Cytokine 95 (2017) 126–135

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Review article

Retinal pigment epithelium-secretome: A diabetic retinopathy perspective

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ARTICLE INFO

Article history:
Received 18 October 2016
Received in revised form 12 January 2017
Accepted 14 February 2017

Keywords:
Retinal pigment epithelium
Secretory factors
Diabetic retinopathy
VEGF
Neovascularization
Cytokines

ABSTRACT

Diabetic retinopathy is a major complication of diabetes mellitus that can lead to retinal vascular abnormalities and visual impairment. While retinal endothelial pathology is well studied, retinal pigment epithelium (RPE) layer modifications and the patho-physiological regulations are not widely understood. The RPE is a highly specialized pigmented layer regulating not only physiological functions such as transport of nutrients, ions, absorption of light, phagocytosis of photoreceptor membranes, but also secretion of a number of cytokines, chemokines, angiogenic and anti-angiogenic factors. The RPE secretome, though crucial in health and disease, remains elusive in diabetic retinopathy. A knowledge of these secreted factors would help explain and correlate the clinical phase of the disease aiding in improved disease management. A comprehensive knowledge of the secreted factors of the RPE is a potential tool for understanding the differential treatment regime of early diabetic retinopathy, diabetic proliferative retinopathy and diabetic macular edema. In this review, we have delineated the importance of factors secreted by the retinal pigment epithelium and its regulation in the pathogenesis of diabetic retinopathy.

Contents

1. Introduction

Anatomically, the retinal pigment epithelium (RPE) is a monolayer of pigmented cells of neuroectodermal origin located between the neural retina and the choroid and helps in maintaining the structural and functional integrity of the retina. The RPE constitutes the outer blood retinal barrier (BRB), wherein the apical side is directed towards the neural retina and the basal side towards the Bruch's membrane, followed by choroid. The functionality of RPE, apart from imparting a physical barrier, is to maintain retinal homeostasis by a series of secretory factors. The RPE plays a major role in (a) absorption of light and protection against photo-oxidation (b) regulation of nutrients, ions and water between the neural retina (apical side) and the choriocapillaris (basal side) (c)

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http://dx.doi.org/10.1016/j.cyto.2017.02.013
1043-4666/

exchange of 11-cis retinal and all-trans-retinol between the photoreceptors and RPE in the visual cycle (d) phagocytosis of shed photoreceptor outer segments (e) the secretion of various growth factors [1].

The physiological functions of RPE are deregulated in retinal diseases such as proliferative diabetic retinopathy (PDR), diabetic macular edema (DME) and age related macular degeneration (AMD). The pathogenesis of diabetic retinopathy (DR) involves altered permeability of the inner BRB, pericyte loss, retinal capillary occlusion, basement membrane thickening and retinal neuronal abnormalities. Moreover, the inner and outer BRB, which are safe guarded by endothelial cells and RPE, undergo alterations thereby steering patho-physiological edema [1–3].

Hyperglycemia, that is seen in DR, influences several biochemical pathways such as polyol, advanced glycation end products, and protein kinase C (PKC) pathways [2]. Activation of these pathways leads to increased oxidative stress, inflammation, induced leukostasis, induced growth factors, cytokines and vascular dysfunctions [4,5]. Retinal pigment epithelium exposed to high glucose have structural alterations, modulations in the secretion of growth factors/cytokines and barrier dysfunctions [6–8]. Though the RPE secretome plays a vital role in the clinical manifestation of DR, studies so far have only focused on understanding the vascular leakage of endothelial cells [8]. Intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents is the preferred drug of choice for an effective suppression of neovascular proliferation and edema in the retina [9]. Though anti-VEGF agents have been used indiscriminately for DR, in ~40% of those treated the clinical manifestations persist and the patients are deemed as non-responders [10]. Based on a microarray study, we have shown that in the DME non-responder group. Gene expression of interleukin (IL)-8 was 6-fold higher with a down regulation of VEGF receptor-2 (VEGFR) compared to the responder cohort [11]. In another study, it was observed that the vitreous in PDR contains high levels of IL-6, IL-8 and monocyte chemo-attractant protein-1 (MCP-1) and did not respond to the anti-VEGF treatment suggesting the role of cytokines and chemokines in neovascularization [12]. It is well established that the underlying pathology of DME involves a combination of VEGF as well as pro inflammatory components [13–15]. A lot of insights into the role of inflammatory markers have come from clinical studies. There are specific systemic as well as local inflammatory markers that are considered as potential biomarkers for DR [16]. Studies have shown that apart from VEGF, systemic levels of MCP-1, IL-I beta, IL-6, IL-8, sIL-2R and TNF-alpha strongly correlate with the severity of DR [17–19]. Vitreous levels of cytokines such as IL-6, IL-8, IL-10, IL-13, IP-10, MCP-1, MIP-1beta, PDGF, ICAM-1, and RANTES have shown a strong correlation with DR staging [19,20]. Though anti-VEGF remains the primary treatment modality, many patients turn non-responders after an initial good response. This implicates the involvement of additional factors beyond VEGF in DR disease progression and response to therapy. With the inflammatory component in the disease now proven, a combinatorial treatment paradigm provides a better management approach [13]. BRB breaking down, a salient feature of DR is most likely the consequential effect of the aberrant release of cytokines and growth factors from RPE [1], Further, a few clinical studies have shown a fluorescein leakage diffusion from the RPE layer, though an apparent evidence for DME was not observed [21,22]. Hence, a detailed study of the RPE secretory factors is warranted to understand the progression and complications of PDR and DME. Understanding the cytokines and their specific role in disease would pave way for developing novel drugs for anti-VEGF treatment non-responders.

In an attempt to provide concise information about the secretory factors of RPE, this review is focused on the synthesis and the criticality of salient growth factors, anti-angiogenic factors, and cytokines in health and diabetic retinopathy. This know-how would provide scope not only for the development of alternative drug targets but also to improvise available therapeutic strategies for better effectiveness.

2. Effect of diabetes on RPE cells

Electron microscopic images of the cellular and subcellular structures show an irregular arrangement of plasmalemma infoldings, degeneration of organelle (mitochondria), nucleus and increased permeability in the diabetic rat and human RPE cells [23,24] (Fig. 1). It is suggested that in high glucose conditions, RPE cells downregulate GLUT-1 and reduce the levels of antioxidants (glutathione, superoxide dismutase and ascorbic acid) leading to retinal tissue damage [25–27]. Apart from inducing inflammation by the trafficking microglia/macrophages in the subretinal space with its numerous pores, the RPE shows early dysfunction (alterations in barrier) concomitant with hyperglycemia followed by photoreceptor damage [28,29]. Leakage of fluorescein in the RPE during fundus fluorescein angiography in early DR and optical coherence tomography during late DR is probably an outcome of DM induced structural alterations in the RPE [21,22]. Diabetes induced abnormalities in RPE permeability has been observed in patients as well as animal models which leads to increased leakage of blood and water contents [24,30] (Fig. 1). Hence, it can very well be envisaged that it is the deformed structure of RPE that instigates the BRB leakage in DM.

3. RPE secretory factors in normal and diabetic retinopathy conditions

In polarized epithelial cells like the RPE, the secretion of proteins is regulated through the plasma membrane via vesicle transport or ion channels. The secretary proteins from the RPE cells are released either on the apical cell side by the NaK-ATPase channel or the basal side by the anion channel [1].

The RPE cells secrete a number of growth factors, anti/pro-angiogenic and neurotrophic factors such as the pigment epithelium-derived factor (PEDF) [31–33], VEGF [34], fibroblast growth factors (FGF-1, FGF-2, and FGF-5) [35], transforming growth factor-β (TGF-β) [36], insulin-like growth factor-I (IGF-I) [37], nerve growth factor (NGF) [38], brain-derived growth factor (BDNF) [39], connective tissue growth factor (CTGF) [40], platelet-derived growth factor (PDGF) [41], lens epithelium-derived growth factor (LEDGF) [42], members of the interleukin family [43], matrix metalloproteases (MMPs) [44], tissue inhibitor of matrix metalloproteases (TIMP) [44], placental growth factor (PIGF) [45], and angiogenin [46]. Recently, few more factors have also been found to be synthesized in the RPE cells, such as somatostatin [47], erythropoietin (EPO) [48], and apolipo protein (Apo) A1 [49]. Elaborate proteomics studies of RPE cells in a diabetic condition have implicated the involvement of these proteins in protecting/inducing stress, structural modifications, mitochondrial trafficking, apoptosis and in other metabolic events early in the course of the disease [50–52]. Proteomics of diabetic pre-retinopathy cadaver RPE has revealed alterations in the proteins involved in membrane dynamics, metabolic events, and cytoskeletal structure [51]. Another study has showed 55 differentially secreted proteins from RPE cells cultured in high glucose that are functionally associated with cytoskeleton adhesion/junction and cell survival. This study also showed that differential regulation of multidrug resistance (MDR) - associated proteins-1 [52]. All the above suggests that the secretome of RPE is differential and concomitantly multifunctional.