Update on Anterior Segment Development with Emphasis on Genetics and Correlation with Pathogenesis of Developmental & Primary Open Angle Glaucoma

Abstract

The ocular anterior segment structures are derived from periocular mesenchyme, which consists of neural crest cells and cranial paraxial mesoderm. Many embryological facts have been developed based on the fates of neural crest and mesoderm in mice and in chick. The interactions between the ocular mesenchyme and the surface ectoderm derived cells are also essential for the coordination of anterior segment development. These interactions are mediated by several *transcription factors* expressed in both the epithelial and mesenchymal cells and are being extensively studied. Anterior Segment dysgenesis (ASD) is a spectrum of disorders of variable phenotypic expressions caused by abnormal migration and differentiation of neural crest cells. Patients with ASD are susceptible to develop infantile glaucoma, congenital endothelial dystrophy, sclerocornea and aniridia. There has been an evident overlapping observation in the genetic mutations between the ASD phenotypic spectrum and glaucoma especially the primary congenital glaucoma (PCG) since it involves abnormal development of Schlemm's canal and the drainage structures. In this review, we are highlighting the steps in the embryological development of the anterior segment chamber structures. We also present the role of various transcription factors and link the above information to some of the genetic abnormalities, which are known in association with the pathogenesis of glaucoma.

Keywords: Anterior segment development; Embryology; Glaucoma; Transcription factor; Genetic

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Abbreviations: ASD: Anterior Segment Dysgenesis; PCG: Primary Congenital Glaucoma; TM: Trabecular Meshwork; ARS: Axenfeld-Rieger Syndrome; TGFα: Transforming Growth Factor α; EGF: Epidermal Growth Factor; TGFB1: Transforming Growth Factor B1; BMP4: Bone Morphogenic protein 4; POAG: Primary Open Angle Glaucoma; OHT: Ocular Hypertension

Introduction

There are 3 elements which contribute to the development of the human eye in the primitive embryo: the surface ectoderm, the neuroectoderm, and the neural crest which has been recognized as a potential source of mesenchymal tissue. The meso-dermal contribution is limited to the formation of extra ocular muscles and blood vessels endothelium [1]. The vertebrate neural crest not only gives rise to melanocytes, Schwann cells, neuroblasts and ganglion cells of the peripheral nervous system, but also has extensive contribution to the formation of facial cartilage, bone and teeth [1]. The primary function of the periocular mesenchyme is to establish cell lineages essential for the development of anterior segment structures [2,3]. Experiments in chicks have shown that this ocular mesenchyme is derived mostly from cranial neural crest in addition to a minor component from paraxial mesoderm [4,5]. It has been also demonstrated that the fates of neural crest and mesoderm in mice are similar to those in chick; however the mesoderm provides more contribution to the anterior segment structures in the mouse [6].

Through the course of the ocular development, the origin of various ocular structures will be as follows: The surface ectoderm will form the corneal epithelium and the lens, the neural ectoderm will form the retina and iris/ciliary body epithelia, while the corneal stroma, endothelium, sclera, iris/ciliary body stroma and muscle, trabecular meshwork are all derived from periocular mesenchyme which consists of neural crest cells and cranial paraxial mesoderm [3]. Schlemm's canal forms by re-modeling of the vasculature in the corneoscleral transition zone [7]. The interactions between the ocular mesenchyme and the surface ectoderm derived cells are essential for the coordination of anterior segment development. These interactions are mediated by transcription factors expressed in both the epithelial and mesenchymal cells [2].

Basic Embryology

In chicken embryos the tissues surrounding the anterior chamber, the cornea, the anterior chamber angle and the iris stroma are basically formed by successive waves of neural crest cells which migrate between the lens and the cranial epithelium between E4 and E7 [4]. The first wave of migration of the neural crest cells closest to the lens extends between the lens and the corneal epithelium. The lens capsule and the primary corneal stroma secreted by the corneal epithelium are important substrates for this migration [8,9]. These cells differentiate to form a simple cuboidal epithelium which is the future corneal

endothelium that separates the primary corneal stroma from the lens. The second wave begins at E6 and invades the primary corneal stroma. The cells populate the entire stroma and give rise to the corneal stromal fibroblasts [10]. The cells of a third wave contribute to the formation of the stromal component of the iris [3].

The cells at the anterior chamber angle (where the anterior surface of the iris meets the lateral ends of the corneal endothelium) begin to differentiate into the trabecular meshwork (TM) by E9 then continue to mature until hatching [11,12]. In the mouse it appears that there is a single influx of mesenchymal cells which later differentiate into the corneal endothelium and the stromal fibroblasts [13,14]. It is still undetermined whether the corneal endothelium in these eyes is specified before the migration and arrival of the cells or whether they are induced to become endothelium because of their location along the inner aspect of the cornea [15]. Gould and co-authors have summarized and illustrated the development of the anterior segment in 2 stages:

Prenatal development

Includes migration of the periocular mesenchyme between the corneal epithelium and anterior lens epithelium followed by its differentiation to form corneal endothelial cells and keratocytes by E12.5 [14,15]. The first appearance of the anterior chamber as a small space occurs by E14.5-15.5 when the corneal endothelium is formed. This is followed by extension of the anterior rim of the optic cup (which will form the iris/ciliary body pigmented epithelium) anteriorly and centrally to provide a base for the periocular mesenchyme which will form the iris/ciliary body stroma. By E16.5 the anterior chamber is formed and the presumptive iris stroma is not opposed to the cornea where the number of keratocytes plateaus after being steadily increasing within the stroma. The corneal stromal lamellar arrangement by E17.5 and the secondary lens fibres are produced at the equatorial areas of the lens. At this stage of development, formation of a functional corneal endothelium is thought to be a pre-requisite for the formation of the anterior chamber [15-18].

The lens is also believed to be important for the normal development of the neural crest-de-rived components of the cornea (endothelium and stroma) while its role in the formation of the corneal epithelium is a subject of debate. It has been shown that lens removal from chicken embryos at E4, the migrating cells between the lens and the cornea formed a multi-layered aggregate without identifiable endothelium and the collagen fibres of the corneal stroma were disorganized with heterogeneous diameter similar to the opaque sclera of the eye [19]. Furthermore the cell adhesion molecule, N-Cadherin, which is expressed by the corneal endothelial cells, was found to be dependent on signals from the lens epithelium [20]. The onset of N-Cadherin expression in the corneal endothelium occurs around E15, which suggests that the differentiation of the mesenchymal cells occurs after their arrival in the eye. It has been suggested that the expression of N-Cadherin creates the architectural cells which establish a "non-sticky" surface on the inner aspect of the cornea thus preventing the iris and the lens from becoming adherent to the exposed extracellular matrix (ECM) of the cornea [15].

Postnatal development

At birth, the corneal stroma is filled with keratocytes surrounded by ECM and the endothelium is defined, however Descemet's membrane is evident only by electron microscopy [18,21]. The mesenchyme of the iris stroma begins to synthesize pigment and becomes distinguishable from the mesenchyme of the TM and slight folds in the ciliary pigment epithelium become visible. By the postnatal day (P2 to P4), the cellularity of the corneal stroma decreases, the ciliary folds are more prominent and the iris stroma is darkly pigmented while the mesenchyme of the presumptive TM is densely packed [21].

By P6 to P8 Descemet's membrane is distinct. The iris and ciliary body structures and processes continue to mature by P8 to P10. At this stage, the mesenchymal mass at the iridocorneal angle remodels to allow the flow of aqueous humor through intertrabecular spaces between a network of organized beams originating from the ECM which includes fibronectin, collagen, laminin, elastin and vitronectin. In the mouse, the process of morphogenesis of these closely packed beams followed by tissue remodeling to open up the intertrabecular spaces, occurs without cell death or atrophy [21,22]. The aqueous humor passes through drainage structures known as giant vacuoles towards Schlemm's canal. These vacuoles are present by P18 then the anterior segment is fully developed by P21 except for minor remodeling [21].

The developmental anomalies of the anterior segment include abnormalities of the size and shape of the cornea and most importantly anterior chamber abnormalities. Anterior Segment Dysgenesis (ASD) is a spectrum of disorders caused by abnormal migration and differentiation of neural crest cells. The phenotypic expression of ASD ranges from a simple thickening of the Schwalbe's line (posterior embryotoxon) to more extensive disorganization of the anterior segment, including: iris hypoplasia, iridogoniodysgenesis (50-75% risk of associated glaucoma), Axenfeld-Rieger syndrome anomaly (associated with 50% risk of glaucoma and Peter's anomaly). Systemic features might be present where the term Axenfeld-Rieger syndrome (ARS) is used. Patients with ASD are susceptible to develop infantile glaucoma due to the impaired drainage of aqueous humor through the anterior chamber angle [23]. Other anterior segment anomalies have been correlated to several factors. A develop-mental arrest has been postulated where a layer of endothelial cells of neural crest origin covering the anterior chamber angle fails to regress late in gestation [24,25]. Environmental agents such as alcohol have been shown to produce such malformations [23].

The role of Cadherins in Neural Crest development

Neural crest cells are a population of migratory cells arising from the embryonic ectoderm then migrate to precise destinations in the embryo including the eye. These precursor cells are epithelial in character thus has apicobasal polarity, junctions and a basal lamina [26,27]. The migratory neural crest is a unique multipotent to mesenchymal transition (EMT) which is a process characterized by loss of the cell-cell contracts mediated by cell junctions, reorganization of the cytoskeleton and subsequently acquired motile phenotype. Thus the migratory neural crest cells are mesenchymal in nature and express the intermediate

filament vimentin. [28,29] This facilitates their spreading to precise destinations in the embryo where they differentiate into melanocytes, elements of peripheral nervous system and the cranio-facial skeleton. Distinct cadherins are expressed during the induction, migration and differentiation of the neural crest. These cadherins are a large family of calcium-de-pendent hemophilic binding cell adhesion molecules involved in morphogenetic processes including cell sorting, motility and signaling. Regulation of the cadherins intracellularly involves several catenins [30].

N-cadherin is up regulated in aggregating neural crest cells just prior to their differentiation in the dorsal root ganglia and sympathetic ganglia and in adult organisms. N-cadherin is observed in neural tissue, the retina, endothelial cells and fibroblasts as well as osteoblasts [31]. This has been studied in the eyes of chick embryos where the expression of N-cadherin and the formation of the corneal endothelium were found to be regulated by signals from the lens as mentioned earlier [20]. Furthermore, Cadherin expression in general, is also thought to be regulated through conventional growth factor signalling pathways [30]. The transgenic mice that express either transforming growth factor α (TGFα) or epidermal growth factor (EGF) showed failure of differentiation of the corneal endothelium with multiple anterior segment defects including attachment of the iris and lens to the cornea, reduction in the thickness of the corneal epithelium and corneal opacity. In these eyes N-cadherin expression was inhibited; however there was no molecular explanation for this correlation [15].

In regard to the catenins, it has been hypothesized that p120 catenin has an important role in modulating cadherin-based signalling possibly by inhibiting cadherin degradation thus regulating the total level of cadherin found in the cell [32,33]. This has been recently studied in p120 ctn knockout mice with resulting serious ocular anterior segment abnormalities including iridocorneal angle closure, anterior chamber obliteration with unrecognizable TM and absent or small Schlemm's canal in addition to corneal opacification/malformation with ciliary body hypoplasia. Mutant mice at the age of four months also showed significant decrease in the number of retinal ganglion cells. Optic nerves at the age of 3 months showed more nuclei and replacement of nerve fibres by glial cells with clear loss of myelin. These last 2 findings where indicative of an induced glaucoma. The migration of neural crest cells however was not affected indicating an effect on differentiation [34].

They also pointed out that the ocular defects in p120 ctn mutant mice has similar phenotype to Peter's anomaly which has been linked to several mutations such as AX6 on 11p13, PTTX2 on 4q 25q, 26, CYP1 B1 on 2 p22 p21 and FOXC1 on 6p25, however so far it has not been linked to any mutation in the p120 ctn-encoding CTnnD1 gene on 11q 12.1. Therefore the analysis of p120 ctn status in human ocular disorders might be justified in future studies [34]. The ocular phenotype of the TGFα transgenic mice mentioned before also has features in common with Peter's anomaly in humans, therefore the authors have exam-ined the expression pattern for the possible mutation of PAX6 in both TGFα trans-genic and non-transgenic eyes, but no differences in PAX6 expression were detected [15]. On the other hand, in both Peter's anomaly and α mouse model of fatal alcohol syndrome, the lens vesicle development and separation from the surface ectoderm are delayed leading to a persistent lens stalk which interferes with the normal migration of corneal mesenchymal cells [35].

This was not the case in the TGFα transgenic mice where the lens vesicle separation appeared to be normal [15]. The authors in that study have also speculated that in the TGFα and EGF transgenic mice, over stimulation of the TGF receptor in the corneal mesenchymal cells may have inhibited the TGFB/SMAD signaling pathway, which is essential for corneal endothelial specification and differentiation [15]. Several studies have shown that TGFB signaling appears to be essential for the formation of normal cornea during early eye development [36,37,38]. The TGFB super-family of secreted signaling molecules has an influence on several biological processes including: cell proliferation, cell differentiation, cell death, bone morphogenesis and wound repair [16]. It is divided into two separate branches with similar function: the bone morphogenetic protein/growth and differentiation factor (BMP/GDF) and the transforming growth factor- B1 (TGFB1) branch. Their activity involves ligand binding which initiates a cytoplasmic signal cascade that activates special SMAD proteins.

TGFB2 is another signaling ligand involved in anterior segment development. The corneas of TGFB2 -1- mice are thin with densely packed keratocytes and accumulation of ECM. The corneal endothelium also fails to differentiate and the anterior chamber is not formed [37]. There is an overlap in the pathways of the above signaling path-ways and it is possible that ECM components are actually downstream targets of these signaling molecules. ECM is known to be important for the development of many tissues and affect cellular metabolism and processes such as migration and differentiation [39,40]. The TGFB1/SMAD signaling pathway is thought to be affected in the TGFα transgenicmice in an earlier study mentioned before [15]. The effects of higher concentrations of TGFB1 on the lens and cornea were studied in constructed transgenic mice. Their corneas were thickened. The transgenic corneal stroma was vascularized and densely populated by star-shaped cells indicating that the stromal cells retained a mesenchymal phenotype [38].

The endothelium failed to differentiate. Accordingly, the anterior chamber and the stroma of iris/ciliary body did not develop supporting the idea, which was suggested by others that the formation of the corneal endothelium is essential for anterior chamber development [15,18]. Transgenic stromal fibroblasts in that study expressed α- smooth muscle actin similar to the situation in adult cornea. In addition, these corneas showed absence of collagen type VI, which is expressed in high amounts in the stroma of transparent differentiated cornea. In contrast, fibronectin and perlecan were present in significant amounts similar to adult cornea after injury and scar formation. These results support the hypothesis regarding the critical role of TGFB1 in the response of the cornea to injury and that antibodies against TGFB1 prevent corneal fibrosis. [41,42].

Genetics

Traditionally, physicians have classified ASD into different sub-types based on their clinical phenotypes: aniridia, Axenfeld's anomaly, Rieger's anomaly, iridogoniodysgenesis, Peter's anomaly

and posterior embryotoxon. On the other hand, primary con-genital glaucoma PCG is not traditionally grouped with forms of ASD that associate with glaucoma because such patient's do not present with visible malformations of the anterior chamber structures. Some researchers advocate grouping PCG in the spectrum of ASD phenotypes when studying their genetic background because PCG involves abnormal development of Schlemm's canal and the TM drainage structures and also because of the overlap in the genetic mutations behind their occurrence [43].

The overlap is evident with specific genes within the ASD spectrum, which do not uniquely associate with the same specific phenotypes. A good example is FOXC1 mutations, which have been implicated in iridogoniodysgenesis, Axenfeld-Rieger syndrome and Peter's anomaly that progress to glaucoma in 50% to 75% of affected cases [44-70]. On the other hand CYP1B1 which is typically associated with primary con-genital glaucoma (PCG), can also be associated with Peter's anomaly and glaucoma of later onset [71-74]. This proves the phenotypic heterogeneity resulting from the nature of the gene mutation itself or other factors suggested by the authors such as interaction with a known mutant gene to modify the phenotype with the example of PCG [43]. Presence of a dominant modifier locus was also proposed to influence the presence or absence of PCG in homozygous CYP1B1 mutation individuals from Saudi Arabian families [73]. Gould and John demonstrated the nine genes that affect ocular development and are associated with ASD or glaucoma in humans. These are presented in (Table 1), which is adopted from their article with simplification [43].

Table 1: Genes associated with anterior segment dysgenesis (ASD) or glaucoma in mouse and human*.

Gene/Name	Type	Mouse Phenotype		Human Disease	Human Location
		Heterozygous	Homozygous		
CYP1B1 Cytochrome P 450, family 1, subfamily B polypeptide 1	Enzyme	Normal	Iridocorneal angle dysgenesis [16]	Congenital glaucoma [44]	2p22
FOXC1 *Forkhead box C1*	Transcription factor	ASD [45,46]	Congenital hydrocephalus and ASD [45,47,18]	ASD [48,49]	6p25
FOXE3 Forkhead box E3	Transcription factor		Microphthalmia and ASD(abnormal lens) [50]	ASD+Cataract [51]	1p32
PAX6 Paired box protein Aniridia Type II protein AN2	Transcription factor	Microphthalmia [52]	Anophthalmia [52]	Aniridia+ASD [53]	11p13
PITX2 Paired-like homeodomain transcription factor 2 Pituitary Homeobox 2	Transcription factor	ASD [54]	ASD [55,56]	Axenfeld-Rieger +ASD [57]	4q25
PITX3 Paired-like homeodomain transcription factor 3 Pituitary Homeobox 3	Transcription factor		Aphakia [58]	ASD [59]	10q25
LMX1β LIM homeodomain class transcription factor 1, beta	Transcription factor	normal [60]	Microphthalmia and ASD [60,61]	Nail-patella syndrome [62,63]	9q34
MAF Musculoaponeurotic fibrosarcoma oncogene homolog	Transcription factor	normal [64]	Microphthalmia [64]	ASD+Cataract [65]	16q23
Eya1 Eyes absent homolog 1 (Drosophilia)	Nuclear protein		Open eyelids [66]	ASD [67]	8q13

* Adopted from Gould and John 2002, ASD= Anterior Segment Dysgenesis.

Other candidate genes were also mentioned for future studying in humans provided that a gene is evaluated in a significant number of patients in different populations with careful assessment of regulatory regions and check up of duplication and deletions [43]. The authors also advocated flexibility when defining human candidates based on mouse models so that a gene causing ASD in an animal model should not be discounted as a risk factor if not found by itself to cause human ASD [43]. The candidate most important genes include the growth factor. Bone morphogenic protein 4 (BMP4) where heterozygous mutant mice show dysgenesis of the ocular drainage structures, [75] with the human locus for this gene in a chromosome 14q22 [43] and another transcription factor FOXC2 which is involved in causing ASD in heterozygous mutant mice and its location is on chromosome 16q24 [46].

Recent studies have been investigating the role of known genes implicated in ASD in types of glaucoma, such as FOXC1, which has particular association with Axenfeld-Rieger syndrome [76]. The authors have shown that this gene exhibits a limited role in PCG where they have found only 5 novel mutations among their 210 cases of PCG. These mutations were not observed in ASD and all 5 cases didn't have any other extra ocular features [76]. Based on the identified genes in developmental glaucoma which include: CYP1B1, LMX1B, FOXC1, TGFB2 and bone morphogenic protein 4 (BMP4), in relation to adult glaucoma, the CYP1 is known to cause PCG, but is also involved in cases of juvenile open angle glaucoma while a CYP1B1 polymorphism has been also implicated as a susceptibility factor for POAG [77,78], LMX1B mutations cause dominantly-inherited Nail-Patella syndrome in which, approximately 33% of patients over 40 years of age had developed glaucoma and LMX1B haplotypes have shown to influence susceptibility to POAG [79,80].

Another group of researchers has selected the remaining 3 candidate genes for primary open angle glaucoma (POAG) susceptibility (TGFB2, BMP4 and FOXC1) with the hypothesis that sub-clinical mutations/polymorphism in these 3 genes may produce subtle abnormalities in anterior segment structure and function which can be a factor for ocular hypertension (OHT) and POAG [81]. The reasons to justify their selection included: first the fact that these genes are crucial for the normal development of the drainage system, second: elevated levels of TGFB2 have been found in cases of POAG and third the evidence that high IOP in POAG is due to increased resistance to aqueous outflow with associated biochemical and morphological changes in the TM [81]. The study however failed to demonstrate any significant allelic or haplotype associations between TGFB2, BMP4, FOXC1 and OHT/POAG and concluded that the common variants in these 3 genes do not play a major role in the pathogenesis of POAG within their population of British Caucasians [81].

Several ideas are subject to further future studies such as Mf1 which encodes a winged-helix/forkhead transcription factor and has been shown to be involved in the development of a differentiated corneal stroma and endothelium [18]. Then it has been more recently suggested to be involved in the regulation of TGFB1 signaling during the development of the anterior segment or vice versa [38]. On the other hand, more studies have been conducted for better understanding of the potential role of CYP1B1 in the pathogenesis of several PCG phenotypes in various geographical locations [82].

Summary

There are 2 general types of activities in the development of the eye: growth, which includes multiplication of cells and directional change in shape, structure and function of these cells- and induction of one ocular tissue by another. Anterior segment development is a complex process with most of the structures being derived from periocular mesenchyme consisting of neural crest cells and cranial mesoderm. ASD is a genetically heterozygous group of developmental disorders where the primary defect is in the migration and/or differentiation of the mesenchymal cells or even primary defect in the lens. Experiments in mice and other species provide useful information about developmental roles and pathways affected by ASD genes and they compliment further human studies, which are recommended for better understanding of ocular diseases and possible gene therapy in the future.

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