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Mini review

The role of matricellular proteins in glaucoma

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ABSTRACT

Glaucoma is an optic neuropathy affecting approximately 60 million people worldwide and is the second most common cause of irreversible blindness. Elevated intraocular pressure (IOP) is the main risk factor for developing glaucoma and is caused by impaired aqueous humor drainage through the trabecular meshwork (TM) and Schlemm's canal (SC). In primary open angle glaucoma (POAG), this elevation in IOP in turn leads to deformation at the optic nerve head (ONH) specifically at the lamina cribrosa (LC) region where there is also a deposition of extracellular matrix (ECM) molecules such as collagen and fibronectin.

Matricellular proteins are non-structural secreted glycoproteins that help cells communicate with their surrounding ECM. This family of proteins includes connective tissue growth factor (CTGF), also known as CCN2, thrombospondins (TSPs), secreted protein acidic and rich in cysteine (SPARC), periostin, osteonectin, and Tenascin-C and -X and other ECM proteins. All members appear to play a role in fibrosis and increased ECM deposition. Most are widely expressed in tissues particularly in the TM and ONH and deficiency of TSP1 and SPARC have been shown to lower IOP in mouse models of glaucoma through enhanced outflow facility. The role of these proteins in glaucoma is emerging as some have an association with the pathophysiology of the TM and LC regions and might therefore be potential targets for therapeutic intervention in glaucoma.

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1. Introduction

1.1. Glaucoma

Glaucoma is the second leading cause of irreversible blindness worldwide, thought to affect 60 million people (Kelliher et al., 2006; Quigley and Broman, 2006). In the western world, glaucoma affects

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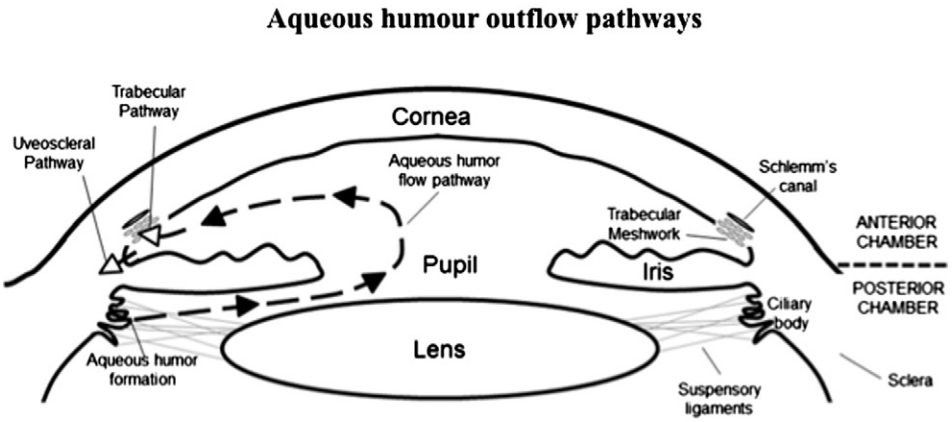

Fig. 1. Aqueous humor outflow pathways. The primary risk factor for onset and progression of glaucoma is raised intraocular pressure (IOP). IOP is generated in the anterior eye via the aqueous humor circulation system. The aqueous humor is secreted by the ciliary epithelium and flows to the anterior chamber to leave through the trabecular meshwork (TM) outflow pathways. In primary open angle glaucoma (POAG) the resistance to outflow increases in the TM, particularly in the juxtacanalicular connective tissue (JCT) region culminating in elevated IOP. The TM and Schlemm's canal (SC) provide the major route for the outflow of the aqueous humor from the eye and it is here responsible for the increased IOP associated with POAG due to increased outflow resistance. Changes in extracellular matrix (ECM) are thought to be involved in the increased outflow resistance in POAG. While the molecular events responsible for the impaired TM drainage and deposition at the ONH are not well understood, it is thought that ECM turnover in these regions and the proteins responsible may be contributory factors. Cellular contraction and relaxation of TM and SC cells are also important factors in the maintenance of normal aqueous humor outflow facility and agents that can alter contraction can change outflow rates. *Genetics and Environmental Stress Factor Contributions to Anterior Segment Malformations and Glaucoma by Yoko A. Ito and Michael A. Walter*, "*Glaucoma — Basic and Clinical Aspects*" *edited by Shimon Rumelt, ISBN 978-953-51-1064-4, InTech, April 4, 2013.*

1–2% of the population over the age of 40 and the prevalence rises to 5% of those aged 70 years and over. It is a chronic progressive optic neuropathy with characteristic extracellular matrix (ECM) changes in the optic nerve head (ONH) and subsequent visual field defects. The primary risk factor for onset and progression of glaucoma is raised intraocular pressure (IOP) (Anon., 1998a,b; Gordon et al., 2002; Leske et al., 2004; Spry et al., 2005). IOP is generated in the anterior eye via the aqueous humor circulation system. The aqueous humor is secreted by the non-pigmented ciliary epithelium and flows to the anterior chamber to leave through the trabecular meshwork (TM) outflow pathways (Tamm, 2009). The TM and Schlemm's canal (SC) provide the major route for the outflow of the aqueous humor from the eye and it is here responsible for the increased IOP associated with primary open angle glaucoma (POAG) due to increased outflow resistance (Moses, 1977; Maepea and Bill, 1992). In POAG the resistance to outflow increases (Johnson et al., 2002) in the TM, particularly in the juxtacanalicular connective tissue (JCT) region culminating in elevated IOP (Johnson, 2006) (Fig. 1). Changes in ECM are also thought to have a role in the increased outflow resistance of the TM in POAG. While the molecular events responsible for the impaired TM drainage and ECM deposition at the ONH are not well understood, it is thought that ECM turnover in these regions and the proteins responsible may be contributory factors. Cellular contraction and relaxation of TM and SC cells are important factors in the maintenance of normal aqueous humor outflow facility and agents that can alter contraction can change outflow rates (Epstein et al., 1987, 1999; Tian et al., 2000; Wiederholt et al., 2000; Rao et al., 2005; Tian and Kaufman, 2005; Yu et al., 2008).

Chronic elevation in IOP causes a deformation at the ONH specifically at the lamina cribrosa (LC) region in the ONH. Hernandez et al., showed that it is the LC which undergoes fibrosis and mechanical failure in POAG (Hernandez et al., 1990). The LC region of the ONH consists of perforated fibroelastic plates through which the unmyelinated retinal ganglion cell axons pass through before they converge as the optic nerve (Anderson, 1969). ONH astrocytes and LC cells are members of the glial cell population of the ONH and attach to the basement membrane. LC cells can be differentiated from astrocytes by their non-expression of glial fibrillary acid protein (Hernandez et al., 1988). These laminar plates contain ECM such as elastin and collagens I, III, V and VI and it is here the nerve axons degenerate in parallel with the apoptotic cell death of retinal ganglion cells and results in progressive visual field loss. Axonal degeneration may be caused by the blockade of the anterograde and retrograde axonal transport systems at the level of the LC leading to a deprivation of neurotrophic signals (Quigley, 2011) and is accompanied by a local remodeling of the ECM in the ONH. The disturbed ECM remodeling at the ONH is particularly evident in the LC region (Burgoyne et al., 2005).

The ECM is a key component of multicellular organisms forming an intricate proteinaceous network that fills the extracellular spaces and provides structural support and tissue organization (Ozbek et al., 2010). Maintaining the integrity of the ECM is necessary for the normal structure and function of connective tissue. However, in fibrosis there is an excessive deposition of ECM to pathological rather than physiological levels. Alterations in the levels of modulators of ECM homeostasis such as matrix metalloproteinases (MMPs) −2 −3 and −14 also occur in the POAG LC (Yan et al., 2000a; Yuan and Neufeld, 2001). MMPs are zinc-dependent endopeptidases that degrade ECM components such as collagen and fibronectin. MMPs have been described as important modulators of aqueous humor outflow through their ability to remodel the TM ECM and maintain a constant outflow resistance and ensuing IOP (De Groef et al., 2013). MMPs are therefore potential therapeutic targets for the treatment of glaucoma specifically their ability to modulate aqueous humor outflow (De Groef et al., 2013).

The connective tissue changes in POAG affect the TM and the LC and may result from a common defect in these cells. It has been proposed that the TM and the LC are biochemically similar tissues and that the cells cultured from the two are very similar (Hernandez et al., 1987; Rehnberg et al., 1987; Morrison et al., 1989; Yun et al., 1989; Wilson et al., 1993; Clark et al., 1994; Steely et al., 2000; Kirwan et al., 2009). The fibrotic phenotype associated with glaucoma in the LC and TM regions has been widely reported (Rehnberg et al., 1987; Hann et al., 2001; Kirwan et al., 2009). In glaucoma, the LC undergoes thickening (Yang et al., 2010) and posterior migration (Yang et al., 2011) in the early stages of the disease process, and later undergoes shearing and collapse of the LC plates finally leading to a thin fibrotic connective tissue structure/scar (Jonas et al., 2003) where we observe disturbed ECM metabolism (Burgoyne et al., 2005) and increased deposition of collagens and elastin (Hernandez and Pena, 1997). Similar to the LC, the TM of patients with POAG is characterized by the build-up of ECM material (Tektas and Lutjen-Drecoll, 2009) and this accumulation eventually results in increased ouflow resistance with subsequent elevated IOP. Pseudoexfoliation (PXF) syndrome is currently the single most important identifiable risk factor for open-angle glaucoma (Schlotzer-