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Research review paper

Walking through trabecular meshwork biology: Toward engineering design of outflow physiology

Cula N. Dautriche, Yubing Xie, Susan T. Sharfstein *

SUNY College of Nanoscale Science and Engineering, 257 Fuller Road, Albany, NY 12203, USA

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ABSTRACT

According to the World Health Organization, glaucoma remains the second leading cause of blindness in the world. Glaucoma belongs to a group of optic neuropathies that is characterized by chronic degeneration of the optic nerve along with its supporting glia and vasculature. Despite significant advances in the field, there is no available cure for glaucoma. The trabecular meshwork has been implicated as the primary site for regulation of intraocular pressure, the only known modifiable factor in glaucoma development. In this review, we describe the current models for glaucoma studies, primary culture, anterior eye segments, and animal studies and their limitations. These models, especially anterior eye segments and animal tissues, often require careful interpretation given the inter-species variation and are cumbersome and expensive. The lack of an available *in vitro* 3D model to study trabecular meshwork cells and detailed mechanisms of their regulation of intraocular pressure has limited progress in the field of glaucoma research. In this paper, we review the current status of knowledge of the trabecular meshwork and how the current advances in tissue engineering techniques might be applied in an effort to engineer a synthetic trabecular meshwork as a 3D *in vitro* model to further advance glaucoma research. In addition, we describe strategies for selection and design of biomaterials for scaffold fabrication as well as extracellular matrix components to mimic and support the trabecular architecture. We also discuss possible uses for a bioengineered trabecular meshwork for both developing a fundamental understanding of trabecular meshwork biology as well as high-throughput screening of glaucoma drugs.

Contents

* Corresponding author. Tel.: +1 518 437 8820; fax: +1 518 437 8687.
E-mail address: ssharfstein@albany.edu (S.T. Sharfstein).

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Introduction

The leading cause of irreversible and preventable blindness in the world, glaucoma is the chronic degeneration of the retinal ganglion cells along with their supporting glia and vasculature leading to the characteristic optic-nerve cupping (Kwon et al., 2009b). Significant advances in glaucoma research have identified 1) elevated intraocular pressure (IOP) as the critical risk factor, 2) the inner wall region of the trabecular meshwork (TM) outflow pathway as the primary site of aqueous humor outflow resistance, 3) approximately 30 genes providing a genetic basis for glaucoma, including myocilin, optineurin, and SPARC, and 4) several classes of IOP lowering agents for the management of open-angle glaucoma (Zhang et al., 2012). Progress, however, has been impeded by limitations in the availability of proper *in vitro* models to study TM cells and detailed mechanisms of their regulation of IOP.

The currently available *in vitro* models include freshly isolated cells and tissues as well as cultured cell lines; however, all have their limitations. The small amount of TM tissue obtained from a single eye limits many biochemical and pharmacological experiments (Pang et al., 1994). Establishment of primary TM cell culture was first described by Polansky et al. (1984) and remains the principal means of studying these cells *via* biochemical and pharmacological experiments. The development of a fast-growing and stable human TM (HTM) cell line (Pang et al., 1994) may provide a valid model for pharmacological studies, but it is not ideal for understanding TM biology and physiology when used in conventional 2D studies on tissue culture plastic. Currently, anterior segments of animal or human cadaver eyes are used to study the outflow facility and test the effects of medications on the TM, but these perfusions are cumbersome and expensive.

The impetus for an *in vitro* model is evident and its implications are endless. Glaucoma therapy would be significantly improved by an understanding of the molecular mechanisms that drive outflow resistance. Such a model would facilitate more rapid advances in understanding TM physiology, glaucoma pathology, and drugs affecting the TM. To exploit the advances in tissue engineering and micro-/nanofabrication to create an *in vitro* model of the TM will require a firm understanding of the TM ultra-structure, TM biology and outflow physiology, as well as the pathogenic process of the glaucomatous TM. Mimicking the complex architecture of the TM and its functions presents an important frontier in the field of eye tissue engineering. Nanotechnology provides a variety of useful tools for engineering a synthetic TM as many nanoscale materials and fabrication techniques can be adapted to mimic the complex 3D architecture of the trabecular meshwork.

This review will highlight the current school of thought on TM cell biology and physiology with respect to the challenges they pose in recreating the TM, followed by nano-engineering strategies to create an *in vitro* TM outflow system for understanding TM physiology and evaluating potential anti-glaucoma drugs.

Ultra-structure, biochemistry and cell biology of the trabecular meshwork

Trabecular outflow pathways are the major drainage sites of aqueous humor from the eye. From its production in the ciliary body, aqueous humor enters the anterior chamber of the eye where it is filtered by the TM to the endothelial lining of Schlemm's canal (SC) to the collecting channels and finally joins the aqueous veins (Fig. 1) (Fan and Wiggs, 2010). The literature supports the TM and/or the endothelial lining of SC as primary sites of outflow resistance. Thus, it appears that the main cause of primary open angle glaucoma (the most common form of glaucoma) is increased resistance to flow of aqueous humor through the TM and/or SC due to structural and/or biochemical changes.

Trabecular meshwork in vivo

Porous in nature and spanning an average thickness of 70 μm in the anterior portion and between 100 and 130 μm in the posterior portion (Dietlein et al., 2000), the TM encompasses three regions which differ in structure and origin, allowing for unidirectional filtration of the aqueous humor. Examining the TM through the anterior chamber of the eye, the inner uveal trabecular meshwork (UTM) is first encountered, followed by the deeper corneoscleral trabecular meshwork (CTM), and last, the juxtacanalicular tissue (JCT) or cribriform region, which is localized directly adjacent to the inner wall endothelium of

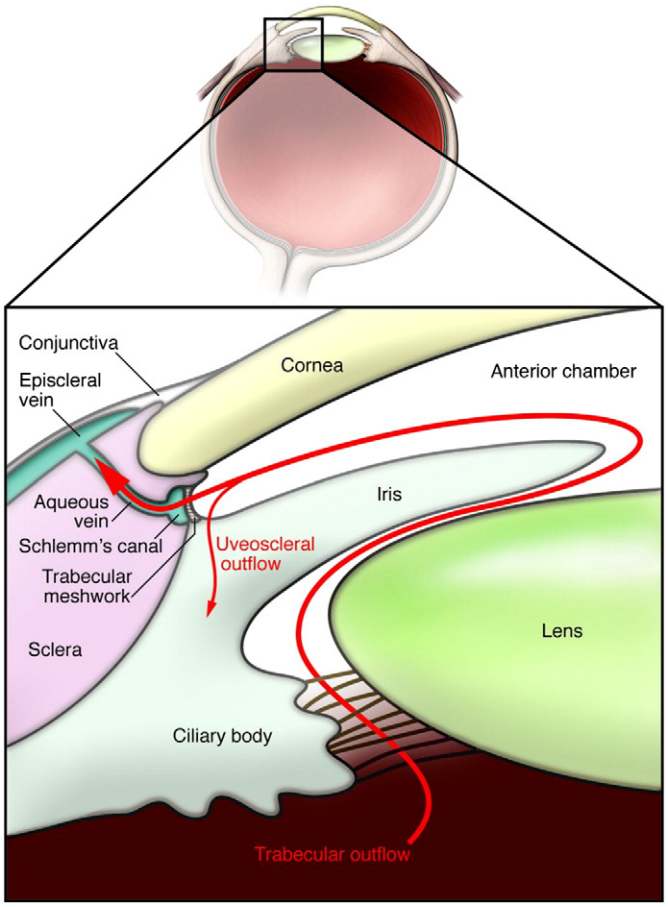

Fig. 1. Anterior chamber structures involved in aqueous humor production and outflow in the eye.
Reproduced with permission of American Society for Clinical Investigation from Fan, B.J. and J.L. Wiggs, Glaucoma: genes, phenotypes, and new directions for therapy. J Clin Invest, 2010. 120(9): p. 3064–72.