Review Article

The Retinal Pigment Epithelium: Something More than a Constituent of the Blood-Retinal Barrier—Implications for the Pathogenesis of Diabetic Retinopathy

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Received 29 June 2009; Revised 28 September 2009; Accepted 16 November 2009

Academic Editor: Karl Chai

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The retinal pigment epithelium (RPE) is a specialized epithelium lying in the interface between the neural retina and the choriocapillaris where it forms the outer blood-retinal barrier (BRB). The main functions of the RPE are the following: (1) Transport of nutrients, ions, and water, (2) Absorption of light and protection against photooxidation, (3) Reisomerization of all-trans-retinal into 11-cis-retinal, which is crucial for the visual cycle, (4) Phagocytosis of shed photoreceptor membranes, and (5) Secretion of essential factors for the structural integrity of the retina. An overview of these functions will be given. Most of the research on the physiopathology of diabetic retinopathy has been focused on the impairment of the neuroretina and the breakdown of the inner BRB. By contrast, the effects of diabetes on the RPE and in particular on its secretory activity have received less attention. In this regard, new therapeutic strategies addressed to modulating RPE impairment are warranted.

1. Introduction

The retinal pigment epithelium (RPE) is a monolayer of pigmented cells situated between the neuroretina and the choroids. The RPE is of neuroectodermal origin and is therefore considered to be part of the retina. The apical membrane of the RPE faces the photoreceptor’s outer segments and its basolateral membrane faces Bruch’s membrane, which separates the RPE from the fenestrated endothelium of the choriocapillaris (Figure 1). The RPE constitutes the outer blood-retinal barrier (BRB). The inner BRB is mainly constituted by endothelial cells. Tight junctions between neighbouring RPE cells and neighbouring endothelial cells are essential in the strict control of fluids and solutes that cross the BRB as well as in preventing the entrance of toxic molecules and plasma components into the retina. Therefore, this sealing function is essential for the integrity of the retina [1].

The main functions of the RPE are the following: (1) Transport of nutrients, ions, and water (2) Absorption of light and protection against photooxidation, (3) Reisomerization of all-trans-retinal into 11-cis-retinal, which is a key element of the visual cycle, (4) Phagocytosis of shed photoreceptor membranes, and (5) Secretion of various essential factors for the structural integrity of the retina.

Apart from these functions, the RPE stabilizes ion composition in the subretinal space, which is crucial for the maintenance of photoreceptor excitability [2]. In addition, the RPE contributes to the immune privileged status of the eye as part of the BRB and by the secretion of immunosuppressive factors inside the eye. In recent years it has become clear, mainly from in vitro studies, that RPE cells play an important role in immune responses by the expression of major histocompatibility complex (MHC) molecules, adhesion molecules, Fasl and cytokines [3]. With these different complex functions, the RPE is essential for...
visual function. A failure of any one of these functions can lead to degeneration of the retina, loss of visual function, and blindness.

Diabetic retinopathy (DR) remains the leading cause of blindness among working-age individuals in developed countries [4]. Whereas proliferative diabetic retinopathy (PDR) is the commonest sight-threatening lesion in type 1 diabetes, diabetic macular edema (DME) is the primary cause of poor visual acuity in type 2 diabetes. Because of the high prevalence of type 2 diabetes, DME is the main cause of visual impairment in diabetic patients [5]. In addition, DME is almost invariably present when PDR is detected in type 2 diabetic patients [6]. Neovascularization due to severe hypoxia is the hallmark of PDR whereas vascular leakage due to the breakdown of the blood retinal barrier (BRB) is the main event involved in the pathogenesis of DME [7, 8]. Most of the research on the physiopathology of DR has been focused in the impairment of the neuroretina and the breakdown of the inner BRB. By contrast, the effects of diabetes on the RPE have received less attention.

In the following sections the functions of the RPE mentioned above will be described in more detail, and the deleterious effects of diabetes will be summarized. Although there is growing evidence pointing to RPE as an active secretor epithelium, it seems that this important function has been less recognized. For this reason, this review will focus on this essential propriety of RPE and its impairment in DR.

2. Transepithelial Transport

In one direction, the RPE transports electrolytes and water from the subretinal space to the choroid, and in the other direction, the RPE transports glucose and other nutrients from the blood to the photoreceptors.

2.1. Transport from Blood to Photoreceptors. The RPE takes up nutrients such as glucose, retinol, ascorbic acid, and fatty acids from the blood and delivers these nutrients to the photoreceptors.

To transport glucose, the RPE contains high amounts of glucose transporters in both the apical and the basolateral membranes. Both GLUT1 and GLUT3 are highly expressed in the RPE [9–11]. GLUT3 mediates the basic glucose transport while GLUT1 is responsible for inducible glucose transport in response to different metabolic demands.

Another important function of the RPE is the transport of retinol to ensure the supply of retinal to the photoreceptors. The bulk of the retinol is exchanged between the RPE and the photoreceptors during the visual cycle in which all-trans-retinol is taken up from the photoreceptors, isomerized to 11-cis-retinal, and delivered to photoreceptors [12].

Delivery of fatty acids such as docosahexaenoic acid (DHA) to the photoreceptors is a third kind of transport of importance for visual function [13]. DHA is an essential omega-3 fatty acid that cannot be synthesized by neural tissue but is required as structural element by membranes of neurons and photoreceptors. DHA is synthesized from its precursor, linolenic acid, in the liver and transported in the blood bound to plasma lipoprotein where it is taken up in a concentration-dependent manner [1, 14]. Apart from the RPE’s functional integrity, DHA is the precursor of neuroprotectin D1 (NPD1), a docosatriene that protects RPE cells from oxidative stress [15, 16].

Recently it has been demonstrated that high glucose downregulates GLUT-1 by Akt pathway activation mediated by the PKC-oxidative stress signaling pathway in ARPE cells (a spontaneously immortalized line of RPE cells) [17]. In addition, the transport of retinol may be altered due to a downregulation of the interstitial retinol binding protein (IRBP) that occurs in diabetic patients (see below). Finally an impairment of the transport of ascorbic acid also exists in the presence of hyperglycemia, thus limiting the RPE’s antioxidant defence [18, 19]. To the best of our knowledge, there is no information regarding the potential effects of diabetes on NPD1 or its precursor DHA.

2.2. Transport from Subretinal Space to Blood. The RPE transports ions and water from the subretinal space or apical side to the blood or basolateral side [1]. The Na⁺−K⁺-ATPase, which is located in the apical membrane, provides the energy for transepithelial transport [20–23].

There is a large amount of water produced in the retina, mainly as a consequence of the large metabolic turnover in neurons and photoreceptors. Furthermore, intraocular pressure leads to a movement of water from the vitreous body into the retina. This establishes the need for the constant removal of water from the inner retina to the choriocapillaris [24]. Water in the inner retina is transported by Müller cells, and water in the subretinal space is eliminated by the RPE [25, 26]. Constant elimination of water from the subretinal space produces an adhesion force between the retina and the RPE that is lost by inhibition of Na⁺−K⁺-ATPase by ouabain [27]. The transport of water is mainly driven by a transport of Cl⁻ and K⁺ [24, 28–30].

Tight junctions establish a barrier between the subretinal space and the choriocapillaris [31, 32]. Paracellular resistance is 10 times higher than transepidermal resistance, classifying the RPE as a tight epithelium [33, 34]. For this reason, water cannot pass through the paracellular transport route and water transport occurs mainly by transepithelial pathways facilitated by aquaporin-1 [35–37].

Recently we have found that high glucose concentrations result in a reduction of permeability in ARPE-19 cells [38] that was unrelated to tight junction (occludin, ZO-1 and claudin-1) changes. In this regard, in cultured bovine RPE cells it has been demonstrated that hyperglycemia induces a loss of Na⁺/K⁺-ATPase function, which responds to aldose reductase inhibitor treatment [39]. Therefore, hyperglycemia could impair the transport of water from subretinal space to the choriochapiplanar and, consequently, might contribute to DME development.

At present, there is no information regarding the potential effects of diabetes on aquaporin expression in the RPE.

3. Absorption of Light and Protection against Photooxidation

The retina is the only neural tissue that has a direct and frequent exposure to light. This circumstance favours the
photooxidation of lipids which become extremely toxic to retinal cells [40]. In addition, the retina is the part of the body that proportionally consumes more oxygen, thus generating a high rate of reactive oxygen species (ROS). The RPE is essential in counterbalancing the high oxidative stress that exists in the retina, and it does this by means of three lines of defence.

The first line is the absorption and filtering of light. For this purpose, the RPE contains a complex composition of various pigments (i.e., melanin, lipofuscin) that are specialized to different wavelengths and special wavelength-dependent risks [41–43]. The second line of defence is made by antioxidants. As enzymatic antioxidants, the RPE contains high amounts of superoxide dismutase [44–47] and catalase [45, 48]. As nonenzymatic antioxidants, the RPE accumulates carotenoids, such as lutein and zeaxanthin [42, 43] or ascorbate [42, 49]. In addition, glutathione and melanin are important contributors to antioxidant defence.

DR is characterized by reduced levels of molecules with antioxidant activity such as glutathione [50, 51], superoxide dismutase (SOD) [50, 52], and ascorbic acid [18, 53], thus favouring retinal tissue damage induced by oxidative stress.

4. Visual Cycle

In vertebrate retina, vision is initiated and maintained by the photolysis and regeneration, respectively, of light sensitive pigments in the disk membranes of the photoreceptor outer segments. This cyclical process depends on an exchange of retinoids between the photoreceptors and the RPE.

Light transduction is initiated by the absorption of light by rhodopsin which is composed of a seven transmembrane domain G-coupled receptor protein, opsin, and the chromophore 11-cis-retinal [54]. Absorption of light changes the conformation of 11-cis-retinal into all-trans-retinal. Photoreceptors lack cis-trans isomerase and, therefore, all-trans-retinal is metabolized into all-trans-retinol and transported...
to the RPE. In the RPE retinol is reisomerized by means of cis-trans isomerase to 11-cis-retinal and then redelivered to the photoreceptors. The protein RPE65 (retinal pigment epithelium-specific protein 65 kDa) is the protein responsible for isomerization of the all-trans-retinaldehyde to its photoactive 11-cis-retinaldehyde and is essential for the visual cycle. In this regard, it has been shown that RPE65 mutations cause severe retinal diseases such as Leber congenital amaurosis [55].

There is a great deal of evidence that the transport of retinoids between these cellular compartments is mediated by the interphotoreceptor retinoid-binding protein (IRBP), a large glycoprotein synthesized in the photoreceptors and extruded into the interphotoreceptor matrix (IPM) that fills the subretinal space [56–58]. IRBP functions to solubilize retinal and retinol, which are otherwise insoluble in water, and mediates the targeting of these compounds and defines transport direction [59–62]. This role for IRBP is further supported by the observation that IRBP is not only present in the IPM but also in endosomes of the RPE [63]. Transport direction is then defined by the rapid turnover of IRBP between the IPM and the RPE. Apart from participating in the visual cycle, IRBP is important in fatty acid transport and is essential to the maintenance of the photoreceptors [58, 64]. Recently, it has been demonstrated that lower IRBP production is an early event in the human diabetic retina and is associated with retinal neurodegeneration [65, 66]. In addition, the content of cellular retinaldehyde binding protein (CRALBP), a protein also related to retinoid metabolism, has been found increased in RPE from diabetic subjects with no clinically apparent diabetic retinopathy in comparison with control donors [67].

5. Phagocytosis

Another function in the maintenance of photoreceptor excitability is the phagocytosis of shed photoreceptor outer segments [68–70]. Photoreceptors are exposed to intense levels of light, thus leading to accumulation of photodamaged proteins and lipids. Thus, during each day, the concentration of light-induced toxic substances increases
inside the photoreceptors [42]. Light transduction by photoreceptors is dependent on the proper functioning and structure of proteins, retinal, and membranes. Therefore, to maintain the excitability of photoreceptors, the photoreceptor outer segments (POSs) undergo a constant renewal process [69, 71, 72]. In this renewal process POSs are newly built from the base of outer segments, at the cilium. The tips of the POS that contain the highest concentration of radicals, photodamaged proteins, and lipids are shed from the photoreceptors. Through coordinated POSs tip shedding and the formation of new POS, a constant length of the POS is maintained. Shed POSs are phagocytosed by the RPE. In the RPE, shed POSs are digested and essential molecules, such as docosahexaenoic acid and retinal, are redelivered to photoreceptors to rebuild light-sensitive outer segments from the base of the photoreceptors [69, 73].

An impairment of phagocytosis has been described in long term diabetes [74] and, therefore, it is possible that this could also happen to RPE cells. However, specific studies addressed to this issue are needed.

6. Secrecion

The RPE is known to produce and to secrete a variety of growth factors [7, 75] as well as factors that are essential for the maintenance of the structural integrity of the retina [76, 77] and choriocapillaris [78]. Thus, the RPE produces molecules that support the survival of photoreceptors and ensure a structural basis for the optimal circulation and supply of nutrients. The RPE is able to secrete pigment epithelium-derived factor (PEDF) [7, 79, 80], VEGF [7, 81–85], fibroblast growth factors (FGF-1, FGF-2, and FGF-5) [7, 86–91], transforming growth factor-β (TGF-β) [7, 92–94], insulin-like growth factor-I (IGF-1) [95, 96], nerve growth factor (NGF), brain-derived growth factor (BDNF), neurotropin-3 (NT-3), ciliary neurotrophic factor (CNTF) [97, 98], platelet-derived growth factor (PDGF) [7, 99, 100], lens epithelium-derived growth factor (LEDGF) [101], members of the interleukin family [102–104], chemokines, tumor necrosis factor α (TNF-α), colony-stimulating factors (CSF), and different types of tissue inhibitor of matrix metalloprotease (TIMP) [105–110]. Among these factors, PEDF and VEGF seem the most significant.

6.1. PEDF and VEGF. In the healthy eye, the RPE secretes PEDF [7, 80–82], which helps to maintain the retinal as well as the choriocapillaris structure in two ways. PEDF was described as a neuroprotective factor because it was shown to protect neurons against glutamate-induced or hypoxia-induced apoptosis [76, 111, 112]. In addition, PEDF was shown to function as an antiangiogenic factor that inhibited endothelial cell proliferation and stabilized the endothelium of the choriocapillaris [7, 81, 82]. These effects on vascularization also play an important role in the embryonic development of the eye [113, 114]. Using PEDF-deficient (PEDF−/−) mice, it has been confirmed that PEDF is an important modulator of early postnatal retinal vascularization and that in its absence retinal vascularization proceeds at a faster rate and is more susceptible to hypoxia-mediated vessel obliteration [115].

Another vasoactive factor synthesized by the RPE is VEGF, which is secreted in low concentrations by the RPE in the healthy eye [7, 83, 86] where it prevents endothelial cell apoptosis and is essential for an intact endothelium of the choriocapillaris [116]. VEGF also acts as a permeability factor stabilizing the fenestrations of the endothelium [117]. In a healthy eye, PEDF and VEGF are secreted at opposite sides of the RPE. PEDF is secreted to the apical side where it acts on neurons and photoreceptors whereas most of VEGF is secreted to the basal side where it acts on the choroidal endothelium [118, 119].

Overproduction of VEGF plays an essential role in the development of PDR. The pathogenesis of DME remains to be fully understood but VEGF and proinflammatory cytokines have been involved in its development. Nevertheless, the balance between angiogenic (i.e., VEGF) and antiangiogenic factors (i.e., PEDF) will be crucial for the development of DR. In this regard, advanced glycation end products increase retinal VEGF expression in RPE [120]. Downregulation of PEDF expression by elevated glucose concentration in cultured human RPE cells was also observed [121]. Therefore, strategies in blocking VEGF or stimulating PEDF have been proposed as new therapeutic approaches for DR.

Apart from the factors mentioned above, in recent years new molecules have been found to be synthesized in RPE. Among them, somatostatin, erythropoietin, and ApoA1 seem to be of special interest because they could open up new therapeutic strategies for the treatment of DR.

6.2. Somatostatin. Somatostatin (SST) is a peptide that was originally identified as the hypothalamic factor responsible for inhibition of the release of growth hormone (GH) from the anterior pituitary [122]. Subsequent studies have shown that SST has a much broader spectrum of inhibitory actions and that it is much more widely distributed in the body, occurring not only in many regions of the central nervous system but also in many tissues of the digestive tract, including the stomach, intestine, and pancreas [123]. SST mediates its multiple biologic effects via specific plasma membrane receptors that belong to the family of G-protein-coupled receptors having seven transmembrane domains. So far, five SST receptor subtypes (SSTRs) have been identified (SSTRs 1–5) [124].

In the setting of this review it must be pointed out that SST is produced by the retina of various species, including humans [125–130]. Furthermore, SSTRs are also expressed in the retina, with SSTR1 and SSTR2 being the most widely expressed [127, 131–134]. The production of both SST and its receptors simultaneously suggests an autocrine action in the human retina.

The amount of SST produced by the retina is significant as can be deduced by the strikingly high levels found in the vitreous fluid. In fact, intravitreal levels of SST are higher than in plasma. It must be emphasized that the intravitreal level of total proteins is at least 20-fold less...
than in serum [135, 136]. Thus, the higher intravitreal concentration of a particular protein in relation to its plasma levels strongly suggests an important rate of intraocular production. The main source of SST in humans is RPE. Thus, it has been demonstrated that SST expression and content is higher in RPE than in the neuroretina (Figure 2) [137].

The main functions of SST for retinal homeostasis are the following (1) SST acts as a neuromodulator through multiple pathways, including intracellular Ca$^{2+}$ signaling [138], nitric oxide function [139], and glutamate release from the photoreceptors [140]. In addition, a loss in SST immunoreactivity was found after degeneration of the ganglion cells [141]. It should be noted that retinal ganglion cells (RGCs) are the earliest cells affected and have the highest rate of apoptosis in diabetes [137, 142]. This could be because RGCs are more sensitive to hypoxic conditions and glutamate excitotoxicity [143]. Therefore, the neuroretinal damage that occurs in DR might be the reason for the decreased SST levels detected in the vitreous fluid of these patients. In fact we have recently found that low SST expression and production is an early event in DR and is associated with retinal neurodegeneration (apoptosis and glial activation) [137]. (2) SST is an angiostatic factor. SST may reduce endothelial cell proliferation and neovascularization by multiple mechanisms, including the inhibition of postreceptor signalling events of peptide growth factors such as IGF-I, VEGF, and PDGF [144]. Using a mouse model of hypoxia-induced retinopathy, it has been demonstrated that in retinas overexpressing subtype 2 receptor of somatostatin (sst2) neovascularization was lower than in wild type retinas [145]. In addition, also using a mouse model of hypoxia-induced retinopathy it has been observed that retinal neovascularization increased in sst(2)-KO mice [146]. Furthermore, both SSR2- and SSTR3-selective analogues directly inhibit retinal endothelial cell growth in vitro [147, 148]. It is worth of mention that the intravitreal levels of SST lie within the same range as those showing antiangiogenic effect in experimental studies [149–151]. Therefore, SST can be considered as a good candidate to be added to the list of the natural inhibitors of angiogenesis. (3) SST has been involved in the transport of water and ions. As previously mentioned, various ion/water transport systems are located on the apical side of the RPE, adjacent to the subretinal space, and, indeed, a high expression of SST-R2 has been shown in this apical membrane of the RPE [131]. Nevertheless, the specific mechanisms involved in ion/water transport driven by SST remain to be elucidated.

In DR there is a downregulation of SST that is associated with retinal neurodegeneration [137]. Thus, a lower expression of SST has been found in RPE and neuroretina as well as a dramatic decrease of intravitreal SST levels [137, 152–154]. As a result, the physiological role of SST in preventing both neovascularisation and fluid accumulation within the retina is reduced, and consequently the development of PDR and DME is favoured [153, 154]. In addition, the loss of neuromodulator activity also contributes to neuroretinal damage. For all these reasons, intravitreal injection of SST analogues or gene therapy has been proposed as a new therapeutic approach in DR [155].

6.3. Erythropoietin. Erythropoietin (Epo) was first described as a glycoprotein produced exclusively in fetal liver and adult kidney that acts as a major regulator of erythropoiesis [156]. However, Epo expression has also been found in the human brain [157] and in the human fetal retina [158]. In recent years, we have demonstrated that not only Epo but also its receptor (Epo-R) is expressed in the adult human retina (Figure 3) [159, 160]. Epo and EpoR mRNAs are significantly higher in RPE than in the neuroretina [160].

In addition, intravitreal levels of Epo are ~3.5-fold higher than those found in plasma [159]. The role of Epo in the retina remains to be elucidated but it seems that it has a potential neuroprotective effect [161, 162]. In this regard, it has been shown that Epo protects cultured neurons from hypoxia and glutamate toxicity [163–165], and its systemic administration reduces neuronal injury in animal models of focal ischemic stroke and inflammation [166–168]. In addition, it has been demonstrated using an in vitro model of bovine blood-brain barrier (BBB) that Epo protects against the VEGF-induced permeability of the BBB and restores the tight junction proteins [169]. Since BRB is structurally and functionally similar to the BBB [170], it is possible that Epo could act as an antipermeability factor in the retina. In fact, Epo was able to improve DME when administered for treatment of anemia in diabetic patients with renal failure [171].

Epo is upregulated in DR [159, 160, 172, 173]. Epo overexpression has been found in both the RPE and neuroretina of diabetic eyes [159, 160]. This is in agreement with the elevated concentrations of Epo found in the vitreous fluid of diabetic patients (∼30-fold higher than plasma and ∼10-fold higher than in non diabetic subjects) [159]. Hypoxia is a major stimulus for both systemic [156] and intraocular Epo production [174]. In fact, high intravitreal levels of Epo have recently been reported in ischemic retinal diseases such as PDR [159, 172, 173, 175]. In addition, it has been reported that Epo has an angiogenic potential equivalent to VEGF [173, 176]. Therefore, Epo could be an important factor involved in stimulating retinal angiogenesis in PDR. However, intravitreal levels of Epo have been found at a similar range in PDR to that in DME (a condition in which hypoxia is not a predominant event) [159]. In addition, intravitreal Epo levels are not elevated in non diabetic patients with macular edema secondary to retinal vein occlusion [177]. Finally, a higher expression of Epo has been detected in the retinas from diabetic donors at early stages of DR in comparison with non diabetic donors, and this overexpression is unrelated to mRNA expression of hypoxic inducible factors (HIF-1α and HIF-1β) [160]. Therefore, stimulating agents other than hypoxia/ischemia are involved in the upregulation of Epo that exists in the diabetic eye.

The reason why Epo is increased in DR remains to be elucidated but the bulk of the available information points to a protective effect rather than a pathogenic effect, at least in the early stages of DR. There have been several
reports on the protective effects of Epo in the retina [175, 178–185]. In addition, Epo is a potent physiologic stimulus for the mobilization of endothelial progenitor cells (EPCs) [186] and, therefore, it could play a relevant role in regulating the traffic of circulating EPCs towards injured retinal sites. Recruitment of EPCs to the pathologic area would be beneficial because their capability of integrating into damaged vasculature can lead to the reendothelialization of acellular vessels. It has recently been shown that a reduction of EPCs exists in nonproliferative DR [187] and it has also been demonstrated that EPCs from diabetic donors are less effective in repairing damaged vasculature [188]. In this regard, the increase of intraocular synthesis of Epo that occurs in early stages of DR (i.e., in nonproliferative DR) can be contemplated as a compensatory mechanism for repairing the damage induced by the diabetic milieu through an increase in EPC recruitment. However, in advanced stages of DR (i.e., in the setting of PDR) a dramatic increase of both VEGF [7] and mature EPCs has been detected [187]. In this setting, Epo could potentiate the effects of VEGF, thus contributing to neovascularisation and, in consequence, worsening PDR [181, 189].

The potential advantages of Epo or EpoR agonists in the treatment of DR include neuroprotection, vessel stability, and enhanced recruitment of EPCs to the pathological area. However, as mentioned above, timing is critical since if Epo is given at later hypoxic stages, the severity of DR could even increase. However, in the case of the eye, disease progression is easy to follow without invasive investigation and allows timing of the administration of drugs to be carefully monitored, hopefully resulting in better clinical outcomes.

6.4. Apolipoprotein A1. Apolipoprotein A1 (apoA1) has been recently proposed as a key factor for intraretinal reverse transport of lipids, thus preventing lipid accumulation in the retina [190]. In a proteomic analysis of human vitreous fluid we found that apoA1 was highly intraocularly produced in patients with proliferative DR in comparison with non-diabetic subjects [65]. In addition, we have recently shown higher apoA1 (both mRNA levels and protein) in the retinas from diabetic donors in comparison with non-diabetic donors (Figure 4) [191, 192]. Moreover, apoA1 immunofluorescence was detected in all retinal layers but mRNA was more abundant in RPE [55]. This finding suggests that RPE is the main source of apoA1 in the human retina. These results are consistent with those reported by Li et al. [193] which demonstrated the immunolocalization of apoA1 to Bruch’s membrane (a thin connective tissue between the basal surface of the RPE and the choriocapillaris) in postmortem human eye specimens as well as the presence of apoA1 transcripts in the RPE and neural retina. Several independent lines of research indicate that the RPE contains LDL receptors (LDLRs) and/or scavenger receptors by which lipoproteins (LDL) are internalized and serve as a significant supply of lipids to the retina [194–196]. Taken together, the RPE, due to its capacity in internalizing and extruding lipids, can be considered as the most important regulator of lipid transport in the retina.

The reason why apoA1 is overexpressed in the diabetic retina needs to be elucidated but one possibility is that the diabetic milieu stimulates apoA1 production by the retina. In this regard, Kawai et al. [197] observed an increased secretion of apoA1 from the main lacrimal gland in patients with DR, but it was not detected in healthy subjects. In recent years new insights have been gained into the transport of lipids within the retina [190, 194], thus allowing us to hypothesize that the mechanisms regulating intraretinal lipid transport rather than serum levels are more important in the pathogenesis of DR [191, 192, 198]. In this regard, ABCA (ATP binding cassette transporter A1) and apoA1 have been found in several layers of monkey retina, thus suggesting the existence of an intraretinal mechanism to export HDL-like particles [190]. Ishida et al. [199] have demonstrated that HDL stimulates the efflux of radiolabelled lipids, of photoreceptor outer segment origin, from the basal surface of RPE cells in culture. The role of this HDL-based intraretinal lipid transport could be important in preventing lipotoxicity. The fact that the retina is the only neural tissue that has a direct and frequent exposure to light prevents a significant problem. This is because many lipids, especially polyunsaturated fatty acids (which are mainly located in the photoreceptor outer segments) and cholesterol esters, are highly susceptible to photo-oxidation and these oxidized lipids become extremely toxic to retinal cells [40]. In DR, this problem could be aggravated by the increase of oxidative stress and lipid peroxidation associated with diabetes. Apart from preventing or arresting lipotoxicity, apoA1 is a potent scavenger of reactive oxygen species [200, 201]; therefore, it could play an important role in protecting the retina from the overall oxidative stress due to diabetes. In this regard, it should be noted that retinopathy has been associated with apoA1 deficiency of genetic origin [202, 203].

Lipoprotein deposition plays an essential role in the pathogenesis of age-related macular degeneration (ARMD) [204, 205], but little is known about the origin of lipoproteins in the retina of diabetic patients and their potential role in the pathogenesis of DR. The role of apoA1 in extruding lipids out of the retina permits us to hypothesize that apoA1 is increased in diabetic patients as a compensatory mechanism in order to prevent the development of DR [67]. In other words, those diabetic patients with less capacity for apoA1 production by the retina would be more prone to develop lipid deposition (hard exudates) in the retina and, in consequence, to initiate DR.

Given that apoA1 has antioxidant properties and prevents lipid deposition in the retina, the design of new treatment strategies addressed to promoting the overexpression of apoA1 in order to reduce the development of DR seems warranted.

7. Concluding Remarks

The RPE lies in the interface between the neural retina and the choriocapillaris where it forms the outer BRB. To retard transepithelium diffusion between cells, the cells of the epithelium are bound together by a partially occluding
seal, the tight junction. The tight junction subdivides the plasma membrane into two functionally distinct domains. The apical membrane faces the photoreceptors of the neural retina, while the basolateral membrane faces the fenestrated choriocapillaris.

As a layer of pigmented cells the RPE absorbs the light energy focused by the lens on the retina. To regulate transport across the monolayer, various pumps, channels, and transporters are distributed specifically to either the apical or the basolateral membrane. The RPE transports ions, water, and metabolic end products from the subretinal space to the blood and, conversely, takes up nutrients such as glucose, retinol, and fatty acids from the blood and delivers these nutrients to the photoreceptors. To maintain photoreceptor excitability retinal is constantly transported from the photoreceptors to the RPE where it is reisomerized to 11-cis-retinal and transported back to the photoreceptors. This is the key component of the visual cycle. Another function that contributes to the maintenance of photoreceptor excitability is the phagocytosis of the shed photoreceptor outer segments. The photoreceptor outer segments are digested, and essential substances such as retinal are recycled and returned to the photoreceptors for rebuilding light-sensitive outer segments from the base of the photoreceptors. In addition, the RPE is able to secrete a variety of growth factors as well as factors that are essential for the maintenance of the structural integrity of the retina and the choriocapillaris. Furthermore, the secretory activity of the RPE plays an important role in establishing the immune privilege of the eye by secreting immunosuppressive factors.

Most investigations into the pathogenesis of DR have been concentrated on the neural retina since this is where clinical lesions are manifested. However, RPE is essential for neuroretina survival and, consequently, for visual function. In recent years, various abnormalities in both the structural and secretory functions of RPE have been found in DR. Therefore, future scenarios involving new therapeutic strategies addressed to modulating RPE impairment are warranted.

Acknowledgments

This study was supported by grants from the Generalitat de Catalunya (2009SGR739) and the Ministerio de Ciencia e Innovación (SAF2006-05284). CIBER de Diabetes y Enfermedades Metabólicas Asociadas is an initiative of the Instituto de Salud Carlos III. Marta Villarreal is a recipient of a grant from the Institut de Recerca Hospital Vall d’Hebron.

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