Biomechanical aspects of axonal damage in glaucoma: A brief review☆

Cheri Stowell [a, 1], Claude F. Burgoyne [a, 1], Ernst R. Tamm [b, 1], C. Ross Ethier, PhD [c, *], The Lasker/IRRF Initiative on Astrocytes and Glaucomatous Neurodegeneration Participants[2]

[a] Optic Nerve Head Research Laboratory, Discoveries in Sight Research Laboratories, Devers Eye Institute, Legacy Health System, Portland, Oregon, USA
[b] Institute of Human Anatomy and Embryology, University of Regensburg, Regensburg, Germany
[c] Department of Biomedical Engineering, Georgia Institute of Technology/Emory University, Atlanta, GA, USA

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ABSTRACT

The biomechanical environment within the optic nerve head (ONH) is complex and is likely directly involved in the loss of retinal ganglion cells (RGCs) in glaucoma. Unfortunately, our understanding of this process is poor. Here we describe factors that influence ONH biomechanics, including ONH connective tissue microarchitecture and anatomy; intraocular pressure (IOP); and cerebrospinal fluid pressure (CSFp). We note that connective tissue factors can vary significantly from one individual to the next, as well as regionally within an eye, and that the understanding of ONH biomechanics is hindered by anatomical differences between small-animal models of glaucoma (rats and mice) and humans. Other challenges of using animal models of glaucoma to study the role of biomechanics include the complexity of assessing the degree of glaucomatous progression; and inadequate tools for monitoring and consistently elevating IOP in animal models. We conclude with a consideration of important open research questions/challenges in this area, including: (i) Creating a systems biology description of the ONH; (ii) addressing the role of astrocyte connective tissue remodeling and reactivity in glaucoma; (iii) providing a better characterization of ONH astrocytes and non-astrocytic constituent cells; (iv) better understanding the role of ONH astrocyte phagocytosis, proliferation and death; (v) collecting gene expression and phenotype data on a larger, more coordinated scale; and (vi) developing an implantable IOP sensor.

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Contents

1. Introduction

Previous controversies as to whether and how intraocular pressure (IOP) is important in the pathogenesis of glaucoma have faded over the past 20 years. There is now broad consensus among both scientists and clinicians that IOP and the mechanisms by which the relevant tissues respond to IOP are critical in the pathogenesis of glaucoma. It is also recognized that glaucomatous damage can be initiated at any level of IOP; further, additional

genetic and/or environmental risk factors contribute to the eye-specific risk of developing the disease, some of which are IOP-related and some of which are IOP-independent. Nonetheless, while the biomechanical processes by which IOP contributes to retinal ganglion cell (RGC) axon damage within the optic nerve head (ONH) are considered to be a fundamental part of the pathogenesis of glaucoma, they are not fully understood.

This article focuses on the role of ONH biomechanics in glaucoma. For the purposes of this discussion we define the ONH to include the tissues within and immediately surrounding the scleral canal. In this article we identify fundamental questions and discuss the usefulness (including benefits and limitations) of various animal models to answer these questions. We will also identify important developments over the last five years and propose experiments for the next five years. Because the Lasker Meeting sessions dealing with astrocytes (Tamm et al., 2017) and ONH biomechanics (the present report) were combined into a single discussion session, some overlap between the articles devoted to each session is necessary to ensure that each summary is complete.

2. Questions related to ONH structure and glaucoma susceptibility

We first focus on connective tissues elements of the ONH, principally the lamina cribrosa (LC) and peripapillary scleral (pp-sclera), since these elements provide the majority of the structural support to the ONH in the face of IOP. Are all humans formed equally with respect to the quality and quantity of their ONH connective tissues? The answer is almost certainly "no" for any genetically diverse species, including humans. Moreover, the likelihood of intra-individual (between-eye) and regional (within-eye) differences in connective tissue properties and glaucomatous damage susceptibility must be borne in mind.

ONH connective tissue variability arises from both macro- and micro-architectural factors. Macro-architectural (anatomical) factors include the size and shape of the scleral canal; the thickness of the LC and pp-sclera; and LC beam and pore dimensions. Micro-architectural factors include the density, quantity, orientation and molecular nature of relevant fibrillar and non-fibrillar extracellular matrix (ECM) components, which ultimately depend on the ability of fibroblasts and astrocytes to robustly maintain and remodel ECM components. The micro-architectural factors determine the local tissue material properties. We must also recall that each of these factors likely change with age and disease state. Taken together, differences in these factors will influence the biological, mechanical and physical properties of the ONH connective tissue elements.

The combination of macro-architecture (anatomic) features and material properties defines the overall structural stiffnesses of ONH connective tissues, which in turn dictate the magnitude of global and local deformations (strains) experienced by the ONH tissues for a given pressure-related load, including loads due to IOP, cerebrospinal fluid pressure (CSFp) and possibly even orbital pressure.

Apart from determining the material properties of a given connective tissue, micro-architectural features also influence diffusion coefficients (including those of signaling molecules) and the ease with which monocytes and macrophages pass into and within those tissues. These issues should be of special importance within the LC beams, as the lamina is the only location in the central nervous system where astrocyte processes do not directly contact local capillaries (Burgoyne, 2011; Hogan et al., 1971). Because the RGC axons have no direct blood supply within the LC, it is believed they are dependent upon local astrocytes for nutrient delivery. The ECM of LC beams, as well as the basal laminae of the LC beam endothelial cells and astrocytes, are thus potential barriers to nutrient delivery to the RGC axons within this region.

To further complicate the situation, signaling molecules that cause cells to modify ECM quality or quantity, such as those of the transforming growth factor-β (TGF-β) family, can bind to ECM components and be activated and released from the ECM in response to mechanical cues. Consequently those molecules likely play an important role in ONH biomechanics and its changes with aging and glaucoma (Burgoyne and Downs, 2008; Tamm et al., 2017).

ONH connective tissues stiffen with age (Fazio et al., 2014a, 2014b; Grytz et al., 2014), although it is not clear if the individual components of those tissues stiffen at different rates. The process may not progress at comparable rates in all humans, as there is strong evidence that it is influenced by genetic factors (Fazio et al., 2014b). It is currently assumed that the LC contributes to RGC axon susceptibility within the ONH at all levels of IOP and at all ages, but the critical molecular components of this susceptibility remain unknown. Some humans develop glaucomatous optic neuropathy at low ("normal") levels of IOP, while others can be followed with IOPs in the 30–40 mmHg range without evidence of the neuropathy for 5–10 years (there currently are no studies that extend beyond 10 years of follow up). Are there specific biological/mechanical/physical properties of the ONH connective tissues that can wholly or partially explain these differences in susceptibility?

With these concepts in mind, another question is: What are "good" and "bad" properties of the ONH connective tissues? One would presume that "good" properties are those that prevent reactive changes in ONH astrocytes and microglia, keep monocytes and macrophages out of the ONH, and facilitate normal function of RGC axons. Still, what is the exact role of those cells in glaucoma? Do glial cells become reactive to protect from neuronal damage or do they accelerate it? Is it better to have rigid or compliant ONH scleral connective tissue elements to achieve all or some of those goals? Alternatively, is a mismatch of a stiff LC and compliant sclera best? What makes for a robust versus a weak LC in terms of axonal preservation? These important questions remain unanswered.

A related point concerns the role of focal laminar defects ("pits") (Irvine et al., 1986; Ohno-Matsui et al., 2013). While it might be argued that a "good" LC is one without pits, pits might instead be beneficial strain relievers for the rest of the ONH connective tissue elements. Clinically, some patients have focal LC defects, and although RGC axons in the pit area will sustain damage regardless of the IOP, the rest of the ONH and its optic nerve axons remain stable. Overall, better phenotyping of the biomechanical responses of the ONH connective tissues along with improved molecular characterization is required to allow their contributions to RGC axon susceptibility to be determined.

Years ago, two laboratories independently demonstrated that in both monkeys (non-human primates) and humans the connective tissue beams of the LC are made of collagen I, III, and IV (the latter especially in the endothelial and astrocyte basal lamina), and elastin (Hernandez et al., 1990; Morrison et al., 1988, 1990). The respective roles of those molecules for the biomechanical properties of the LC are as yet unclear. If monkeys could be genetically modified, the effects of changing collagen and elastin in the ONH scleral connective tissue elements (including the LC) could be assessed. Unfortunately, as of now, such genetic modifications are only feasible in mice in which the ONH contains a cellular (glial) rather than a connective tissue LC (Sun et al., 2009).

It should be noted that the biomechanical environment of the LC is intricately linked to that of the pp-sclera (Burgoyne et al., 2005; Sigal et al., 2009a, b), since the pp-sclera establishes the boundary conditions for the LC beam insertions into and through the scleral canal wall. The magnitude of pp-scleral load delivered to the LC is likely larger than the load due to the translaminar pressure difference (defined as IOP minus retrolaminar tissue pressure, which is