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Review

From DNA damage to functional changes of the trabecular meshwork in aging and glaucoma

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ABSTRACT

Glaucoma is a degenerative disease of the eye. Both the anterior and posterior segments of the eye are affected, extensive damage being detectable in the trabecular meshwork and the inner retina-central visual pathway complex. Oxidative stress is claimed to be mainly responsible for molecular damage in the anterior chamber. Indeed, oxidation harms the trabecular meshwork, leading eventually to endothelial cell decay, tissue malfunction, subclinical inflammation, changes in the extracellular matrix and cytoskeleton, altered motility, reduced outflow facility and (ultimately) increased IOP. Moreover, free radicals are involved in aging and can be produced in the brain (as well as in the eye) as a result of ischemia, leading to oxidation of the surrounding neurons. Glaucoma-related cell death occurs by means of apoptosis, and apoptosis is triggered by oxidative stress via (a) mitochondrial damage, (b) inflammation, (c) endothelial dysregulation and dysfunction, and (d) hypoxia. The proteomics of the aqueous humor is significantly altered in glaucoma as a result of oxidation-induced trabecular damage. Those proteins whose aqueous humor levels are increased in glaucoma are biomarkers of trabecular meshwork impairment. Their diffusion from the anterior to the posterior segment of the eye may be relevant in the cascade of events triggering apoptosis in the inner retinal layers, including the ganglion cells.

Contents

Abbreviations: AC, anterior chamber; AH, aqueous humor; CLAN, cross-linked actin network; CM, ciliary muscle; CTM, corneo-scleral trabecular meshwork; ECM, extracellular material/matrix; EGL, endothelial glycocalyx layer; ET, endothelin; GSH, glutathion; HTG, high-tension glaucoma; IOP, intraocular pressure; JCT, juxtacanalicular tissue; LC, lamina cribrosa; LGN, lateral geniculate nucleus; LPA, lysophosphatidic acid; MGP, inhibitor of calcification matrix Gla; miRNAs, microRNA; NOS, nitric oxide synthase; NTG, normal-tension glaucoma; ONH, optic nerve head; PKA, protein kinase A; PKC, protein kinase C; POAG, primary open-angle glaucoma; PS, posterior segment of the eye; PRDX2, oxidized peroxiredoxin-2; RGC, retinal ganglion cell; ROS, free radicals; SC, Schlemm's canal; SIPS, stress-induced premature senescence; SPARC, secreted protein acidic and rich in cysteine; TM, trabecular meshwork; TNF, tumor necrosis factor; UPR, unfolded protein response; UTM, uveal trabecular meshwork; VEGF, vascular endothelial growth factor.

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1. Introduction

Glaucoma is a multi-factorial disease that results in apoptosis of retinal ganglion cells (RGCs). Attempts to explain how the damage that occurs in the anterior segment can propagate to the posterior segment have made reference to "Increasing intraocular pressure (IOP)" (Ha, 1999) and 'ischemia' (Flammer, 1994), both acting on the trabecular meshwork (TM) and on the optic nerve head (ONH).

1.1 Pathogenetic hypothesis

One theory does not exclude the other. According to the pressure theory, IOP causes optic nerve axonal compression at the lamina cribrosa (LC), blockage of axoplasmic flow, interference in retrograde neurotrophin transport to RGCs, and apoptosis-driven cell death. Indeed, it has been shown that pressure alone can stimulate apoptosis in neuronal cell cultures (Agar et al., 2000). According to the vascular/ischemic theory, a perfusion deficit could induce atrophy of the optic nerve and progression of glaucomatous neuropathy. The pre-laminar ONH contains the last branches of the central retinal artery, which supply the inner retina and the most superficial portion of the ONH (Onda et al., 1995). It is possible that damage to these vessels contributes to RGC injury (Hayreh, 1969; Hayreh et al., 2004). Blood vessel injury in glaucoma may contribute to altered local blood flow modulation. This latter theory could explain cases of normal tension glaucoma (NTG) better than the former (Shields and Wadsworth, 1977). Retinal ischemic injury results in a self-sustained cascade involving neuronal depolarization, calcium influx and oxidative stress; this cascade is triggered by an energy deficit and an increase in glutamatergic stimulation (Osborne et al., 2004), leading to the loss of RGC (Sucher et al., 1997; Chidlow and Osborne, 2003; Goto et al., 2002; Lafuente et al., 2002; Wang et al., 2002). The regulation of extracellular levels of glutamate in both physiological and pathological conditions seems to be a prerequisite for the prevention of neurodegeneration, especially in the retina, where increased levels of this neurotransmitter are associated to the development of glaucoma (Dreyer et al., 1996; Osborne et al., 1999). Glutamate appears to be increased by different types of stimuli, including injury, ischemia and elevated IOP (Vorwerk et al., 2000; Martin et al., 2002; Arundine and Tymianski, 2004). However, the exact cellular mechanisms remain unclear, although, biomechanical factors can change the function of the TM, determining the IOP increase (Saccà et al., 2016). Furthermore, moderate pressure elevation may directly damage RGC integrity by injuring mitochondria (Ju et al., 2009). IOP, cerebrospinal fluid pressure and arterial blood pressure are physiologically correlated with each other (Wang et al., 2014). It seems very likely that the orbital cerebrospinal fluid space is associated with cerebrospinal fluid pressure, and that the estimated cerebrospinal fluid pressure correlates better with open-angle glaucoma-related parameters than IOP does (Jonas et al., 2014).

1.1. Noxious factors

After exposure to ischemia and elevated hydrostatic pressure, RGCs and glial cells secrete tumor necrosis factor alpha (TNF-α), nitric oxide (NO) and other noxious agents, and RGC apoptosis has been seen to be attenuated by about 66% by a neutralizing antibody against TNF-alpha and by 50% by a selective inhibitor of inducible NOS (Tezel and Wax, 2000). In this case, the secretion of TNF-alpha and the glial cells would have pathogenic relevance even though oxidative stress is an early event in hydrostatic pressure/IOP-induced neuronal damage (Liu et al., 2007). In any case, the retinal response to mechanical stress involves a diversity of signaling pathways that sense and transduce mechanical strain and orchestrate both protective and destructive secondary responses (Križaj et al., 2014).

1.2. Genetic factors

Many genetic factors may determine the disease, from vascular endothelial growth factor (VEGF), one of the main factors respon-