• Review Article •

Insights into the pathogenesis of cystoid macular edema: leukostasis and related cytokines

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Abstract

• Cystoid macular edema (CME) is the abnormal collection of intraretinal fluid in the macular region, especially in the inner nuclear and outer plexiform layers. CME leads to severe visual impairment in patients with various retinal diseases, such as diabetic retinopathy, retinal vascular occlusion, choroidal neovascularization, and uveitis. Although various retinal conditions lead to CME, a shared pathogenesis of CME is involved in these diseases. Accordingly, the pathogenesis of CME based on vasogenic mechanisms is first discussed in this review, including vascular hyperpermeability, leukostasis, and inflammation. We then describe cytotoxic mechanisms based on retinal Müller cell dysfunction. This comprehensive review will provide an understanding of the pathogenesis of CME for potential therapeutic strategies.

• **KEYWORDS:** cystoid macular edema; cytokine; leukostasis; pathogenesis
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INTRODUCTION

Macular edema is defined as the swelling or thickening of the neurosensory retina within the macular region, which results from fluid collection within or below the retina[1]. Cystoid macular edema (CME) is a type of macular edema characterized by the formation of radially oriented multiple cyst-like spaces within the neurosensory retina[1-2]. Excess fluid predominantly accumulates in the inner nuclear layer and the outer plexiform layer of Henle[2].

Diabetic retinopathy and retinal vascular occlusions are the most common underlying diseases of CME[1-2]. CME may also be complicated in severe hypertensive retinopathy, uveitis, macular telangiectasia, vitreoretinal interface abnormalities, or following intraocular surgery[1]. This is a nonspecific sequela of many ocular diseases, which eventually cause impaired central vision. The pathophysiological mechanisms vary from the underlying etiologies, while there are also common features of CME essential for the development of therapeutic strategies.

In this review, we focus on the common pathophysiology of CME, regardless of underlying retinal diseases. We first discuss the pathophysiology based on vasogenic mechanisms, including vascular hyperpermeability and inflammation, and then describe cytotoxic mechanisms based on retinal Müller cell dysfunction.

MECHANISMS OF TISSUE EDEMA

Starling's Principle of Fluid Exchange The occurrence and amount of edema in microcirculation are determined from Starling's equation[3-4]. The two main driving forces for the movement of fluid across the capillary wall are the transcapillary hydrostatic pressure difference and the effective osmotic pressure difference[3-4]. In ordinary tissues, except the brain and the eye, there is a semipermeable membrane that allows fluid movement across the capillary wall through a combination of transcellular and paracellular pathways[2]. There is a net inflow of fluid into the venous side of the capillary in ordinary tissues, according to Starling's equation[2]. Active water channels like aquaporins act as major transcellular pathways at endothelial membranes[5-6].

Any changes of hydrostatic pressure, osmotic pressure, or vascular permeability disrupting the balance of fluid movement result in fluid collection, *i.e.*, tissue edema. These imbalances resulting from the difference of the outflow and inflow at the capillary level can be modified by the lymphatic system in ordinary tissues, while no lymphatic system has been found in the eye[2].

Unique Features of the Retina Besides the absence of a lymphatic system, the retina, especially the macula, has unique anatomical features, so that its response differs with regard to common insults like ischemia or inflammation. Unlike other body tissues, the accumulation of fluid is confined to the macular region, without involving the whole retina. This might be due to specific anatomical features of the macula.

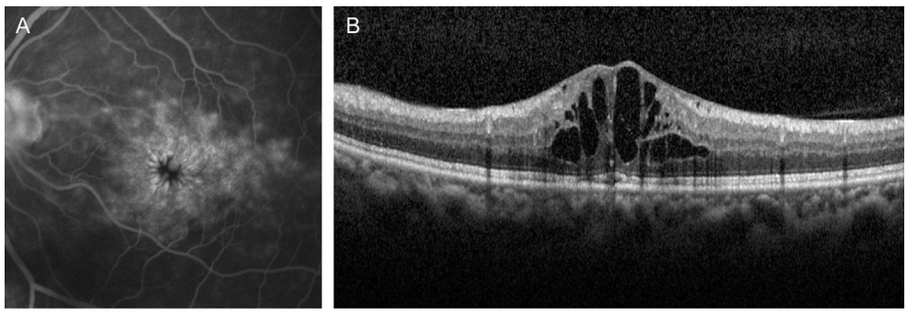

Figure 1 Fluorescein angiography (A) and optical coherence tomography (B) of a patient with pseudophakic cystoid macular edema (Irvine-Gass syndrome).

The macula is a highly specialized region of the retina that ensures precise vision. The fovea, the central area of the macula, contains an extremely high cellular density, resulting in high metabolic activity. The center of the fovea is composed of cone photoreceptors and specific retinal Müller cells, and is generally avascular due to centrifugal movement of inner retinal layers during development[1,7]. The axons of photoreceptors and retinal Müller cells become longer and densely packed in the foveal region, while deviating away from the center to form Henle's fibers[8-9]. These connecting fibers located in the outer plexiform layer provide a potential space for fluid accumulation because of loose lateral binding[8]. The inner nuclear layer as well as the ganglion cell layer are also displaced laterally[9], so that these features contribute to "cyst" formation around the fovea in pathological conditions. These features appear as a petaloid pattern of fluorescein dye accumulation in fluorescein angiography and intraretinal cystoid spaces in optical coherence tomography (OCT; Figure 1). Clinical studies based on fluorescein angiography and OCT show enlarged foveal avascular zones and microaneurysms around the perifoveal capillary network, suggesting that ischemia and leakage from these microaneurysms may cause CME[10].

Intraocular Fluid Movement and Cyst Formation The retina is resistant to fluid and macromolecular movement from the vitreous to the choroid, functioning as a relative barrier. However, small amounts of fluid seep into the retinal interstitial tissue due to intraocular pressure[11]. Retinal pigment epithelial cells remove excess fluid from the retina to the choroid by active transport, while retinal Müller cells remove fluid from the retinal interstitial tissue[12-14]. Excess fluid accumulates under the neurosensory retina following intraretinal accumulation, which is usually absorbed by the healthy retinal pigment epithelium (RPE). RPE cells function like the lymphatic system of other tissues, to maintain retinal attachment, along with choroidal osmotic pressure, and keep the subretinal space dry[15].

The histological characteristics of internal and external limiting membranes may explain cyst formation in specific retinal layers during CME. The internal limiting membrane consists of basement membranes of retinal Müller cells, which do not provide resistance to water or solute movement from the vitreous to the choroid[11]. However, the external limiting membrane formed by adherent junctions between retinal Müller cells and inner segments of photoreceptors act as a barrier, although it is not as tight as the tight junctions between the RPE[11]. Albumin and other proteins that accumulate in the interstitial spaces increase the osmotic pressure near the external limiting membrane, attracting water and developing macular edema[11]. The synaptic portions of the outer and inner plexiform layers also act as high resistance barriers against fluid movement[11], resulting in fluid from the intermediate and deep capillary plexus accumulating in the inner nuclear layer, resulting in cyst-like configurations.

VASOGENIC MECHANISMS: EXTRACELLULAR EDEMA

Blood-Retinal Barrier The brain and the eye share common features related to vascular permeability, involving the blood-brain barrier and blood-retinal barrier (BRB), respectively. The BRB regulates the passage of ions, proteins, and water flux between retinal vessels (intravascular compartment) and retinal tissues (extraretinal compartment), and prevents leakage of macromolecules[16]. In the retina, there are two BRBs, which act as physical and chemical barriers to regulate immune cell passage and prevent the influx of harmful toxins[16]. The inner BRB consists of non-fenestrating endothelial cells, tight junctions between endothelial cells, and surrounding pericytes and glial cells[16-17]. The outer BRB is formed by tight junctions between the RPE and the external limiting membrane, separating the neurosensory retina from the fenestrated choriocapillaris[16-17].

Increased levels of vascular endothelial growth factor (VEGF) and hepatic growth factor in ischemic or inflammatory conditions lead to damage of occludins and trigger internalization of tight junction complexes in endothelial and RPE cells[18]. Because pericyte-derived lipidic mediators modulate the inner BRB, dysfunctions of pericytes also contribute to the breakdown of the BRB[1]. In addition, any conditions involving

metabolic dysfunctions may affect RPE function, which is crucial for the regulation of solutes and water transport in the healthy retina[13,19]. Accordingly, breakdown of the BRB facilitates a fluid shift from the intravascular compartment to interstitial spaces, resulting in vasogenic edema.

Enhanced Vascular Permeability The two main blood supplies for the retina are from the choroidal and from retinal circulation. The choroid, a highly vascularized tissue between the retina and the sclera, supplies nutrients and oxygen to the outer-third of the retinal layer by diffusion[20]. The inner two-thirds of the retina is supplied by the retinal capillaries arranged in three layers: the superficial capillary plexus located in the nerve fiber and ganglion cell layers, and the intermediate and deep capillary plexus located in the inner nuclear layer[21]. However, an adequate retinal capillary supply is lacking at the fovea, which makes the fovea more vulnerable to ischemic vascular insults, resulting in macular edema[22].

Pericytes reinforce the tightness of capillary walls by ensheathing the endothelial cells[18,23]. The ratio of pericytes to endothelial cells is very high in the retina, compared to other body tissues[18,23]. Pericytes and endothelial cells share their basement membranes, and communicate *via* gap junctions and paracrine signal molecules[24]. These shared basement membranes act as a regulatory matrix for the passage of molecules, although it is not a real diffusion barrier. The contractile properties of pericytes may play an important role in the autoregulation of retinal capillaries[25]. Loss of pericytes, well known as a hallmark of early diabetic retinopathy, results in the breakdown of the BRB and increased vascular permeability[18,26].

Inflammation Inflammation increases the vascular permeability through enhanced migration of immune cells, followed by breakdown of the BRB. Inflammation of the retina occurs not only in inflammatory diseases such as uveitis or ocular infections but also in diabetic retinopathy and age-related macular degeneration[27]. It is widely involved in many retinal diseases, leading to macular edema. In healthy eyes, the BRB separates the immune-privileged retina from blood-derived soluble factors, and excludes the entry of leukocytes[18-19]. However, the breakdown of BRB due to inflammatory mediators and growth factors results in leukocyte infiltration, which in turn provides more cytokines and chemokines[28]. Activated endothelial cells, microglial cells, infiltrating monocytes, and retinal Müller cells are considered to be the main source of proinflammatory cytokines in the retina[29].

Leukostasis In acute inflammatory conditions, the following vascular reactions eliminate the initial insults: dilation of small vessels, increased blood flow, increased vascular permeability, leakage of plasma proteins, and migration of leukocytes[29-30]. Recruited leukocytes accumulate along with vascular endothelial cells, which in turn activate these cells by releasing cytokines such as tumor necrosis factor-alpha (TNF-α) or interleukin-1 (IL-1)[31]. Cytokines and chemokines secreted by endothelial cells, microglia, and perivascular leukocytes increase the affinity between integrins of endothelial cells and their leukocyte receptors, resulting in firm adhesion of leukocytes to the endothelium[31]. Adherent leukocytes are also associated with capillary endothelial damage as well as the obstruction of the microvasculature, leading to capillary non-perfusion, ischemic damage, and vascular leakage[30,32]. They contribute to the disruption of tight junctions and the breakdown of the BRB induced by the induction of fenestrations and vesiculo-vacuolar organelles[8,27].

In clinical observations using OCT angiography, compromised deep capillary plexus flow due to inflammation was suggested to be the main reason for CME. It has been hypothesized that excess fluid originating from superficial retinal vascular areas may be absorbed through the deep capillary plexus or the action of retinal Müller cells, depending on the deep capillary plexus[2]. The absence of deep capillary plexus flow due to leukostasis leads to the accumulation of fluid in the form of cysts within the retina.

Vascular endothelial growth factor Cytokines associated with macular edema have been investigated in studies with diabetic retinopathy and retinal vascular occlusions[2,33]. VEGF is a well-known proinflammatory mediator involved in many retinal vascular disorders. VEGF is produced mainly in retinal Müller cells, and inhibition of Müller cell-derived VEGF results in decreased expression of TNF-α and intercellular adhesion molecule-1 (ICAM-1)[33-34]. VEGF triggers and potentiates inflammation by recruiting leukocytes, while inflammatory conditions also inversely stimulate VEGF expression.

VEGF-A is a key regulator of vasculogenesis and angiogenesis among VEGF subtypes, whose level is elevated in response to hypoxia in the retina[35]. It binds to two tyrosine kinase receptors, *i.e.*, vascular endothelial growth factor receptor (VEGFR)-1 and VEGFR-2, and mediates vascular hyperpermeability by increasing both paracellular and transcellular permeabilities[1]. Among different forms of VEGFR, VEGFR-2 is the main receptor for most responses of vascular endothelial cells to VEGF under both physiological and pathological conditions[36]. VEGFR-2 serves as the major mediator of the angiogenic and permeability-enhancing effect of VEGF[35]. VEGF is therefore critical to the breakdown of BRB and vascular hyperpermeability, *via* inducing fenestration of endothelial cells and phosphorylating the tight and adherent junctional proteins of the BRB[18].

Intravitreal anti-VEGF injections are widely used to treat macular edema including CME associated with diabetic retinopathy, retinal vascular occlusions, and other retinal diseases. Commercially available anti-VEGF agents not only inactivate VEGF but also alleviate secondary inflammatory reactions mediated by VEGF[2,37]. Corticosteroids also improve CME by reducing both inflammation and VEGF expression, so that their actions are sometimes more effective than anti-VEGF agents in CME associated with diabetes[34,38].

Other inflammatory cytokines Besides VEGF, there are multiple cytokines involved in the pathogenesis of CME. It is well-known that levels of several cytokines are elevated in eyes with macular edema secondary to diabetic retinopathy and retinal vein occlusions: TNF-α, interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1), pigment epithelium-derived factor, and ICAM-1[27] are found in elevated amounts in ocular fluids with CME, which may be the cause and also the result of macular edema[1]. However, there is also evidence of inflammatory pathways in CME, such as the clinical efficacy of intravitreal corticosteroid for CME secondary to retinal vascular diseases[39].

TNF-α, mainly produced by macrophages and dendritic cells, recruits inflammatory cells by inducing the expression of proangiogenic molecules[1]. This is also associated with tissue damage via reactive oxygen species (ROS), followed by the breakdown of the BRB. Corticosteroids reduce proinflammatory mediators associated with vascular leakage including VEGF and TNF-α[2,40]. They also increase the expression of occludin, which in turn may improve the functioning of tight junctions[2]. Anti-TNF-α agents have been recently introduced for the treatment of refractory CME in diabetic retinopathy or uveitis, although their roles in first-line therapy need further investigation[41-42].

IL-6 is another important cytokine in acute inflammatory responses, secreted by macrophages, vascular endothelial cells, and fibroblasts[43]. IL-6 has been detected in ocular fluids derived from diabetic macular edema, which stimulates VEGF production and leads to the breakdown of the BRB[44]. Intraocular implants that allow sustained release of corticosteroid or intravitreal injections of corticosteroids are currently used for the treatment of macular edema[45].

Ischemic Hypoxia The retinal vasculature shows relatively low blood flow rate, while a high blood flow rate is noted in choroidal circulation[25,46]. As the retina supply is dual but not overlapping with these two circulations, the oxygen tension is lowest in the watershed zone, making the retina doubly vulnerable to ischemia[47]. Vasoactive substances are released by endothelial cells and glial cells in the response to hypoxia.

Nitric oxide and nitric oxide synthase Enhanced production of nitric oxide (NO) *via* nitric oxide synthase (NOS) has been reported in hypoxic retina[48]. Among NOSs, neuronal nitric oxide synthase (nNOS) and endothelial nitric oxide synthase (eNOS) are constitutively expressed, while inducible nitric oxide synthases (iNOSs) are stimulated by intracellular calcium-dependent pathways during hypoxic conditions[48]. The iNOS is produced by glial cells and infiltrating leukocytes, and NO produced by iNOS and nNOS contributes to cytotoxic effects on ganglion and glial cells[48]. The eNOS produces NO under low oxygen conditions, which in turn dilate vessels to provide blood flow to ischemic retinal areas. However, this process is also associated with BRB breakdown involved in VEGF-induced vascular hyperpermeability[49].

Oxidative stress Under hypoxic conditions, oxidative stress occurs due to the imbalance between production and removal of ROS. ROS affect the integrity of the BRB through disruption of tight junction proteins, adherent tight junction proteins, and the cytoskeleton[29,48]. Because retinal endothelial cells possess low levels of superoxide dismutase while releasing high levels of superoxide, they are more vulnerable to oxidative stress[25]. Hypoxia also triggers activation of hypoxia-inducible transcription factors (HIF), whose accumulation upregulates various genes associated with vasodilation and angiogenesis[50]. Overexpression of HIF-2α in retinal Müller cells appears to induce the breakdown of the BRB[46].

Angiotensin I and II, the peptides of the renin-angiotensin system, are found in higher concentrations in the retina and the choroid than in the plasma[51]. Angiotensin II potentiates oxidative stress and inflammatory responses by promoting leukocyte recruitment. Leukostasis is promoted *via* upregulation of adhesion molecules like selectins and integrins, and release of cytokines and chemokines like IL or MCP-1[8]. Angiotensin II also causes pressure-mediated mechanical injury to endothelial cells and activates VEGF expression *via* transactivation of human epidermal growth factor receptors, which in turn lead to the breakdown of the BRB[43,51-52].

CYTOTOXIC MECHANISMS: INTRACELLULAR EDEMA

Retinal Müller Cell Dysfunction CME occurs as a result of cytotoxic events like glial cell swelling. Retinal Müller cells are important for the functioning of retinal glial cells, because they regulate the fluid and ion homeostasis and preserve the functioning of the BRB[53-54]. These cells also contribute to the survival of ganglion cell neurons and photoreceptors, modulate inflammatory and immune responses, and stabilize retinal structure[54-55]. Fluid movement from retinal Müller cells to the vitreous or to blood vessels is associated with aquaporin-4, a water-selective channel[56], along with potassium ion transportation through Kir channels. Surges in potassium ions from abnormal neural functioning or from altered homeostasis caused by diseases such as retinal ischemia can result in

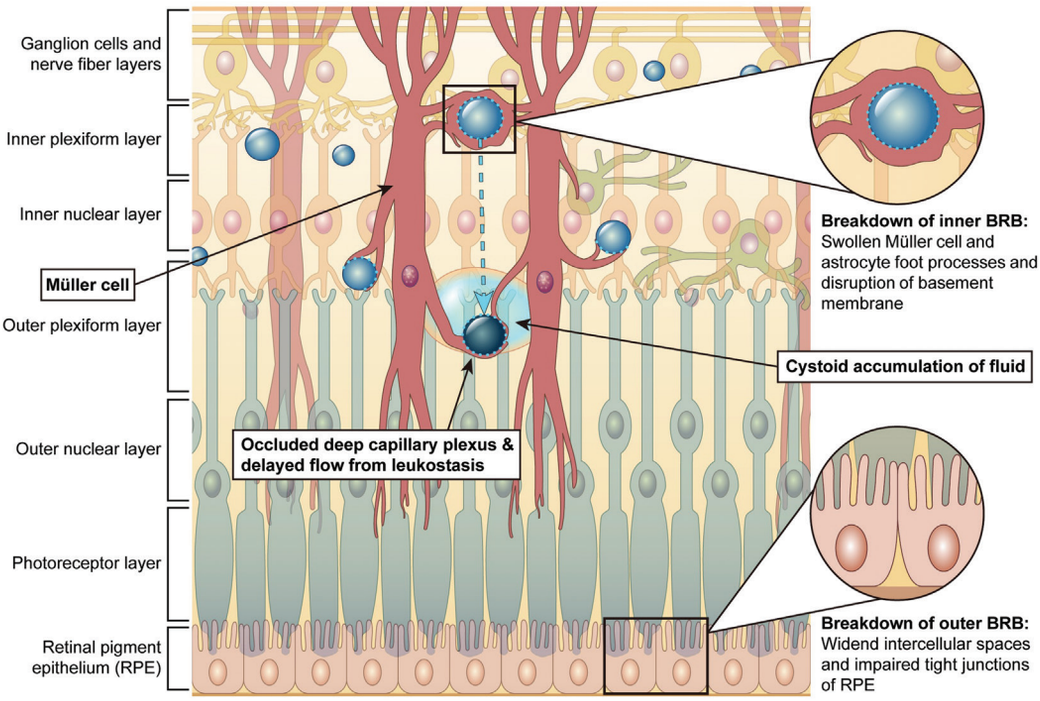

Figure 2 Pathophysiologic mechanisms of cystoid macular edema BRB: Blood-retinal barrier; RPE: Retinal pigment epithelium. Blue dots: Disrupted basement membranes.

osmotic swelling of these cells[27,57]. Müller cell bodies in diseased retinas show swelling during hypoosmotic conditions, probably due to potassium accumulation within the cells[54]. Corticosteroids, including triamcinolone acetonide, inhibit Müller cell swelling by inducing endogenous adenosine signaling and opening of ion channels in Müller cell membranes[54,58].

MECHANICAL TRACTION

Besides vasogenic and cytotoxic mechanisms, CME can also occur because of mechanical forces *via* changes of the vitreous. The vitreous, the intraocular space-occupying material composed of 99% water and 1% of extracellular matrix, is firmly attached to the retina at the optic disc, macula, vitreous base, and major retinal vessels[59]. Posterior vitreous detachment occurs during aging, but incomplete separation of the vitreous from the retina can lead to vitreomacular traction, *i.e.*, CME induced by axial tractional force on the macula *via* the vitreoretinal adhesion[60]. CME induced by vitreomacular traction is characterized by metamorphopsia, subtle asymmetry of foveal thickening, and the absence of leakage on fluorescein angiography[59,61]. Foveal thickening resolves along with visual improvement after surgical or spontaneous release of vitreomacular traction[62]. In case of a coexisting epiretinal membrane, the strength of adhesion between the vitreous and the macula is increased, which prevents spontaneous separation of the vitreous[59,63].

Because pathogenesis originates by mechanical force, vitrectomy to release the vitreomacular traction is the treatment of choice for this type of CME[64]. Ocriplasmin, a recombinant protease that acts against the vitreoretinal interface, has been recently reported to be effective in releasing vitreomacular traction[65].

CONCLUSIONS

The pathophysiology of CME discussed in this review is summarized in Figure 2. Currently available treatments for CME have emerged from the understanding of its pathogenesis based on vasogenic and cytotoxic mechanisms. Intravitreal injections of anti-VEGF agents and corticosteroids improve CME by decreasing VEGF and other proinflammatory mediators, although they need to be injected repeatedly to prevent the recurrence of macular edema. Further studies on the mechanisms of CME may therefore lead to innovative treatment strategies.

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