The mouse anterior chamber angle and trabecular meshwork develop without cell death

ABSTRACT

These results support morphogenic mechanisms involving organization of cellular and extracellular matrix components without cell death or atrophy.

INTRODUCTION

Background Abnormal anterior segment development is often associated with elevated intraocular pressure (IOP), an important risk factor for the blinding disease glaucoma. The anterior segment of the eye is filled with a clear fluid known as the aqueous humor or aqueous. Maintenance of IOP is dependent on a balance between aqueous formation and aqueous outflow. The primary source of aqueous is blood flowing through the arteries of the ciliary body. The aqueous is secreted by the ciliary body into the posterior chamber between the iris and lens. It then flows into the anterior chamber, the space between the cornea and iris, before draining from the eye at the iridocorneal junction. The iridocorneal junction is located in a region known as the iridocorneal angle because of the aqueous filled angular recess between the iris root and cornea. One drainage route consists of a trabecular meshwork (TM) of connective tissue covered by endothelial like trabecular cells and a Schlemm's canal (SC). The aqueous percolates through channels or intertrabecular spaces in the TM before entering SC. The fluid collected by SC drains into aqueous veins that connect to the canal. This route is generally accepted to be the major drainage pathway for the aqueous. Egress via the loose connective tissue meshwork and blood vessels of the uvea (choroid, iris and ciliary body) and the outer wall of the eye (sclera) also contributes to aqueous drainage . Primary access of aqueous to the uveoscleral route is likely deep in the angle recess at the iridocorneal junction. The resistance to aqueous flow presented by the tissues of the TM, SC, and likely uvea and sclera are important determinants of the rate of aqueous outflow and IOP. The molecular mechanisms responsible for normal or abnormal development of the iridocorneal angle, its structures, and increased resistance to aqueous drainage in glaucoma are not well defined. Cell migration, proliferation, and differentiation are important for the development of this ocular region. Cells of the periocular mesenchyme migrate into the developing eye and differentiate into various anterior segment structures including components of the ciliary body, the TM, iris stroma, corneal endothelium and corneal stroma. The origin of the periocular mesenchyme was originally suggested to be the paraxial mesoderm. Later fate mapping studies using quail-chick chimeras show extensive cranial neural crest contribution to this tissue. Based on these avian studies, the mammalian periocular mesenchyme is generally accepted as neural crest derived. Recent cell grafting and cell labeling studies of craniofacial morphogenesis in mouse embryos confirm a neural crest derivation of the mammalian periocular mesenchyme. Additionally, however, they demonstrate the presence of cranial paraxial mesoderm-derived cells in this tissue. Thus, aberrations of both neural crest and mesoderm cell migration or differentiation may contribute to anterior segment dysgenesis and glaucoma. After the migrating mesenchymal cells reach the anterior margin of the developing optic cup they must form the tissues of the iridocorneal angle. The iridocorneal angle is initially occupied by a densely packed mass of mesenchymal cells. As TM development proceeds the cellular mass differentiates, organizes and develops channels to produce the mature meshwork. The developing TM

and iris separate forming the deep angle recess through which the aqueous passes to access the TM. The mature meshwork consists of trabecular beams separated by intertrabecular spaces through which the aqueous percolates. The trabecular beams are covered on both surfaces by endothelial-like trabecular cells and the cores of the beams are composed of extracellular matrix components such as collagen and elastic tissue. How the complex TM develops and how spaces form in the initially continuous cellular tissue is not clear. Several theories have attempted to explain the differentiation and morphogenesis of the mesenchyme that forms the tissues of the iridocorneal angle (see [, ,]). Some of these theories propose atrophy or resorption of the mesenchyme as development progresses to create the structures and spaces important for aqueous drainage while others propose a reorganization of cells with no cell death or atrophy. Whether cell death or atrophy occurs during TM and iridocorneal angle development remains controversial. Cell death was prominent in rat, but not in monkey, human or dog eyes. It is not clear if different mechanisms are important in rodents as compared to these other species, if there is something unusual about the studied rat strain, or if cell death occurs in the other species but was not detected due to inadequate tissue sampling or the stages analyzed. The mouse represents an important experimental model for understanding mammalian development and diseases caused by its abnormalities. In studied mammalian species, iridocorneal angle development is incomplete at birth. Although various studies have characterized in detail the prenatal development of the mouse eye there is very little published about the normal structure or postnatal development of the mouse iridocorneal angle [, ,]. The aims of this work were to determine the developmental profile of the mouse iridocorneal angle to its mature form and to assess the role of cell death in modeling the angle recess and TM. We present a light and electron microscopic (EM) evaluation of iridocorneal angle development in staged embryos and through eight postnatal weeks, when the angle structures have reached full maturity. The mouse and human TM and SC have similar structures, and the developmental progression is similar except for the accelerated time frame in mice. Extensive use of light microscopy, EM and a cell death assay (on sections spanning complete eyes) failed to identify cell death at all tested ages in various mouse strains. These results substantiate models of iridocorneal angle mesenchymal differentiation and modeling that involve organization of cellular and extracellular matrix components without cell death or atrophy, and they suggest a conservation of developmental mechanisms between mice and non-rodent mammals.

CONCLUSION

Conclusions Our results support a model of mesenchymal differentiation and iridocorneal angle development that involves reorganization of cellular and extracellular matrix components without cell death or atrophy. The use of genetically different mouse strains indicates that the absence of cell death is typical in mice and not unique to an individual strain. The lack of cell death, similar developmental profile, and similarities in mature angle structure in both humans and mice suggests a conservation of general developmental mechanisms between mice and non-rodent mammals. For general anterior segment development, this is supported by the observations that genetic deficiency of transcription factors such as PAX6, PITX2, FOXC1, and LMX1B that are expressed in the periocular mesenchyme results in anterior segment dysgenesis in both humans and mice. In general, however, previous mouse studies have not examined the effects of mutations on the TM and SC. This is partly due to limited documentation of the sequence of events underlying iridocorneal angle

development and limited documentation of the mature angle structures in mice. The current study provides important baseline information for mechanistic studies of angle development in the existing mouse models of anterior segment dysgenesis. Additionally, it will facilitate experiments with mutant mice to determine how newly identified genes function in angle development and how the pathways in which they participate overlap or interact with each other. These experiments will enhance understanding of the developmental processes involved in anterior segment formation, and glaucomas associated with anterior segment dysgenesis.