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ABSTRACT
Development of the anterior segment of the eye is closely associated with neural crest cell migration and specification. Its development is complex as it requires the functioning of a combination of local factors, receptors, inductors, and signalling between tissues such as the optic cup and periocular mesenchyme (POM). POM is comprised of neural crest-derived mesenchymal progenitor cells that give rise to numerous important anterior segment structures such as the cornea, and trabecular meshwork. Several genes involved in the migration and specification of the POM have been identified, including *PITX2, FOXC1,* and *Tfap2b*. The author, with the help of Judith West-Mays and Vanessa Martino, has conducted an extensive literature search on recently published articles surrounding anterior segment dysgenesis and its associated genes and transcription factors in order to construct this review paper.

INTRODUCTION

Anterior segment dysgenesis (ASD) is a developmental abnormality in which the anterior segment of the eye is affected, in particular the cornea, iris, lens, and structures of the iridocorneal angle. Approximately 50% of ASD patients are at risk for developing glaucoma, a leading cause of vision loss nationwide.[1-3] Proper development of anterior segment tissues is crucial in maintaining the healthy, normal-functioning eye as these tissues serve important functions ranging from visual acuity, and light transmission and refraction, to maintaining an optimal intraocular pressure (IOP). Differentiation and specification of the neural crest-derived mesenchymal progenitor cells into their prospective anterior segment tissues mark one aspect of proper development of the anterior segment of the eye.

Neural crest cells (NCC) are multipotent, migratory stem cells that emerge from the dorsal neural tube and serve critical functions in embryonic development.[4-6] They migrate to different regions of the body and form diverse cell lineages and structures, including the peripheral nervous system, craniofacial skeleton, as well as numerous ocular and periocular structures.[4,6] Improper development of the neural crest can cause craniofacial and ocular defects such as Axenfeld-Rieger syndrome (ARS).[7-10] ARS is a disorder that affects anterior segment structures derived from the periocular mesenchyme (POM) and has been found to cause glaucoma in up to 75% of patients after early childhood diagnosis.[13-16] NCC, with respect to ocular development, are generally derived from the forebrain (prosencephalon) and midbrain (mesencephalon). They give rise to corneal endothelium and stroma, iris stroma, ciliary body stroma, and trabecular meshwork, all of which are important anterior structures of a normal, healthy eye.[4,5,11,12] Many clinical entities of ASD exist with distinct manifestations, contributing to the complexity of the disorder. This paper aims to focus on differentiation and specification of NCC in relation to the onset of ASD, an area that necessitates further research.

NCC originate at the neural plate border where the neural folds join to form the neural tube.[4-6] An array of neuroectoderm-derived cranial NCC, otherwise known as POM, migrates distinctively from the prosencephalon and mesencephalon into the eye in three waves.[4] The first wave of cells moves and settles in the space between the anterior surface of the lens and surface ectoderm to form the corneal endothelium.[4,6] The second wave of cells migrates into either the space between the surface ectoderm or the corneal epithelium and the endothelium to form portions of the corneal stroma.[4,6] Lastly, the third wave moves in between the corneal endothelium and the anterior rim of the optic cup, giving rise to the ciliary body stroma, iris stroma, and trabecular meshwork.[4,6] Interruption in any of these three waves of NCC migration could potentially contribute to defective anterior segment tissues and development of ASD.

ASD GENES

PITX2 and FOXC1

There are two ASD genes, *PITX2** and *FOXC1*, that have been extensively researched in the past decade. Numerous studies have demonstrated their close relation to the embryonic development of the anterior segment of the eye and their extensive role in

* PITX2, not italicized and in capital letters, represents a transcription factor. *PITX2*, italicized and in capital letters, represents a human gene. Pitx2, in lower case, represents an animal gene.

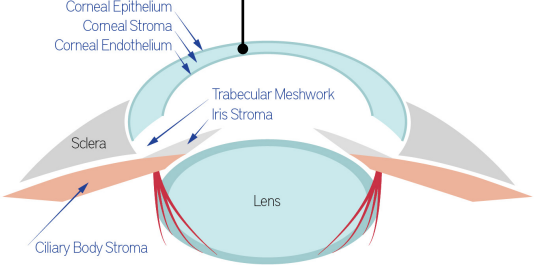

FIGURE 1: NCC migration/specification. Here, NCC give rise to all the structures labelled in blue.