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Review

Retinal fibrosis in diabetic retinopathy

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ABSTRACT

In response to injury, reparative processes are triggered to restore the damaged tissue; however, such processes are not always successful in rebuilding the original state. The formation of fibrous connective tissue is known as fibrosis, a hallmark of the reparative process. For fibrosis to be successful, delicately balanced cellular events involving cell proliferation, cell migration, and extracellular matrix (ECM) remodeling must occur in a highly orchestrated manner. While successful repair may result in a fibrous scar, this often restores structural stability and functionality to the injured tissue. However, depending on the functionality of the injured tissue, a fibrotic scar can have a devastating effect. For example, in the retina, fibrotic scarring may compromise vision and ultimately lead to blindness. In this review, we discuss some of the retinal fibrotic complications and highlight mechanisms underlying the development of retinal fibrosis in diabetic retinopathy.

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1. Introduction

Fibrosis is an intricate, reparative process that develops in response to acute or chronic injury. It requires a normally functioning vascular network, and its success in restoring the damaged tissue depends at least in part on the proper remodeling of extracellular matrix (ECM). Following injury-induced release of chemotactic agents, the vascular system facilitates timely recruitment of appropriate inflammatory cells to mediate the reparative process and facilitate synthesis and remodeling of new ECM. However, if the new ECM deposition is altered and leads to disturbed tissue architecture, it can contribute to a compromised fibrotic process. Additionally, the success of the reparative process and restoration of the functionality of the damaged tissue is, at least in part, dependent on the location of such fibrotic processes (Yang et al., 2013). In the retina, for example, the location of the damaged area can profoundly affect retinal functionality and visual acuity.

The involvement of fibroblasts in the fibrotic process is well established. Fibroblasts exist ubiquitously in connective tissues extrinsic to the central nervous system (CNS) and are distinct from epithelial cells in that they are nonpolar and are not bound to the basal lamina unilaterally, allowing migratory ability across surfaces. A primary function of fibroblasts is to respond to injury by synthesizing various ECM components including collagens, elastic fibers, glycosaminoglycans, and glycoproteins, and thereby mediating a reparative process. The glial cells, particularly the Müller cells, mediate the tissue-healing response in the retina, much like the fibroblasts in non-CNS tissue.

Cell proliferation, ECM expansion, and neovascularization are key steps in the development and progression of proliferative diabetic retinopathy (PDR) (Ban and Twigg, 2008). These events are typically growth factor-driven in response to hypoxia and inflammatory insults, and they promote the formation of fibrotic tissue on the retinal surface or in the vitreous cavity (Friedlander, 2007; Ban and Twigg, 2008). Ultimately, the tractional forces generated by the fibrotic process during neovascularization result in the separation of the inner neurosensory retina from the outer retinal pigment epithelium (RPE) resulting in retinal detachment (Yang et al., 2008). Although it is unclear which cell types participate in generating tractional force contributing to retinal detachment in PDR, Müller cells are known to produce stress fibers that are well established in providing mechanical strength to the retinal detachment process (Guidry et al., 2003).

Two types of fibrotic tissues, fibrovascular proliferative tissue and avascular proliferative tissue, can develop in patients with PDR and contribute to retinal detachment (McMeel, 1971). Fibrovascular proliferative tissue is formed when abnormal new vessels grow during PDR on the retinal surface. Avascular proliferative tissue is less common and consists of amorphous avascular membranes. Of the three types of retinal detachment, rhegmatogenous, traction, and exudative, PDR is most often associated with traction retinal

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detachment. During traction retinal detachment, the scar tissue on the retinal surface "pulls" at the retina, detaching it from the underlying layer, whereas during rhegmatogenous retinal detachment, retinal tears develop allowing fluid accumulation in the subretinal space (Humphrey et al., 1993). This fluid together with the tractional force of the vitreous on the retina can promote retinal detachment.

2. Histopathology of retinal fibrosis

Histopathologic studies of PDR have demonstrated that fibrovascular proliferative tissue and avascular proliferative tissue are closely associated with the development of PDR. Fibrovascular proliferative tissue is most common and histological studies indicate that new vessels originating and extending from the superficial plexus or capillaries of the retina often develop within the fibrous network (McMeel, 1971). The extension of the newly formed vessels and the appearance and progression of contracture of connective tissue is believed to contribute to retinal fibrosis (Dobree, 1964). In the early stages of retinal fibrosis, abnormal new vessels proliferate devoid of fibrotic tissue, followed by an intermediate stage in which translucent fibrotic connective tissue progressively fills the intervascular spaces, resulting in the formation of a dense, white, avascular scar in the late stage. The fibrovascular proliferative tissue expands peripherally from its origin, while avascular proliferative tissue is typically a thin membrane that extends from the edges of fibrovascular proliferation (McMeel, 1971). Of note, fibrotic tissue may also develop secondary to iatrogenic intervention, typically at sites of therapeutic treatment such as photocoagulation, especially in areas of flat neovascularization (McMeel, 1971).

3. Müller cells mediate retinal fibrosis

Retinal Müller cells play an important role in retinal fibrosis by participating in the maintenance of retinal homeostasis (Reichenbach et al., 1993; Newman and Reichenbach, 1996; Mizutani et al., 1998; Bringmann and Reichenbach, 2001); however, following retinal injury, disturbed homeostatic balance activates Müller cells resulting in increased cell proliferation, cellular shape change, and vascular endothelial growth factor (VEGF) production (Humphrey et al., 1993; MacLaren, 1996; Amin et al., 1997; Reichenbach et al., 1997; Dyer and Cepko, 2000). Müller cells are reported to assume the role of fibroblasts, which likely do not exist in the retina (Friedlander, 2007). Importantly, the Müller cells, astrocytes, and microglia together with the vascular cells participate in the fibrotic process (Bringmann and Reichenbach, 2001; Guidry, 2005; Friedlander, 2007; Yang et al., 2013).

Apart from Müller cells, astrocytes and microglial cells contribute to retinal fibrosis as well. A study suggests that in the mouse retina, astrocytes act as a proangiogenic cell type in the retinal vascular system because they are capable of producing VEGF and fibronectin, and contribute to retinal angiogenesis in retinal fibrosis (Uemura et al., 2006). Additionally, much like Müller cells astrocytes express intermediate filament, glial fibrillary acid protein (GFAP) in response to injury (Lewis and Fisher, 2003). Another study reported that microglia in human diabetic retina expresses CTGF, which promotes ECM formation, fibrosis, and angiogenesis (Kuiper et al., 2004).

Although Müller cell-mediated fibrosis is essential for retinal repair, this process may also contribute to the progression of diabetic retinopathy (Amin et al., 1997; Lieth et al., 1998; Dyer and Cepko, 2000; Friedlander, 2007; Yafai et al., 2013) (Fig. 1). In PDR, increased vitreal insulin-like growth factor-1 (IGF-1) upregulates hypoxia-inducible factor-1α (HIF-1α) (Grant et al., 1993; Meyer-Schwickerath et al., 1993; Boulton et al., 1997; Poulaki et al., 2004; Jiang et al., 2013; Tarr et al., 2013). Hypoxic Müller cells increase the stability of HIF-1α and induce its nuclear localization (Xin et al., 2013), leading to VEGF overexpression (Rodrigues et al., 2013). HIF-2α has also been implicated in the activation of Müller cells and their response to hypoxia (Mowat et al., 2010). As such, the HIF factors mediate Müller cell activation. Müller cells respond to hypoxia by expressing increased levels of VEGF and basic fibroblast growth factor (bFGF) (Ai et al., 2013; Rodrigues et al., 2013; Xin et al., 2013; Yafai et al., 2013), which together promote retinal neovascularization (Cheng et al., 1998). Growth of aberrant vasculature on the retinal surface promotes retinal gliosis inducing tractional forces, which significantly increases the risk of retinal detachment and subsequent vision loss (Guidry, 2005; Friedlander, 2007; Morello, 2007).

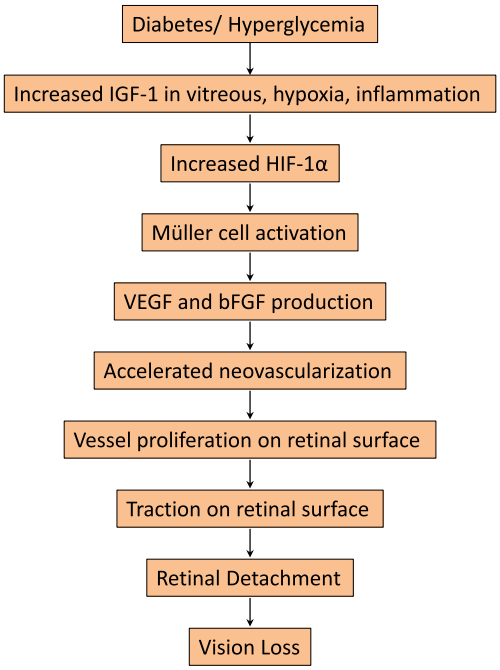

Fig. 1. A schematic flowchart showing potential effects of diabetes or hyperglycemia on retinal fibrosis and vision loss in diabetic retinopathy. Diabetes and associated hyperglycemia can increase serum and vitreous levels of IGF-1, an angiogenic neuroprotective factor. IGF-1, hypoxia, and inflammation are all contributing factors, which can increase HIF-1α level. Upregulation of HIF-1α is known to contribute to Müller cell activation and induce angiogenic factors VEGF and bFGF that aid in the development and progression of neovascularization, which contributes to retinal fibrosis. The combined effect of new abnormal blood vessel growth and retinal fibrosis generates tractional forces, which pull on the retina, contributing to retinal detachment and subsequent vision loss in diabetic retinopathy.

Müller cell activation represents one of the earliest steps in the pathogenesis of diabetic retinopathy (Nork et al., 1987; Robison et al., 1990; Amin et al., 1997). Targeting cyclin D and $p27^{Kip1}$, modulators of Müller cell activation, could regulate the progression of fibrosis in diabetic retinopathy, since activation of Müller cells is an early step in both processes (Dyer and Cepko, 2000). In cases of chronic or severe exposure to stress, Müller cells undergo "massive gliosis" (Bringmann and Reichenbach, 2001; Guidry, 2005), which represents significant cell proliferation and subsequent formation of "gliotic scars" both within the retina and on the subretinal and epiretinal surfaces (Guidry, 2005). Since diabetic retinopathy is a long-term complication, the likelihood of massive gliosis due to chronic hyperglycemia may increase (Sueishi et al., 1996; Amin et al., 1997).

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