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# Molecular basis of the inner blood-retinal barrier and its breakdown in diabetic macular edema and other pathological conditions

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ABSTRACT

Breakdown of the inner endothelial blood-retinal barrier (BRB), as occurs in diabetic retinopathy, age-related macular degeneration, retinal vein occlusions, uveitis and other chronic retinal diseases, results in vasogenic edema and neural tissue damage, causing loss of vision. The central mechanism of altered BRB function is a change in the permeability characteristics of retinal endothelial cells caused by elevated levels of growth factors, cytokines, advanced glycation end products, inflammation, hyperglycemia and loss of pericytes. Subsequently, paracellular but also transcellular transport across the retinal vascular wall increases via opening of endothelial intercellular junctions and qualitative and quantitative changes in endothelial caveolar transcellular transport, respectively. Functional changes in pericytes and astrocytes, as well as structural changes in the composition of the endothelial glycocalyx and the basal lamina around BRB endothelium further facilitate BRB leakage. As Starling's rules apply, active transcellular transport of plasma proteins by the BRB endothelial cells causing increased interstitial osmotic pressure is probably the main factor in the formation of macular edema. The understanding of the complex cellular and molecular processes involved in BRB leakage has grown rapidly in recent years. Although appropriate animal models for human conditions like diabetic macular edema are lacking, these insights have provided tools for rational design of drugs aimed at restoring the BRB as well as for design of effective transport of drugs across the BRB, to treat the chronic retinal diseases such as diabetic macular edema that affect the quality-of-life of millions of patients.



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**Abbreviations**

| | |
|---|---|
| AGEs | advanced glycation end products |
| AMD | age-related macular degeneration |
| Ang | angiopoietin |
| AQP | aquaporin |
| BBB | blood-brain barrier |
| BL | basal lamina |
| BRB | blood-retinal barrier |
| BRECs | bovine retinal endothelial cells |
| CNS | central nervous system |
| CTGF | connective tissue growth factor |
| DME | diabetic macular edema |
| DR | diabetic retinopathy |
| ESAM | endothelial cell-specific adhesion molecule |
| GLUT1 | glucose transporter 1 |
| HGF | hepatocyte growth factor |
| HIF-1 | hypoxia inducible factor 1 |
| IL | interleukin |
| JAMs | junctional adhesion molecules |
| KSS | kallikrein-kinin system |
| MCP-1 | monocyte chemotactic protein 1 |
| MMP | matrix metalloprotease |
| NO | nitric oxide |
| NPDR | non-proliferative DR |
| PCDR | pre-clinical DR |
| PDGF | platelet-derived growth factor |
| PDR | proliferative DR |
| PEG | polyethylene glycol |
| PKC-β | protein kinase C beta |
| PLVAP | plasmalemma vesicle associated protein |
| PVR | proliferative vitreoretinopathy |
| ROS | reactive oxygen species |
| siRNA | small interfering RNA |
| STZ | streptozotocin |
| TEER | transendothelial electrical resistance |
| TGF-β | transforming growth factor beta |
| TIMP | tissue inhibitor of metalloproteases |
| TNF-α | tumor necrosis factor alpha |
| VEGF | vascular endothelial growth factor |
| ZO | zona occludens |

## 1. Introduction

Retinal vascular leakage from loss of function of the blood–retinal barrier (BRB) and subsequent macular edema are the main causes of visual loss and blindness in major eye diseases such as diabetic retinopathy (DR), age-related macular degeneration (AMD), retinal vein occlusion and uveitis (Fig. 1). Despite recent advances, there is still a fundamental lack of understanding of the cellular mechanisms underlying both the function of the BRB in physiological conditions as well as its dysfunction in pathological conditions. However, it has become clear that the previously prevailing concept that BRB loss is the result of unspecified endothelial cell damage' has become obsolete. It should be replaced by the notion that dynamic adaptations of endothelial cells and other cell types involved in the BRB underlie vascular leakage in retinal disease.

A complex dual vascular system provides oxygen and nutrients to the metabolically highly active neural retina, a tissue that has a higher oxygen consumption per unit weight of tissue than any other human tissue (Arden et al., 2005). The choriocapillaris provides blood supply to the photoreceptors in the outer retina, while capillaries sprouting from the central retinal artery provide oxygen and nutrients to the inner retina. These two distinct vascular beds not only differ in embryonic origin, but also in their properties and functions in the adult eye. The endothelium of choroidal capillaries is highly fenestrated and permeable. The capillaries in the inner retina have a continuous endothelium with a barrier function and are organized in two parallel layers, whereas the outer retina is completely avascular.

Retinal neural tissue is protected from potentially harmful molecules in the circulation by the inner BRB that regulates the entry of molecules into the inner retina. To complete this protective