Embryonic Development of the Human Lens

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Abstract

The crystalline lens, which is derived from the surface ectoderm in contact with the optic vesicles, is the most important refractive media of the eye. The embryonic lens plays a regulatory role in the process of eye development and anterior segment formation. Any abnormality in embryonic development may lead to the occurrence of lens diseases such as congenital cataracts or even affect normal eye development. Gene transcription regulation is one of the most important factors for lens development and is involved in the whole development process. This chapter focuses on the process of embryonic lens development and its regulatory factors and also discusses the regulatory effect of the embryonic lens on eye development, which will help us understand the nature of lens diseases and explore the possibility of genetic intervention at the early stage of lens development.

The crystalline lens, an important part of the ocular refractive media, develops from the surface ectoderm immediately overlying the optic vesicle. Its development is regulated by multiple transcription factors and plays an important role in the development of the anterior segment of the eye and even the entire eyeball. Any abnormality in the embryonic development of the lens may lead to lens disorders such as congenital cataract or even affect the normal development of the entire eyeball. Therefore, knowledge of the embryonic development of the lens can facilitate our understanding of the molecular mechanism of lens abnormalities.

1.1 Histology and Embryology of Lens Development

1.1.1 The Formation of the Lens Primordium

Originating from the surface ectoderm immediately overlying the optic vesicle, the lens starts to form at the third week of gestation due to the interactive induction between the optic vesicle

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and the surface ectoderm (Fig. 1.1a). The optic vesicle contacts with the overlying surface ectoderm and induces the latter to thicken to form the lens placode, which is the primordium of lens formation (Fig. 1.1b). As the cellular source of the lens placode, the surface ectodermal cells beyond the contact site also divide and proliferate rapidly. They migrate and begin to differentiate when they reach the lens placode.

If the formation of the lens placode is disturbed, lens development will be hindered, which may even lead to aphakia. Isolated aphakia is rare and it is almost concurrent with other developmental disorders of the eyeball [1]. The authors once seen a case of developmental malformation diagnosed as aphakia, which manifested as a bean-sized lump of soft tissue beneath the conjunctiva. Despite its lack of complete ocular structures, consecutive pathological sections revealed partially developed uveal tissues with an irregular arrangement, lumpy and undeveloped retina-like tissue, and lumpy smooth muscle tissue (ciliary muscle). The cornea, trabecular meshwork, iris, lens, and vitreous body were not found. Besides, irregular collagen fiber bundles, adipose tissues, and cartilage lumps were visible.

1.1.2 Development of the Lens Vesicle

Induced by optic vesicle invagination that leads to the formation of the optic cup, the center of the lens placode also invaginates and forms the lens pit (Fig. 1.1c). As the lens pit expands, its bilateral front edges contract and migrate toward the

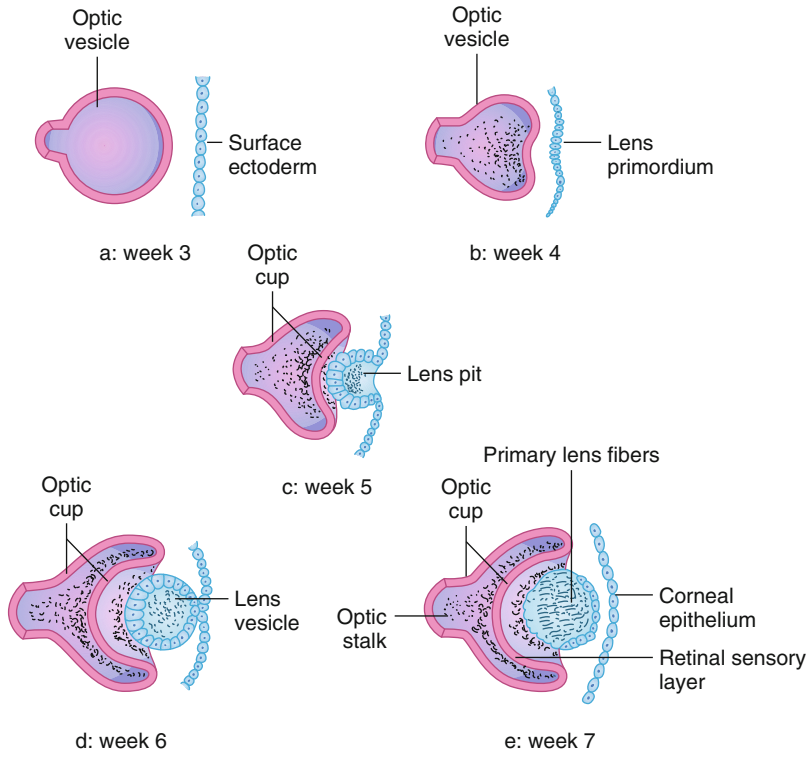

Fig. 1.1 Schematic diagrams of embryonic development of the lens. (**a**) The optic vesicle forms in the third week of gestation and begins to gradually make contact with the surface ectoderm. (**b**) The lens placode forms in the fourth week of gestation. (**c**) The lens placode and the optic vesicle invaginate in the fifth week of gestation. (**d**) The lens vesicle forms completely in the sixth week of gestation. (**e**) The primary lens fibers form in the seventh to eighth week of gestation

center, gradually forming a thin stalk adherent to the surface ectoderm.

In the sixth week of gestation, the lens pit completely separates from the surface ectoderm and forms a vesiculose structure, i.e., the lens vesicle (Fig. 1.1d), which will descend into the optic cup with the further invagination of the optic vesicle. After the separation, differentiation of the lens vesicle accelerates. The cells in the anterior wall of the lens vesicle, i.e., the cells originating from the peripheral lens placode, differentiate into the anterior subcapsular epithelial layer, which remains as a monolayer epithelium throughout life. The cells in the posterior wall, originating from the central lens placode, elongate to form the primary lens fibers that protrude toward the lumen of the vesicle. The apex of these cells continues to grow forward and eventually reaches the anterior wall and transforms into primary lens fibers (Fig. 1.1e). The epithelial cells at the junction of the anterior and posterior wall of the lens vesicle will differentiate into the equatorial epithelium, which will generate secondary lens fibers throughout life (Fig. 1.2). If the development of the lens vesicle is interfered, developmental disorders of the lens will occur and manifest as various lens abnormalities.

1.1.3 Development of Lens Epithelium

Although the mature lens develops from the same lens placode cells, the structures of its various parts are different to some extent. Beneath the anterior lens capsule is a monolayer of epithelial cells, bilateral equatorial zones are constituted by spindle-shaped cells, and there are no cells beneath the posterior lens capsule. To know the reasons for this different differentiation, we need to retrace the morphogenesis of the lens placode. The lens placode cells originate from the surface ectoderm overlying the optic vesicle, and they are the primitive stem cells of the lens. The lens placode is a monolayer of primitive cells and different parts of cells vary in morphology and size. In the lens placode, the cells approximating the center, i.e., the basement cells of the vesicle pit, show a greater level of differentiation and become columnar. The more peripheral cells, which will transform into the anterior surface cells of the lens vesicle, are round and exhibit a lower level of differentiation, as well as features of stem cells. The cells on the peripheral edges are adjacent to the corneal epithelial stem cells, and a potential association exists between the development of these two types of cells.

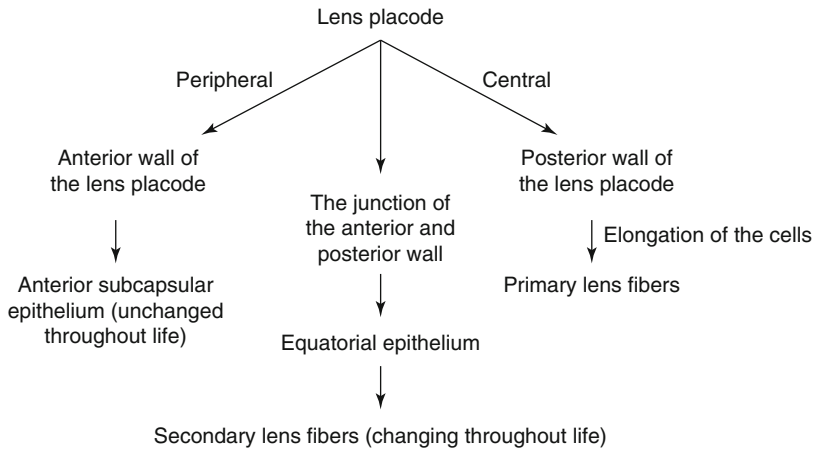

Fig. 1.2 Differentiation of the lens placode cells. The peripheral cells in the lens placode terminally differentiate into the anterior subcapsular epithelium, the central cells terminally differentiate into primary lens fibers, and the cells at the junction of the anterior and posterior wall terminally differentiate into the equatorial epithelium and form the secondary lens fibers

In the sixth to seventh week of gestation, the lens epithelial cells are visible. However, morphologically, they are not the typical monolayer cells but pseudostratified cells with active proliferation. From the fourth month to birth, these epithelial cells remain mostly unchanged.

1.1.4 Formation of Lens Fibers

The lens fibers are divided into primary lens fibers and secondary lens fibers.

1.1.4.1 Primary Lens Fibers

After the lens vesicle separates from the surface ectoderm, the differentiation of the epithelial cells in the vesicle accelerates. The cells of the posterior wall expand and tend to be fusiform shaped. They protrude from the posterior wall toward the center of the lens vesicle, with their nuclei gradually migrating from the center to the front of the cells. Then, the cells gradually elongate and their nuclei move close to the cellular equator. During this process, the lumens in the lens vesicle are getting narrower and narrower, changing gradually from an empty sphere to an arc-filled or crescent-filled sphere. As the fusiform lens fiber cells reach the anterior subcapsular epithelium, the vesicle lumen disappears and a solid sphere comes into being. The nuclei in the elongated fiber cells gradually disappear and finally, the cells differentiate completely into fibers, which are referred to as the primary lens fibers. Thus, the primary lens fibers become the embryonic nucleus. Embryonic nuclear cataract is caused by the malformation of the front apices of the primary lens fibers in the sixth to the eighth week of gestation and manifests as small, sporadic white opacified dots in the central lens. It is less likely to affect visual acuity.

1.1.4.2 Secondary Lens Fibers

In the seventh week of gestation, the epithelial cells derived from the lens equatorial zone begin to differentiate, become spindle shaped, and migrate toward the central core of the lens vesicle. Their anterior pole grows toward the anterior subcapsular epithelium and their posterior pole toward the posterior capsule, meeting the lens fibers coming from the opposite direction at the posterior and anterior poles of the lens. These fibers lie tightly outside the primary lens fibers and encircle the latter layer by layer. The secondary lens fibers encircling the embryonic nucleus are also known as the fetal nucleus. If the lens is impaired in the third month of gestation, fetal nuclear cataract will occur and manifest as opacity between the anterior and posterior Y sutures, which is often combined with embryonic nuclear cataract and impacts visual acuity significantly.

1.1.5 Formation of the Lens Capsule

The lens capsule is a basement membrane formed by the accumulated lamina of substances secreted by lens epithelial cells, and its components mainly include laminin, fibronectin, collagen type IV, and sulfated glycosaminoglycans [2]. In the fifth week of gestation, the homogeneous, transparent, integrated, and ultrathin capsular membrane begins to form. In the seventh week, the structure of the lens capsule is clearly visible. In the tenth week, the thickness of the anterior and posterior polar region is almost the same. In the following period, the thickness of all parts of the capsule will also increase with lens development.

1.1.6 Formation of the Lens Sutures

In the eighth week of gestation, the formation of the lens sutures begins. The lens sutures are the Y-shaped structures, derived from the equatorial secondary lens fibers ending at the specific locations of the anterior and posterior poles (Fig. 1.3). The fibers, which proceed to the fork of the Y suture at the anterior pole, extend to the apex of the Y suture at the posterior pole and vice versa. The lens fibers become tapered and flared at the ends and connect with contralateral fibers precisely. After the Y sutures are formed, the lens gradually becomes ellipsoidal. From the third trimester to after birth, the lens sutures become irregular and appear as complex branches with the growth of the lens and the elongation of lens

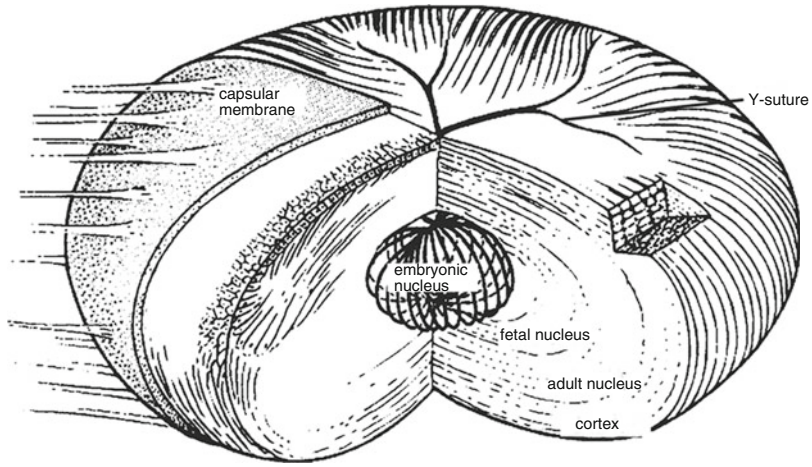

Fig. 1.3 Lens sutures and the layered lenticular structure. Y sutures are formed by lens fibers at the anterior and posterior poles of the lens. The layers of the lens from the core to the surface are embryonic nucleus, fetal nucleus, adult nucleus, cortex, and lens capsule

fibers. Lens impairment in the third month of gestation may lead to sutural cataract, manifesting as opacification of the anterior and posterior sutures.

After the formation of the embryonic nucleus, the new fibers derived from lens epithelial cells at the equatorial zone encircle the previously formed lens sutures, forming a regular and layered structure. If the lens is impaired after the formation of the fetal nucleus, lamellar cataract may occur, manifesting as a white circular opacity surrounding the fetal nucleus. It is shaped like a white shell, which is concentric with the lens capsule. It is transparent within the shell, as well as the outer lens cortex. The arrangements of lens fibers at different developmental stages determine the layered appearance of the lens. The layers of an adult lens, which can be distinguished in a slit-lamp biomicroscopic section, include embryonic nucleus, fetal nucleus, adult nucleus, and cortex (Fig. 1.3).

1.1.7 Formation of the Vascular Sheath of the Lens

Around the embryonic lens, there is a complex network of vessels, which provides nutrition for the embryonic development of the lens and is referred to as the vascular sheath of the lens. In the first month of gestation, the hyaloid artery branches into many confluent vessels, which form a vessel network that covers the entire posterior surface of the lens and is known as the posterior vascular sheath of lens. The capillaries, developing from the branches of the posterior vascular sheath, grow to the equatorial zone of the lens and anastomose with the choroidal veins, forming the capsulopupillary zone of the vascular sheath. Braches from this zone anastomose with the long posterior ciliary artery and form the anterior vascular sheath of the lens. This anastomosis of vessels is also referred to as the pupillary membrane. These vessel networks are completely developed in the ninth week of gestation and will gradually regress with fetal development and disappear by birth. If the posterior vascular sheath fails to regress completely, it will manifest as a small patch of opacity on the posterior capsule, which is known as a Mittendorf dot. Clinically, the remnant of the anterior vascular sheath of lens can also be seen, manifesting as a remnant of linear pigmented tissue in the pupillary zone.

The lens continues to grow and develop after birth and it grows most rapidly in the first year [3–5]. Then the growth gradually slows down

from 1 to 10 years old and continues after the age of 10 but in an extremely slow manner. The lens becomes approximately 0.5 mm thinner before the age of 10 and this usually happens before the age of 3. The radii of anterior and posterior surface increase by 1.0 mm and 0.2 mm, respectively. These changes may be caused by the lens being passively stretched by its equatorial growth, which flatten the lens surface curvature and eventually leads to the decrease of refractive power [6].

1.2 The Main Regulatory Factors of Lens Development

Lens development is regulated by multiple transcription factors and signaling pathways. Abnormal expression of transcription factors and the aberration of signaling pathways may lead to lens dysplasia and cataract. It is essential to study the spatiotemporal regulatory network of the lens development, which in turn will facilitate to better understand the molecular mechanism of lens disorders. Currently, several important transcription factors have been found to be involved in lens development.

1.2.1 *PAX6*

The *PAX6* gene is a highly conserved paired box gene, which acts as a "master control" regulator for ocular development. The products of *PAX6* are DNA-binding proteins and transcription factors. *PAX6* is expressed as early as in the precursor cells of the lens placode and is essential for lens placode formation [7]. *PAX6* proteins are classified within a sparse group of "master" regulatory proteins, including *BSAP*/*Pax5*, *Gata1*, *Gata2*, *MyoD*, *PU.1*, *Runx2*, *Sox9*, and a few others, that work at the top of genetic networks as "molecular switches" that control cell type specification and differentiation. The *PAX6* function is dosage dependent, such as haploinsufficiency. Mutation or loss of one allele in humans leads to a spectrum of eye abnormalities including lack of iris, cataract, corneal opacification, and neovascularization, as well as optic nerve hypoplasia [8]. The first notable phenotype of *PAX6* deficiency was reduced size of the eye with progressively deteriorating eye morphology in mouse or rat. *PAX6* regulates the expressions of various transcription factors, such as *Sox2*, *Maf*, and *Prox1*, which, in turn, regulates lens fiber differentiation and lens formation [9]. During the lens fiber differentiation, *PAX6* ensures the differentiating cells exit from cell cycle, elongation, and expression of lens fiber-specific proteins, such as crystallins, and complete the lens formation. *PAX6* can also act cooperatively with transcription factors, like *Maf*, *Prox1*, *Sox2*, and *Six3*, and exert its function via other factors like *pRB* and *Mitf*. Xia and colleagues examined the expression of *PAX6* at different developmental stages of the lens in mice and found that *PAX6* was expressed on embryonic day (E12.5) and E17.5 and on days 10, 20, and 60 after birth [10]. The expression of *PAX6* was evenly expressed in lens epithelium. The results suggest that *PAX6* is not only required for lens embryonic development but also essential for the continuing lens fiber differentiation after birth. In vitro studies also confirmed that the normal expression of the *PAX6* gene was vital for the proliferation and differentiation of lens epithelial cells [11]. Furthermore, *PAX6* is essential for lens fiber regeneration after cataract surgery [12].

1.2.2 *Maf*

The Maf proteins are a family of transcription factors containing the basic region of bZIP (basic region-leucine zipper). Two copies of the Maf protein or a copy of *Maf* protein and a copy of another related protein form a dimer, which can bind to specific DNA sequences. Members of the Maf family include *L-Mafs*, *C-maf*, *V-maf*, *MafB*, and *NRL*. In 1998, it was discovered for the first time that *L-Maf*, a member of the *Maf* gene family, plays a key role in lens development [5]. It affects the chick αA-crystallin expression by regulating the enhancer αCE2 [13]. Later studies discovered that *C-maf* and *MafB* of the *Maf* family also participate in lens development [14–16]. In addition, studies also confirmed that the

missense mutation of the *Maf* gene can cause congenital cataract [17]. Hence, the *Maf* gene family directly participates in lens development and their mutations may cause cataract. However, recent studies have also shown that for lens development, only *C-Maf* is essential, while *L-Maf* and *MafB* appear redundant [18].

1.2.3 *Sox* Family

The *Sox* family encodes a set of highly conserved transcription factors and their products share a conserved sequence of the HMG domain. At the initial stage of lens differentiation, *Sox2*, *Sox*3, and *PAX6* are expressed in the lens, regulating the expression of δ- and γ-crystallins. After δ-crystallins come into being, *Sox1* begins to be expressed at the depression of the lens placode with the expression of *Sox2/3* decreased and lost [19]. These studies indicated that *Sox2/3* are supposed to only take effect at the initial stage of lens differentiation and that it is Sox1 that plays the key role in the whole lens development process. Furthermore, *Sox11* has also been demonstrated to be involved in ocular anterior segment development. The absence of *Sox11* results in delayed lens development in mice and consequently microphthalmia and even anterior segment dysgenesis at birth. The mechanism of its effect was via regulating BMP signaling to control early eye development [20].

1.2.4 *Six3*

Six3 is a crucial regulatory factor in vertebrate eye development, and it is a key gene that regulates lens formation in the earliest stage. During lens development in mice, *Six3* is first expressed during the formation of the neural plate, and it is also expressed in the formation of the lens vesicle and the lens. Lengler and colleagues discovered that at E14.5, expression of *Six3* in lens fibers decreased while that in the lens epithelium increased, which was similar to the expression of *PAX6*. It was hypothesized that *PAX6* might activate the expression of *Six3* [21]. However, Liu and colleagues reported that *Six3* directly activated *PAX6* expression in the early stage of mammalian lens morphogenesis, which then further activated a series of genes necessary for lens development. These results suggested *Six3* is at the top of the regulatory factor cascades initiating lens development [22].

1.2.5 *Msx2*

As a member of the muscle segment homeobox gene family, *Msx2* is expressed in both the lens placode and the mature lens. A study revealed that *Msx2* has an inhibitory effect on *Sox2* promoters [23]. In 2012, in *Msx2* knockout (KO) mice, Zhao first confirmed that the absence of *Msx2* downregulates *FoxE3* expression, while it upregulates *Prox1* and crystallin expressions, which led to a disturbed lens cell cycle in lens vesicles and eventually caused cornea-lentoid adhesions and microphthalmia [24].

1.2.6 *BMP*

Two members of the bone morphogenetic protein (BMP) family, *BMP4* and *BMP7*, also play an important role in early lens development. Knockout of *BMP7* results in failure of formation of the lens placode and it also downregulates the expression of *PAX6* and *Sox2* [25]. *BMP4* does not affect *PAX6* expression, but it can induce the upregulated expression of *Sox2* [26].

Moreover, *Prox1*, *RARβ/RXRβ*, *HSF2*, *Pitx3*, *Foxe3*, and *GATA-3* are also transcriptional regulators in lens development. They regulate lens development by balancing the effects of synergy and antagonism. Apart from transcriptional regulators, plenty of studies have demonstrated that Wnt, BMP, and FGF signaling pathways also play key regulatory effects in lens development [27–29]. Liu and colleagues also found that calmodulin participates in lens development and cataract formation through the Ca^{2+}/CaM signaling pathway [30]. The abnormality of the above-mentioned factors can lead to dysplasia of the lens and cataract formation.

1.3 The Regulatory Effect of Embryonic Lens on Eyeball Development

The development of embryonic lens is regulated by various transcriptional regulators, signaling pathways, and adjacent tissues; meanwhile, the lens also sends a series of signals back to the adjacent tissues to ensure the normal development of the eyeball.

During the development of the anterior segment of the eye, neural crest-derived mesenchymal cells migrate to the space between the lens and the corneal epithelium and differentiate into the corneal endothelium and stroma, iris stroma, and trabecular meshwork. Early studies found that mechanically removing the developing lens during the early embryonic stage results in the absence of corneal endothelium, dysplasia of corneal stroma, and dysplasia or absence of iris-ciliary body and anterior chamber [31, 32]. For example, Zinn and colleagues removed the lenses in chicks at E4 and found that the corneal endothelium was not formed, while collagen fibers with irregular arrangements and varied diameters were visible in corneal stroma and resembled those in sclera [33].

Mechanical removal of the lens may cause physical damages to the eye and interfere with eye development. To rule out that possibility, researchers investigated the role of lens on eye development by disrupting the normal lens development genetically and observed the development of other eye tissues. They discovered that ablation of lens at early stages not only affects the development of anterior segment but also the development of the posterior segment. Harrington and colleagues used lens-specific alpha A-crystallin promoter to drive the expression of diphtheria toxin to gradual ablate the lens from E12 and found that ablation of lens results in coincided retardation of development of the neuroretina, sclera, and cornea. The anterior lip of the optic cup also failed to differentiate into the normal epithelium of iris and ciliary body, the vitreous body was also not develop in the transgenic mouse [34]. Zhang and colleagues used an attenuated version of diphtheria toxin A subunit driven by a modified crystallin promoter to ablate lens during development and found multiple defects in the anterior chamber, including corneal endothelial cells did not differentiate properly and the differentiation of ciliary body and iris were terminated prematurely [35]. The Rho GTPase signal transduction pathway is essential for lens development, and C3-exoenzyme can selectively inactivate all Rho GTPase. Transgenic mice with lens-specific expression of C3-exoenzyme not only show defects in lens fiber cell differentiation and elongation, and thickened anterior capsule, but also anterior segment abnormalities, such as anterior chamber hemorrhage and iris abnormalities (iridolenticular and iridocorneal adhesions), and posterior segment abnormalities, such as vitreous hemorrhage and hypoplastic vitreous with persistent blood vessels [36]. Collectively, these results suggest that the normal lens development is essential for the development of the corneal endothelium, ciliary body, and iris as well as the development of neuroretina and vitreous.

It appears that lens is the organizer of eye development, but the mechanism remain to be elucidated. It was thought that the embryonic lens produces certain regulatory factors to facilitate the complete development of the anterior and posterior ocular segments, but the specific factors still remain to be discovered.

1.4 Summary

The development of the lens is a precisely regulated process that is controlled by concerted action of multiple factors. The proper lens development is also essential for the development of other eye tissues, such as the corneal endothelium, ciliary body, iris, and neuroretina. A better understanding of lens development process will help to advance knowledge of molecular mechanisms of lens diseases. It is promising that in the future, treatment and correction at the gene level may be achieved in the early developmental stage for prevention of development-related eye diseases.

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