

A MOLECULAR UNDERSTANDING OF MACULAR EDEMA*

Jayakrishna Ambati, MD[†]ABSTRACT

Macular edema (ME) has a number of different etiologies that induce vascular leakage and macular swelling by different pathological mechanisms. Because of this, treatment varies with the etiology. This article reviews the etiologies and loci of ME, the molecules and proinflammatory processes that incite and promote ME, and the role of leukostasis in retinal vessel damage and the breakdown of the blood-retinal barrier. It also addresses the movement and distribution of water through and between cells, the proteins involved in maintaining the integrity of tight junctions between cells in the endothelium and the glia, and the effects of various pharmacological agents including corticosteroids on the molecules and processes involved in ME. (*Adv Stud Ophthalmol.* 2007;4(7):179-181)

Macular edema (ME), or the leakage and accumulation of fluid in the macula, is a final common pathway produced by several disease states and syndromes. Although it is important to understand the differing etiologies of ME, it is equally critical to recognize that each can induce ME by different pathological mechanisms. Therefore, optimal treatment may vary by etiology.

*Based on a presentation at a satellite symposium held at the Retina Society Annual Meeting in Boston, Massachusetts.

[†]University Research Professor, Professor and Vice Chair, Ophthalmology and Visual Sciences, Professor of Physiology, E. Vernon Smith and Eloise C. Smith Endowed Chair, University of Kentucky, Lexington, Kentucky.

Address correspondence to: Jayakrishna Ambati, MD, University Research Professor, Professor and Vice Chair, Ophthalmology and Visual Sciences, Professor of Physiology, E. Vernon Smith and Eloise C. Smith Endowed Chair, University of Kentucky, 740 South Limestone Street, Lexington, KY 40506. E-mail: jamba2@uky.edu.

ETIOLOGIES AND LOCI

Macular edema may be caused by vascular conditions such as diabetes, vein occlusion, and ischemia; uveitis and postoperative inflammation; mechanical traction on the surface of the retina or at the vitreoretinal interface; certain drugs, including prostaglandin (PG) analogues used to treat glaucoma; melanoma and hemangioma; and degenerative or dystrophic conditions such as age-related macular degeneration, retinitis pigmentosa, and cystoid ME.

In the United States, vascular conditions—primarily diabetes, but followed closely by vein occlusions and other forms of ischemia—are by far the leading cause of ME. However, uveitis and postoperative inflammation account for a significant proportion of cases in the United States and worldwide.

Excess fluid in the macula is the distinguishing characteristic of ME, and its locus is an important pathological item to note. Fluid can be intracellular, principally within the Müller glial cells and neuronal cell bodies of the retina, and cause swelling. Fluid can also be present between cells in the intracellular matrix, causing endothelial cell leakage from retinal vessels and leakage through the retinal pigment epithelium (RPE) when that barrier is breached.

INCITING MOLECULES

A number of in vitro and animal studies have identified several classes of molecules as playing a causative role in ME. These inciting molecules include PGs and leukotrienes (LTs), which are hallmarks of inflammation in a variety of disease states; nitric oxide, a neurotransmitter that leads to increased vessel permeability; protein kinase C- β ; and a host of cytokines.

The best studied of the cytokines in retinal disorders is vascular endothelial growth factor A (VEGF-A), a target molecule of several new pharmacologic

agents intended for clinical use. However, several other cytokines also promote ME, including tumor necrosis factor α (TNF- α), interleukin (IL)-1 β , IL-6, insulin-like growth factor-I, and stromal-cell-derived factor (SDF)-1. In fact, several studies of the aqueous/vitreous humor of patients with ME due to a variety of etiologies have found increased levels of VEGF-A, IL-6, interferon γ , hepatocyte growth factor, tumor growth factor β , and prostaglandin E2 (PGE-2). Moreover, recent research has found elevated levels of SDF-1 in the vitreous of patients with ischemic retinopathies and ME.^{1,2}

Studies in nonhuman primates have shown that levels of VEGF-A in the retina can be increased by injecting the cytokine directly into the vitreous or by using an adeno-associated viral system.^{3,4} The former causes endothelial cell damage and widespread retinal leakage, whereas the latter increases the production of VEGF-A by RPE cells and results in ME with cyst formation.

However, studies utilizing other systems to increase VEGF levels in transgenic mice have shown that VEGF per se is not sufficient to maintain retinal vascular leakage and that leakage can occur in the absence of VEGF.^{5,6} As illustrated in Figure 1, focal and diffuse areas of retinal vascular leakage dissipate over time despite persistently elevated levels of VEGF resulting from increased photoreceptor production of VEGF through a specific promoter.⁵ In contrast, VEGF-A blockade with the VEGF receptor kinase inhibitor SU1498 does not reduce retinal leakage induced by IL-1 β or TNF- α in mice.⁶

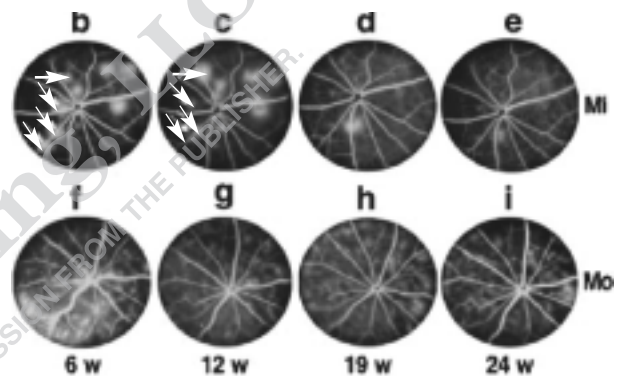
LEUKOSTASIS

Recent investigations in diabetic and normoglycemic rats have elucidated the deleterious role of retinal leukocyte stasis (leukostasis) in vascular permeability, capillary nonperfusion, breakdown of the blood-retinal barrier (BRB), and endothelial cell injury and destruction.⁷⁻⁹ Under normal conditions, leukocytes flow freely through the blood vessels. However, when leukostasis was induced by intravitreal injections of VEGF-A, white blood cells—principally monocytes and neutrophils—adhered to vessel walls and migrated from the vessels to the retinal tissue. As shown in Figure 2, retinal leukostasis in rats is intricately correlated with BRB breakdown, with both increasing with the duration of diabetes.⁹ Thus, leukostasis may be a good surrogate marker for retinal vascular leakage.

These and other studies have shown that the intercellular adhesion molecule (ICAM)-1 and various inte-

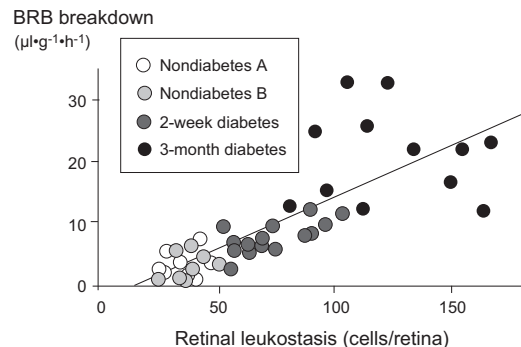
grins and selectins are also involved in the complex processes leading to leukostasis, including attraction of leukocytes to the vessel wall, capture and slow rolling of the leukocytes along endothelial cell surfaces, and transmigration of leukocytes between cells and through cells into the retinal tissue.⁷⁻¹⁰ One study, in fact, demonstrated that blockade of ICAM-1 with a monoclonal antibody reduced both the number of leukocytes escaping into the retinal tissue and vascular leakage.¹⁰ Other studies in various animal and cell culture systems have shown

Figure 1. Vascular Leakage Induced by VEGF-A Is Not Permanent



Focal and diffuse areas of retinal vascular leakage at 6 weeks (b and f) in mild phenotype (Mi) and moderate phenotype (Mo) transgenic mice gradually dissipate over the ensuing 18 weeks, despite persistently high VEGF-A levels. VEGF-A = vascular endothelial growth factor A. Reprinted with permission from Shen et al. *Diabetologia*. 2006;49:1690-1702.⁵

Figure 2. Correlation of Retinal Leukostasis and Breakdown of the Blood-Retinal Barrier in Diabetic and Nondiabetic Rats



BRB = blood-retinal barrier. Reprinted with permission from Ishida et al. *Invest Ophthalmol Vis Sci*. 2003;44:2155-2162.⁹

that corticosteroids, such as dexamethasone, markedly reduce leukostasis,¹¹ in addition to other proinflammatory processes and signaling mechanisms that promote vascular leakage.

STRUCTURAL ASPECTS OF MACULAR EDEMA

The movement of water between and through cells is regulated by tight intercellular junctions in endothelial and glial cells, the internal cytoskeleton of the cell membrane, pinocytosis (caveolae), and various water and ion channels. Abnormal changes within these structures compromise the ability of the vessel walls to maintain their integrity and prevent vascular leakage. It has also been increasingly recognized over the past decade that most water is moved by active transport rather than by diffusion.

A variety of proteins, principally occludin and zonula occludens-1 (ZO-1), are involved in maintaining the integrity of the tight junctions, whereas channels that carry water (aquaporins) and chloride and sodium/potassium adenosine triphosphatase ions are involved in regulating both the number and distribution of tight junction proteins.

A study investigating a rat brain endothelial cell line has shown that treatment with dexamethasone improves the distribution of ZO-1 to the endothelial cell surface and decreases vascular permeability.¹² Other studies in mice have shown that aquaporin-4 is expressed in Müller glial cells in the inner retina and promotes ischemic edema in the plexiform layers of the retina.^{13,14} The latter finding has been replicated in other models and suggests a new target for intervention in ischemic ME.

It is interesting to note that corticosteroids, which are nonselective and have broad-ranging effects, reduce aquaporin-4 levels in animal models and human fetal brain cells.¹⁵ In studies of glial cells from rats and guinea pigs, triamcinolone acetonide reduced swelling in these cells that was induced by arachidonic acid, PGE-2, and diabetes.^{16,17}

CONCLUSIONS

A wide variety of molecules and processes are involved in the pathophysiology of ME. Corticosteroids affect these in several ways. They inhibit the production of PGs and LTs and interrupt the proinflammatory ICAM-1, IL-6, VEGF-A, and SDF-1 pathways. They also decrease retinal vascular permeability and increase tight junction integrity.

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