permeability of vascular endothelial cells, increase blood leakage, and promote the release of other cytokines. TNF- α can increase the permeability of retinal blood vessels, and its expression is abnormally high in aqueous humor in RVO patients, which is related to blood-retinal disorders, and is an important factor affecting the development and outcome of RVO. TNF- α can induce excessive secretion of retinal extravascular matrix, cause the proliferation of blood vessel wall cells, lead to the formation of new blood vessels in the eye, induce endothelial cell death, and destroy the blood-retina barrier. It can act on macrophages, make them secrete more inflammatory cytokines, and further enhance the ocular inflammatory response; TNF- α can also cause abnormal apoptosis of retinal ganglion cells^[7]. Jung et al.^[8] studied the relationship between the concentration of inflammatory factors in aqueous humor and the development of retinal ischemia and the recurrence of macular edema in RVO patients, and found that the level of TNF- α was overexpressed in aqueous humor in RVO patients, and the increased level of TNF- α at the initial onset was correlated with the severity of retinal ischemia in the later stage.

2.2 Interleukin

Interleukins are cytokines produced by white blood cells, stromal cells and endothelial cells, and play an important role in the regulation of immunity, hematopoietic and inflammatory processes. More than 30 kinds of interleukins have been reported^[9]. IL-1, IL-6 and IL-8, which are closely related to RVO-ME, are described here.

2.2.1 IL-1

IL-1, a key signaling molecule in both the innate and adaptive immune systems, is a highly potent inflammatory cytokine, available in two common forms of IL-1 α and IL-1 β , mediating inflammatory responses to a variety of stimuli. In the state of ischemia and hypoxia, IL-1 β is overexpressed by microglia and Muller cells in the retina, leading to structural and functional damage of RPE cells, resulting in damage of the blood-retinal barrier (BRB), increased vascular leakage, and accelerated development of ME. Recent studies have shown that the concentration of IL-1 α and IL-1 β in aqueous humor of patients in RVO group is significantly higher than that in control group, confirming that IL-1 α and IL-1 β are overexpressed in RVO.

2.2.2 IL-6

IL-6 is a multifunctional pro-inflammatory cytokine that participates in the immune response of the body and is a pro-inflammatory response. IL-6 increases vascular endothelial permeability by disrupting cellular tight junctions, and its action on vascular endothelial cells induces vascular endothelial cell growth and up-regulates the expression of VEGF thus indirectly inducing neovascularization^[10]. When RVO occurs, IL-6 mRNA expression increased in a time-dependent manner, further deepening ME.

2.2.3 IL-8

IL-8 is a potent chemokine produced mainly by monocyte-macrophages and is an activator of neutrophils and T-lymphocytes. IL-8 also promotes neoangiogenesis and tumor metastasis, and its role in retinal vein occlusion is demonstrated in the promotion of angiogenesis. IL-8 production is caused by the exposure of vascular endothelial cells to hypoxia and high levels of VEGF stimulation, which regulates vascular endothelial permeability by activating the NF- κ B signaling pathway to down-regulate tight junctions, altering the endothelial cell tight junctions and disrupting the blood-retinal barrier. Fonollosa et al. ^[11] demonstrated that the intravitreal levels of IL-8 in patients with BRVO were significantly elevated in comparison to the controls, suggesting that there is a correlation between IL-8 and the degree of macular edema.

2.3 MCP-1

MCP-1 belongs to the chemokine family. Its expression is increased by retinal hypoxia, atherosclerosis, and oxidative stress, and it promotes vascular endothelial activation, adhesion, induction of vascular endothelium, and overexpression of extracellular matrix, leading to vascular occlusion, which triggers the formation of microthrombi and neovascularization^[12]. In the retina, MCP-1 can promote the phosphorylation of endothelial cell tight junction proteins, activate monocyte macrophages to produce inflammatory factors, such as TNF- α , disrupt the blood-retinal barrier, increase the permeability of the retinal vasculature, and cause abnormal fluid entry and exit, which then leads to ME.

2.4 ICAM-1

ICAM-1 is an adhesion molecule, glycoprotein that mediates cell adhesion to the extracellular matrix. ICAM-1 is expressed by normal retinal pigment epithelial cells and is involved in cell activation, adhesion, and movement. Retinal hypoxia upregulates ICAM-1 mRNA and protein expression. Upregulation of ICAM-1 expression induces leukocyte stagnation because of increased leukocyte rolling and adherence to the vascular wall, which causes more inflammatory factors adhering to the retinal vessel wall, blood flow stagnation, decreased blood flow velocity, and thrombus formation within the vessel wall, leading to impaired venous return and exacerbating the fundus reaction in RVO. It has been shown that sICAM-1 is significantly elevated in the vitreous cavity of BRVO patients compared to controls, which is related to the degree of macular edema^[13].

3. Pathogenesis of RVO-ME

3.1 VEGF and VEGF receptors

VEGF is a cytokine activated by hypoxia-inducible factors, and thus its expression is upregulated in hypoxia, which promotes phosphorylation of tight junction proteins between endothelial cells, increases vascular permeability, and causes disruption of the blood-retinal barrier. Studies have confirmed that hypoxic retinal tissue in RVO releases angiogenic mediators, such as VEGF and inflammatory mediators, which induce macular edema, vitreous hemorrhage and neovascular glaucoma. During the occurrence of RVO, retinal venous blood return is obstructed, intravascular pressure rises, venous obstruction of blood stagnation causes capillary non-perfusion and tissue ischemia and hypoxia, and inflammatory factors are thus released to promote the outflow of intravascular substances, resulting in the production of large amounts of exudate and hemorrhage

from the accompanying veins and the formation of ME^[14]. In recent years, relevant basic and clinical studies have found that the concentration of VEGF in the vitreous cavity and atrial fluid of patients with RVO secondary ME is higher than that of normal people, and VEGF is the main cause of ocular pathologic neovascularization and a potent mediator of vascular permeability, leading to vascular leakage, and the level of VEGF is positively correlated with the degree of macular edema, which confirms that there is a close relationship between VEGF and the development and occurrence of RVO secondary ME. close relationship between VEGF and the occurrence and development of ME secondary to RVO. Retinal glial cells, retinal pigment epithelial cells, and vascular endothelial cells all express VEGF through cells in the retina. VEGF increases vascular permeability, promotes endothelial cell proliferation, forms neovascularization, and prompts the expression of a series of inflammatory factors, deepening the inflammatory response in patients with RVO-ME, increasing vascular permeability, and increasing fluid leakage.

VEGF signaling is initiated by binding to receptors, two of which (VEGFR-1 and VEGFR-2) are expressed in the retina. Binding of VEGF to the receptors activates autophosphorylation, and transphosphorylation induces a signaling cascade response. Binding of VEGF to receptors expressed by vascular endothelial cells, monocytes, and macrophages promotes macular edema formation. In addition, there is clinical and experimental evidence that both sVEGFR-1 and sVEGFR-2 may influence vascular permeability during inflammatory responses, as VEGF acts as a chemokine for inflammatory cells through its receptor^[15], suggesting that VEGF may promote inflammation and increase vascular permeability, suggesting that the VEGF receptor has an important role in the pathogenesis of macular edema.

3.2 Activation of microglia

Microglia, a class of mononuclear macrophages present in the central nervous system, as the main immune cells of the retina, are mainly involved in inflammatory reactions and play an important role in maintaining the stable state of the retinal microenvironment. Under normal conditions, retinal microglia are resting, located in the inner and outer follower layers, and exercise immune defense mechanisms. Under pathological conditions, RVO leads to retinal tissue damage, ischemic and hypoxic environment, activated microglia transform from branching to amoeboid, show proliferation and migrate to the damaged parts of ischemic and hypoxic regions, phagocytosis increases, inflammatory reaction occurs, vascular permeability increases, the blood-retinal barrier is damaged, and MEs are formed. Andreas E et al. ^[16] showed that in the BRVO animal experiments, the number of activated microglia around the perfusion-free region of retinal vein vascular obstruction was significantly increased.

3.3 Disruption of the blood-retinal barrier

The normal retina has two blood-retinal barriers that keep it dry and transparent, the inner and outer retinal barriers. The inner retinal barrier is formed by closed bands between retinal capillary endothelial cells plus astrocytes, Müller cells, and pericytes in the wall, and the outer retinal barrier is composed of retinal pigment epithelial cells and their tightly connected closed bands. The well-functioning blood-retinal barrier ensures the balance of water and molecular substances in and out of the retina and maintains the stability of the inner retinal environment. When retinal vein occlusion occurs, ischemia and hypoxia occur in the vascular tissues along the venous distribution area of the blocked area, capillary endothelial cells and nerve cells activate VEGF and related inflammatory factors under hypoxia^[17], and the vascular permeability is increased, and the macular fluid leaks outside the blood vessels, thus resulting in ME. In addition, the formation of the capillary non-perfusion zone and the sensitivity of the RPE cells to the hypoxic and ischemic environment lead to

the massive secretion of VEGF, which affects the cells and the blood-retinal environment. VEGF affects the expression of cellular tight junction proteins, which further increases vascular permeability, disrupts oBRB, and forms ME[18].

3.4 Müller cell dysfunction

Müller cells are the largest proportion of glial cells in the retina, accounting for 90% of retinal glial cells, with their nuclei located in the inner nuclear layer and their protrusions distributed throughout the retina. Müller cells carry out retinal intertissue water-liquid transport mainly through the regulation of water channel proteins. Müller cells provide nutritional support and metabolic waste to the retina through water-liquid transport, and the main water channel protein involved is AQP4. Müller cells regulate the interstitial potassium levels in the retinal cells, and their cell membranes express a variety of potassium channel proteins, mainly the inwardly rectifying potassium channel Kir4.1^[19]. Under normal conditions, retinal intertissue aqueous fluid is transported through AQP4 expressed by Müller cells, and the Kir4.1 potassium channel is coupled with water channel proteins, and the fluid produced by neuronal excitation increases osmolality, and potassium ions and aqueous fluid then enter the retinal capillaries, completing aqueous fluid drainage and preventing cellular edema and tissue fluid accumulation. In the pathological state, the ischemic and hypoxic environment causes Müller cells to down-regulate Kir4.1 expression through the expression of water channel protein 4, and water-potassium transport is dysregulated, with increased uptake of potassium ions into the cells and increased flow of water into the cells, resulting in retinal edema.

3.5 Damage to the retinal pigment epithelium

The retinal pigment epithelium is a layer of regular polygonal cellular tissue located between the neurosensory layer of the retina and the choroid. RPE cells, together with Bruch membrane and the choroid, are involved in the composition of the choroid-blood-retinal outer barrier. As a kind of barrier cell, the RPE cells, through its expression of AQP1, strictly control the transportation of aqueous, nutritive, and metabolic substances in and out of the retina between the choroid and the retina to maintain normal retinal function and visual circulation^[20]. Studies have shown that oxidative stress and inflammation can lead to RPE cell damage, and RPE damage affects the water transport by AQP1, leading to fluid accumulation in the subretinal space and promoting ME formation.

4. Summarization and prospect

In summary, the pathogenesis of ME secondary to RVO is complex, with the involvement of multiple cytokines and inflammatory mediators. This article describes the pathogenesis of ME secondary to RVO in terms of impaired Müller cell function, activation of microglia, impaired RPE cell function, and disruption of the blood-retinal barrier. VEGF increases the expression level of a range of inflammatory factors, increases endothelial cell permeability, and affects BRB function. The ischemic and hypoxic environment and inflammatory cells induce retinal neovascularization, increase retinal vascular permeability, and impede fluid drainage from the retina, followed by macular edema. Therefore, the mainstream treatment for RVO-ME is anti-VEGF drugs, laser photocoagulation, hormonal anti-inflammatory drugs, etc., supplemented by traditional Chinese medicine (TCM), and different treatment methods are adopted according to different patients. At the same time, the activation of immune cells after the occurrence of RVO, inflammatory factors as an important factor causing RVO-ME, so clarify the mechanism of inflammatory factors and further research is important for the targeted treatment of RVO-ME, to provide a reference for the clinical prevention and treatment of visual impairment. In this paper, we only initially discussed the pathogenesis of RVO in terms of

inflammatory factors, and its mechanism in terms of oxidative stress, neoangiogenesis, apoptosis, and gene expression still needs to be further explored in depth.

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