Progress in Retinal and Eye Research 32 (2013) 102–180

Contents lists available at SciVerse ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

Role of the retinal vascular endothelial cell in ocular disease

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ARTICLE INFO

Article history:
Available online 11 September 2012

Keywords:
Retina
Endothelial cell
Molecular profiling
Posterior uveitis
Autoimmune uveitis
Infectious uveitis
Diabetic retinopathy
Retinopathy of prematurity

ABSTRACT

Retinal endothelial cells line the arborizing microvasculature that supplies and drains the neural retina. The anatomical and physiological characteristics of these endothelial cells are consistent with nutritional requirements and protection of a tissue critical to vision. On the one hand, the endothelium must ensure the supply of oxygen and other nutrients to the metabolically active retina, and allow access to circulating cells that maintain the vasculature or survey the retina for the presence of potential pathogens. On the other hand, the endothelium contributes to the blood-retinal barrier that protects the retina by excluding circulating molecular toxins, microorganisms, and pro-inflammatory leukocytes. Features required to fulfill these functions may also predispose to disease processes, such as retinal vascular leakage and neovascularization, and trafficking of microbes and inflammatory cells. Thus, the retinal endothelial cell is a key participant in retinal ischemic vasculopathies that include diabetic retinopathy and retinopathy of prematurity, and retinal inflammation or infection, as occurs in posterior uveitis. Using gene expression and proteomic profiling, it has been possible to explore the molecular phenotype of the human retinal endothelial cell and contribute to understanding of the pathogenesis of these diseases. In addition to providing support for the involvement of well-characterized endothelial molecules, profiling has the power to identify new players in retinal pathologies. Findings may have implications for the design of new biological therapies. Additional progress in this field is anticipated as other technologies, including epigenetic profiling methods, whole transcriptome shotgun sequencing, and metabolomics, are used to study the human retinal endothelial cell.

Contents

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[1] Percentage of work contributed by each author in the production of the manuscript is as follows: Arpita S. Bharadwaj: 20%; Binoy Appukuttan: 20%; Phillip A. Wilmarth: 5%; Yuzhen Pan: 5%; Andrew J. Stempel: 5%; Timothy J. Chipps: 5%; Eric E. Benedetti: 5%; David O. Zamora: 5%; Dongseok Choi: 5%; Larry L. David: 5%; Justine R. Smith: 20%.
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http://dx.doi.org/10.1016/j.preteyeres.2012.08.004

1. Introduction

Diseases involving the retinal vasculature, including 2 ischemic vasculopathies (i.e., diabetic retinopathy and retinopathy of prematurity) and various posterior forms of uveitis, are important causes of blindness in both industrialized countries and developing nations. Diabetic retinopathy affects approximately one-third of all persons who suffer from diabetes mellitus (Kempen et al., 2004), a disease that is expected to affect 300 million people worldwide by 2025 (King et al., 1998). Retinopathy of prematurity accounts for up to one-third of childhood blindness, particularly in countries with intermediate infant mortality rates (Gilbert et al., 1997). Uveitis is a relatively uncommon disease, but due to an often substantial impact on vision at a relatively earlier age, its socioeconomic impact is roughly equivalent to that of diabetic retinopathy (Suttorp-Schulten and Rothova, 1996).

Retinal microvessels are complex structures, to which multiple cell populations contribute. Microvascular dysfunction is associated with retinal ischemia and neovascularization in diabetic retinopathy and retinopathy of prematurity, and leukocyte or microbial trafficking and potentiation of retinal inflammation in posterior uveitis. In this review, we focus on the critical participation of the retinal vascular endothelial cell in these pathological processes and highlight elements of the endothelial molecular phenotype that may predispose the retina to involvement in the stated diseases. We introduce our subject with a discussion of relevant anatomy and physiology, as well as descriptions of the model systems that are used to study the basic disease mechanisms.

2. Clinical significance of the retinal vascular diseases

2.1. Posterior uveitis

Inflammations that involve the intraocular tissues are termed uveitis. This large group of diseases is classified anatomically into anterior uveitis (primarily involving the anterior chamber), intermediate uveitis (primarily involving the vitreous), posterior uveitis (primarily involving the retina or choroid), and panuveitis (involving the anterior chamber, vitreous, and retina or choroid) (Bloch-Michel and Nussenblatt, 1987). Up to 10% of blindness in Western nations has been attributed to uveitis (Nussenblatt, 1990; Suttorp-Schulten and Rothova, 1996). In developing countries, the figure may be as high as 25% (London et al., 2010). Although 3 United States population-based studies report different patterns of age-stratified incidence, all show that more cases of uveitis begin during the working years than at any other period in life (Darrell et al., 1962; Gritz and Wong, 2004; Suhler et al., 2008). As a result, uveitis exacts an annual cost on society equivalent to that of diabetic retinopathy (Suttorp-Schulten and Rothova, 1996). In particular, approximately 50% of individuals with uveitis affecting the posterior segment of the eye suffer vision loss (Rothova et al., 1996).

Posterior uveitis is actually a diverse group of diseases with varied etiologies, including both autoimmune and infectious entities (Rodriguez et al., 1996; Suhler et al., 2008). Autoimmune uveitis may occur as part of a systemic inflammatory disease or be confined to the eye. Isolated autoimmune uveitis may take the form of a specific ocular syndrome or, if characteristic clinical features