Chapter 3

Interphotoreceptor Retinoid-Binding Protein Implications in Diabetic Retinopathy

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Additional information is available at the end of the chapter

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Abstract

The interphotoreceptor retinoid-binding protein (IRBP) is the most abundant protein in the interphotoreceptor matrix (IPM) and its levels decrease beginning in the early stages of diabetes. IRBP participates in the delivery of retinoids between retinal cells to carry out the visual cycle and also protects those retinoids against degradation in the IPM. IRBP deficiency is related to several conditions such as retinitis pigmentosa, cone-rod dystrophy, increased oxidative stress in the photoreceptors, and myopia. Decreased IRBP levels in diabetes could be due to the secretion of inflammatory cytokines and a direct effect of hyperglycemia on the photoreceptors. It is known that prior to the occurrence of vascular changes in diabetic retina, electrophysiological alterations occur on early potentials. Alterations on the photoreceptor outer segments and increased oxidative stress indicate an important affliction of the photoreceptors from early stages. Due to the importance of IRBP in photoreceptor wellness, its decreased levels may be linked to early photoreceptor affection. More studies are required to describe in detail the whole impact that decreased levels of IRBP in diabetes may have.

Keywords: interphotoreceptor retinoid-binding protein, IRBP, visual cycle, oxidative stress, ER-stress, light damage, retinitis pigmentosa, cone-rod dystrophy, photoreceptor damage, photoreceptor, S-cones, M-cones, outer segment, diabetes, neurodegeneration

1. Introduction

Typically, the pathological changes described in diabetic retina involve neovascularization and increased blood vessel permeability, a condition known as diabetic retinopathy (DR). Early changes that occur prior to the vascular affection have been acquiring more interest by the scientific community. Retinal proteomic analysis, functional and histopathological studies have revealed alteration in the levels of some proteins and a neurodegeneration state mainly involving ganglion and photoreceptor cells accompanied by reactive gliosis [1–5].

The interphotoreceptor retinoid-binding protein (IRBP), which is the most abundant protein in the interphotoreceptor matrix (IPM) [6–10], is one of the principal elements altered in early stages of diabetes. This protein is expressed mainly by the cone and rod photoreceptor cells [11–13]. It binds to the retinoids in the interphotoreceptor matrix and facilitates their exchange between the IPM and the cells that carry out the visual cycle [14–16].

Aside from the retinoid delivery, IRBP protects retinoids against degradation [17], the retinal cells from oxidative stress and light-induced injury [18, 19], and is important for eye development [20].

2. Pathologies associated with IRBP deficiency

In pathological conditions in which a deficiency of IRBP exists, an important anomaly of the photoreceptor cells and the visual cycle can be detected which leads in some cases to the development of retinitis pigmentosa, accumulation of the cytotoxic bis-retinoid A2E, cone-rod photoreceptor dystrophy and an elongated myopic eye shape [20–25].

IRBP is linked to an autosomal recessive form of retinitis pigmentosa. A heterozygous T-C transition at the position 3024 [26] and a missense mutation of D1080N [22] have been identified. *In vitro* studies of this mutation have shown that it produces a non-secreted protein that induces endoplasmic reticular (ER) stress [27].

Other studies correlate the presence of *IRBP* gene mutations and the occurrence of high myopia in humans. This myopia was accompanied with retinal dystrophy observed by ocular coherence tomography (OCT) and electroretinography (ERG). The ERG showed a delay and reduction in the amplitude of the waves corresponding to the cone response. The *IRPB* gene mutations were c.3454G > T;p.E1152 and c.1530 T > A;p.Y510 which were predicted to lead to a nonsense mediated decay with a complete loss of IRBP function [21]. These findings correlate with animal studies in which IRBP−/− mice have shown ERG alterations and histological findings affecting cones [25]. This animal model has also shown alterations in eye shape and visual acuity [20].

The relationship between IRBP deficiency and accumulation of the lipofuscin precursor A2E has only be demonstrated experimentally on two different animal models. *IRBP*−/− mice have been shown by HPLC a retinal A2E increase of 2.7-fold [25]. Another study using an animal model with Müller cell dysfunction found a decreased expression of IRBP which was also accompanied with accumulation of A2E [24].

3. Diabetes and IRBP levels

Considering visual cycle components, decreased IRBP expression is one of the most characteristic changes in diabetes. Many studies have evaluated the changes in protein levels and IRBP expression and also attempted to explain the reasons for its depletion.

One study revealed decreased expression of IRBP determined by both qPCR and protein quantification on post-mortem samples of diabetic patients [28]. Another study showed that

this decreased expression directly correlated with the evolution of the DR, and also tested the effect of glucose and inflammatory cytokines on IRBP expression *in vitro*. They found that high glucose, TNF-α and IL-1β were able to reduce IRBP's expression [29]. A recent study found decreased IRBP levels in diabetic rats and this finding was accompanied by decreased levels of 11-cRAL and rhodopsin synthesis [30].

The precise mechanisms responsible for the decreased IRBP levels remain unclear. It is known that high glucose and some circulating fatty acids can induce the secretion of inflammatory cytokines by Müller cells [31, 32]. Despite evidence that high levels of glucose and inflammatory cytokines are able to decrease the expression of IRBP [24, 29], other mechanisms may be involved. With the early onset of diabetes, photoreceptors undergo oxidative stress resulting in increased nitrosative-oxidative stress [33, 34]. This biochemical stress can induce damage to proteins promoting their degradation [35]. The unfolded protein response (UPR) has been detected to be active in photoreceptor cells in animal studies [36]; however no studies have linked this process to decreased IRBP levels.

Disruption of the external limiting membrane (ELM) and the outer retinal barrier (ORB) may play a role in leaking of IRBP into the outer nuclear layer or Bruch's membrane. Studies of animals in diabetic conditions have shown decreased occluding abilities in the Müller cell tight junctions compromising the external limiting membrane [37]. Also retinal pigment epithelium (RPE) dysfunction in early stage diabetes has been described in animal models [38]. It is still unclear the impact of these mechanisms over the IRBP levels.

4. Outcomes of IRBP's decreased levels in diabetes

Due to its importance on the visual cycle, it is expected that decreased levels of IRBP produce electrophysiological and morphological changes that manifest itself in the damage to the photoreceptors and the impaired visual cycle.

Deficit of blue-flicker discrimination has been observed in the early stages of diabetes [39]. ERGs have revealed lower oscillatory potential amplitudes suggesting alterations in the photoreceptors and the vision cycle [40–42]. Additionally, color vision has been shown to be altered in these early diabetes stages. Adaptometry studies have also shown alteration in diabetes; even with transient hyperglycemia a patient can have a delay in dark adaptation [43–45].

One study in *Meriones shawi*, an animal model with a human-like macula, after streptozotocin-induced diabetes showed alterations in the morphology of the photoreceptor outer segments. Interestingly, the foveal cones appear to be mostly affected revealing a loss of approximately 30% of the M-cones 7 weeks after type 2 diabetes was induced in the animals [46]. Studies in rats also have shown alterations in the photoreceptor outer segments with the S-cones and the M-cones most severely affected [47].

It has been found that glucose levels can influence the vision cycle rhodopsin regeneration ratio [48, 49]. Recently, one research group found depletion of rhodopsin regeneration with an accompanying decrease in STRA6, IRBP, and 11-cis retinal (11-cRAL) in a diabetic animal model [30].

5. Future directions

IRBP deficiency in diabetes could importantly impact DR progression although the relationship between its levels and the complications in diabetes remain unclear. Previous evidence suggest that it potentially impacts DR outcomes. In addition, some retinoid analogues have shown to be beneficial in the prevention of early stage DR due to their antioxidant properties [50, 51]. IRBP has been shown to have these anti-oxidant properties against some vision cycle retinoid sub-products [18].

IRBP deficiency can promote the accumulation of the cytotoxic bis-retinoid A2E. This molecule has been described to be involved in the pathogenesis of age-related macular degeneration (AMD) [52, 53] and Stargardt disease [54]. A2E is known to be able to produce cytotoxicity by destabilizing membranes, generating reactive oxygen species and producing photo-oxidation [55–58]. Since A2E is a lipofuscin precursor, fundus autofluorescence can be clinically used to detect its presence [59, 60]. However, hard exudates can decrease autofluorescence interfering with the evaluation of lipofuscin [61]. It would be expected that this accumulation of lipofuscin precursors in diabetes would increase the risk for developing AMD. Many studies have shown contradictory results and this relationship has not been established [62–65]. The actual accumulation, as well as the role of A2E in diabetes complications, is unclear and require further investigation.

It is important to reveal the mechanisms responsible for decreased IRBP in diabetes and to establish its role in DR in order to establish novel approaches for the prevention of these vision threatening events.

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