Experimental Eye Research 141 (2015) 42–56

Contents lists available at ScienceDirect

Experimental Eye Research

journal homepage: www.elsevier.com/locate/yexer

Using genetic mouse models to gain insight into glaucoma: Past results and future possibilities

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ARTICLE INFO

Article history:
Received 18 February 2015
Received in revised form
16 June 2015
Accepted in revised form 23 June 2015
Available online 24 June 2015

Keywords:
Neuroinflammation
IOP
Axonal degeneration
Trabecular meshwork
Mouse genetics
Genomics
Neurodegeneration
DBA/2J

ABSTRACT

While all forms of glaucoma are characterized by a specific pattern of retinal ganglion cell death, they are clinically divided into several distinct subclasses, including normal tension glaucoma, primary open angle glaucoma, congenital glaucoma, and secondary glaucoma. For each type of glaucoma there are likely numerous molecular pathways that control susceptibility to the disease. Given this complexity, a single animal model will never precisely model all aspects of all the different types of human glaucoma. Therefore, multiple animal models have been utilized to study glaucoma but more are needed. Because of the powerful genetic tools available to use in the laboratory mouse, it has proven to be a highly useful mammalian system for studying the pathophysiology of human disease. The similarity between human and mouse eyes coupled with the ability to use a combination of advanced cell biological and genetic tools in mice have led to a large increase in the number of studies using mice to model specific glaucoma phenotypes. Over the last decade, numerous new mouse models and genetic tools have emerged, providing important insight into the cell biology and genetics of glaucoma. In this review, we describe available mouse genetic models that can be used to study glaucoma-relevant disease/pathobiology. Furthermore, we discuss how these models have been used to gain insights into ocular hypertension (a major risk factor for glaucoma) and glaucomatous retinal ganglion cell death. Finally, the potential for developing new mouse models and using advanced genetic tools and resources for studying glaucoma are discussed.

1. Introduction

Glaucoma is defined and unified by a distinct pattern of retinal ganglion cell (RGC) death. However, glaucoma is a heterogeneous disorder (often termed 'glaucomas') with RGCs likely insulted in multiple ways. Even within a patient, different RGCs may experience different stresses that trigger or contribute to cell loss (Casson et al., 2012). Age, elevated intraocular pressure (IOP; or ocular hypertension), and family history are major risk factors for glaucoma. IOP regulation is in itself complex and in most cases where IOP is a factor in glaucoma, it is not known why it becomes pathologically elevated. Given this complexity, multiple models of glaucoma are required to fully understand the disease. A single animal model can never precisely model all aspects of all human glaucomas, and modeling specific aspects of the cell biology and/or the genetics of human glaucoma requires careful consideration. The choice of the animal model should be made based on the precise

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http://dx.doi.org/10.1016/j.exer.2015.06.019
0014-4835/

glaucoma-relevant phenotype(s) being assessed. With this perspective, mice are a powerful tool to unlock the genetic causes, susceptibility factors, and physiological pathways underlying human glaucoma. The similarity between human and mouse eyes, coupled with the ability to use a combination of advanced cell biological and genetic tools in mice, make the mouse an excellent system for unraveling the molecular pathways that control glaucoma pathophysiology (see Figs. 1 and 2 for overview).

Several genes that cause glaucoma-relevant phenotypes have recently been identified in mice. Moreover, mouse models with mutations in known human glaucoma genes have been used to study the genetic underpinnings of glaucoma pathobiology. These models provide insight into (i) the cell biology underlying specific phenotypes of glaucoma, (ii) the physiology of glaucoma-relevant tissues, (iii) the pathophysiological response of cells subjected to glaucoma-relevant insults, and (iv) the molecular genetics of glaucoma-relevant phenotypes and endophenotypes. As there are many in depth reviews about mouse models of glaucoma (e.g. Libby et al., 2005b; Lindsey and Weinreb, 2005; Morrison et al., 2011) and about how mouse genetics can be used to study physiology and pathophysiology (Ermann and Glimcher, 2012; Justice et al., 2011; Schofield et al., 2012; van der Weyden et al., 2011), in this review we discuss the strengths and the utility of using genetic mouse models of glaucoma to gain insights into the cell biology and genetics underlying glaucoma-relevant phenotypes (Section 2), key aspects of anterior segment disease (Section 3) and retinal ganglion cell death (Section 4) that have been elucidated through the use of genetic models. Furthermore, we highlight ways that the mouse can be used to address unanswered questions about glaucoma and how it can be used in the future to help unravel the complexities of human glaucoma.

2. Strengths and utility of mice to model glaucoma-relevant phenotypes

In order to study a disease-relevant phenotype, it is ideal, though not always possible, to have characteristics of the phenotype carefully defined in both humans and the animal model. This is especially critical when studying a heterogeneous disease like glaucoma in which multiple distinct pathological insults are observed in several ocular tissues. Mouse models have in the past both improved our understanding of human disease and have proved to be an invaluable tool for discovering therapeutic targets. Overall, current knowledge of the physiology of the anterior segment, retina, and optic nerve in humans and mice strongly support the utility of the mouse to model key phenotypes associated with glaucoma. However, as our understanding of the key molecular pathogenic events in human glaucoma continues to grow, animal models will need to be refined to include specific aspects of human glaucoma as new information becomes available.

2.1. Glaucoma relevance of the mouse anterior segment

Over the last decade, many studies have found that mouse

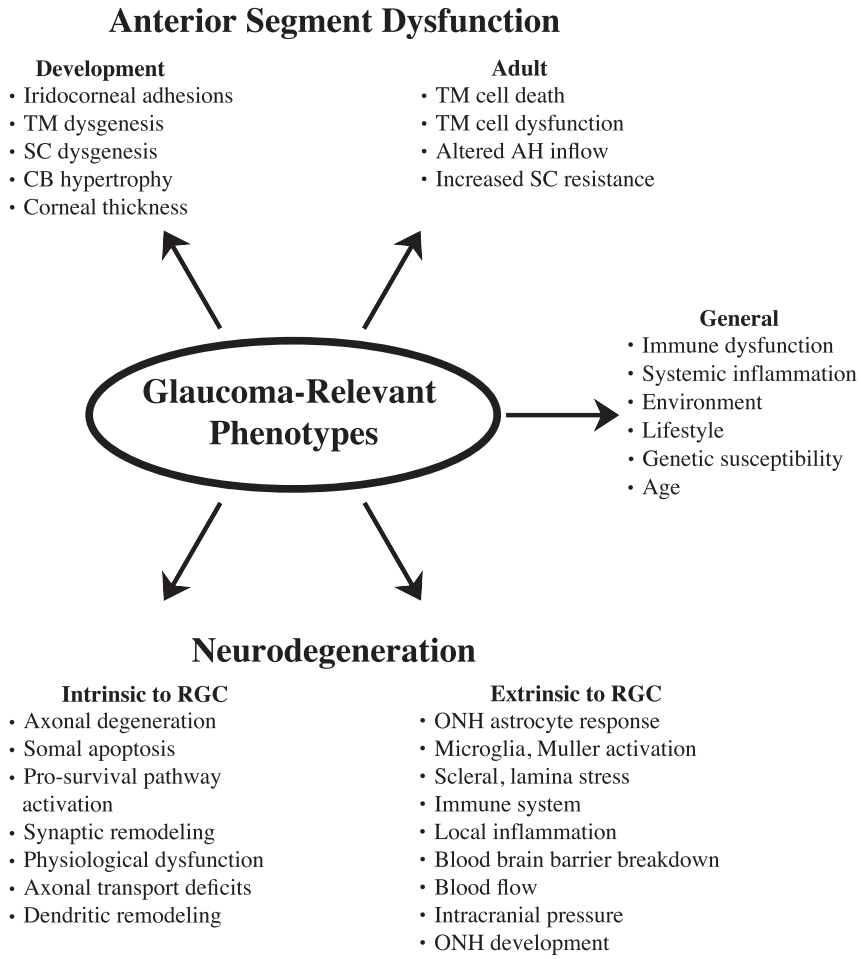

Fig. 1. Glaucoma-relevant phenotypes that can be modeled and studied in mice. To study the cell biology of glaucoma, it is helpful to breakdown the disease into the individual events and/or phenotypes that can contribute to the disease. TM, trabecular meshwork; SC, Schlemm's canal; CB, ciliary body; ONH, optic nerve head; RGC, retinal ganglion cell.