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Biomarker Identification of Vitreous Fluid for Diabetic Retinopathy

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Diabetic retinopathy (DR), a serious and debilitating complication of diabetes, is one of the leading causes of blindness worldwide. Early diagnosis and prevention of retinopathy is crucial in ameliorating diabetes-induced vision loss. Prolonged hyperglycemia in diabetic patients causes irreversible pathological changes in the retina, leading to proliferative DR with retinal neovascularization and diabetic macular edema (DME) [1,2]. Although intensive metabolic control is a highly effective in controlling DR, recent research has identified the key role of vascular endothelial growth factor (VEGF) in the vascular lesions found in DR, and new agents that block VEGF action are effective treatment in patients for whom metabolic control alone is insufficient [3]. Whereas the role of high blood glucose has been suggested to be the primary catalyst for the biomolecular and cellular changes seen in the retina, less is known regarding the intraocular biochemical changes associated with the mechanism that potentially contributes to the pathogenesis of proliferative DR.

For investigating the pathogenesis of DR, 2 main strategies are applied for the analysis of vitreous protein. The first strategy is antibody-based detection of vitreous cytokines. In previous studies of vitreous cytokines in DR, conventional enzyme-linked immunosorbent assay (ELISA) were used [4,5]. Recently, simultaneous analysis of the expression profiles of multiple cytokines and chemokines in the vitreous fluid was performed using an array system of antibody-coated beads [6]. Compared with the control group, interleukin (IL)-6, IL-8, IL-10, IL-13, interferon-inducible 10-kDa protein (IP-10), monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1 beta (MIP-1β), platelet-derived growth factor (PDGF), and VEGF levels in the vitreous fluid were significantly higher in the DR group. The second strategy is proteomic analysis of vitreous proteins [7-11]. Fluorescence-based difference gel electrophoresis (DIGE) combined with matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) has enabled accurate quantitative comparisons of multiple proteins [12]. MALDI-TOF MS analysis of vitreous fluid detected approximately 1300 protein spots, and 25 of these intravitreal proteins were differentially expressed between DME and control groups. Hemopexin, beta-crystallin S, clusterin, and transthyretin were found to be specifically associated with DME. In a study using the same technique, 1242 protein spots were detected containing 19 differentially expressed intravitreal proteins between proliferative DR and control groups [13]. Differences in hemopoxin, clusterin, and pigment epithelium-derived factor (PEDF) levels were also observed between proliferative DR and control groups. Therefore, hemopexin expression was upregulated in DME and proliferative DR, whereas clusterin expression was downregulated in DME and proliferative DR and PEDF expression was downregulated only in proliferative DR.

Hemopexin is an acute-phase plasma glycoprotein and is expressed in multiple cell lines derived from different tissues [14]. Importantly, increasing glucose concentrations in vitro increased hemopexin expression and modulated the reactive oxygen species levels in cells; these effects were partially reversed by addition of reduced glutathione. Clusterin is associated with protection from apoptosis of retinal cells [15]. In a mouse model of DR, clusterin reduced the leakage from vessels in the diabetic retina and restored expression of tight junction proteins [16]. These observations suggested that clusterin may play an important role in preventing diabetes-induced breakdown of the blood–retinal barrier. PEDF is produced by the retinal pigment epithelium and is as a major inhibitor of intraocular angiogenesis [17]. Although whether PEDF levels are altered in patients with proliferative DR is still controversial, PEDF may be a candidate target protein for the treatment of DR.

A combined study using cytokine assays and proteomics should provide the most basic information for comparisons of DR patients and controls. Further studies to evaluate the precise role of these potential biomarkers of DR pathogenesis and their potential as therapeutic targets are warranted.

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