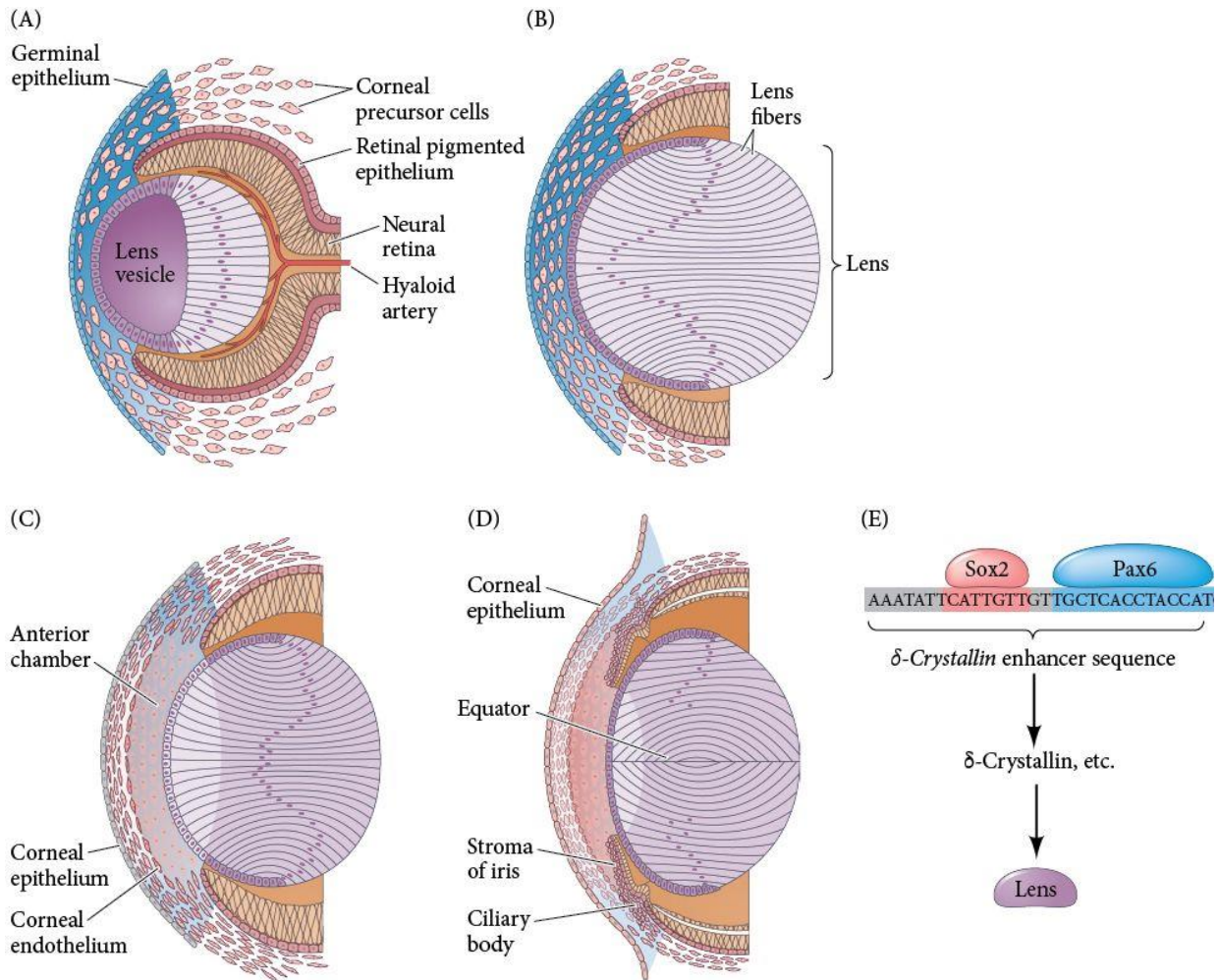


Lens and Cornea Differentiation

The differentiation of lens tissue into a transparent structure capable of directing light onto the retina involves changes in cell structure and shape as well as the synthesis of transparent, lens-specific proteins called crystallins. Crystallins account for up to 90% of the lens-soluble proteins. The lens cells must curve properly, and this curvature is caused by balancing the Rho-generated apical constriction of microfilaments with the Rac-generated actin polymerization that extends the microfilaments along the apical-basal axis (Chauhan et al. 2011).

The crystallin-containing posterior primary fiber cells eventually elongate and fill the lumen of the lens vesicle (Figure 1A, B; Piatigorsky 1981). The anterior cells of the lens vesicle constitute a germinal epithelium, which continues dividing. These dividing cells move toward the equator of the vesicle, and as they pass through the equatorial region, they, too, begin to elongate into secondary cellular fibers (Figure 1C, D). With maturation, these fiber cells lose their cellular organelles and their nuclei are degraded. Thus, the lens contains three regions: an anterior zone of dividing epithelial cells, an equatorial zone of cellular elongation, and a posterior and central zone of crystallin-containing fiber cells. This arrangement persists throughout the lifetime of the animal as epithelial cells at the lens equator differentiate into new secondary fibers that are continuously added to the lens mass (Papaconstantinou 1967).



A-D after A. Cvekl and E. R. Tamm. 2004. *BioEssays* 26: 374-386; E after H. Kondoh et al. 2004. *Int J Dev Biol* 48: 819-827.

Figure 1 Differentiation of the lens and anterior portion of the mouse eye. (A) At embryonic day 13, the lens vesicle detaches from the surface ectoderm and invaginates into the optic cup. Corneal pre-cursors (mesenchymal cells) from the neural crest migrate into this space. The elongation of the interior lens cells begins, producing primary lens fibers. (B) At day 14, the lens is filled with crystallin-synthesizing fibers. The neural crest-derived mesenchyme cells between the lens and surface condense to form several layers. (C) At day 15, the lens detaches from the corneal layers, generating an anterior cavity. (D) The surface ectoderm at the anterior side becomes the corneal epithelium, and at day 15.5, corneal layers differentiate and begin to become transparent. The anterior edge of the optic cup enlarges to form a non-neural region containing the iris muscles and the ciliary body. New lens cells are derived from the anterior lens epithelium. As the lens grows, the nuclei of the primary lens cells degenerate and new lens fibers grow from the epithelium on the lateral sides. (E) Close binding of the Sox2 and Pax6 transcription factors on a small region of the δ -crystallin enhancer.

The initial differentiation of lens-forming tissues requires contact between the optic vesicle and the presumptive lens ectoderm. In addition to preventing neural crest cells from inhibiting the intrinsic lens bias of the anterior pre-placodal region, this contact appears to permit Delta proteins in the optic vesicle to activate Notch receptors on the presumptive lens ectoderm (Ogino et al. 2008). The Notch intracellular domain binds to an enhancer element of the *FoxE3* gene, and in the presence of the Otx2 transcription factor (which is expressed throughout the entire head region), *FoxE3* is activated. The *FoxE3* protein is itself a transcription factor that is essential for epithelial cell proliferation (making and growing the lens placode) and eventually for closing the lens vesicle. In this interaction, we see a principle that is observed throughout development—namely, that some transcription

factors (such as Otx2) specify a particular field and provide competence for cells to respond to a more specific induction (such as Notch) within that field.

Paracrine factors from the optic vesicle also induce lens-specific transcription factors. Regulation of the crystallin genes is under the control of Pax6, Sox2, and L-Maf (Figure 1e). Like Otx2, Pax6 appears in the anterior pre-placodal region long before the lens is formed, and Sox2 is induced in the lens placode by Bmp4 secreted from the optic vesicle (Furuta and Hogan, 1998). Coexpression of Pax6 and Sox2 in the same cells initiates lens differentiation and activates crystallin genes. Appearing later than Sox2, L-Maf is induced by Fgf8 secreted by the optic vesicle and is needed for the maintenance of crystallin gene expression and the completion of lens fiber differentiation (Kondoh et al. 2004; Reza et al. 2007). Later Bmp signaling seems to play a different role and is required for lens fiber cell differentiation (Faber et al., 2002).

Shortly after the lens vesicle has detached from the surface ectoderm, the lens vesicle stimulates the overlying ectoderm to become cornea. The molecules necessary for this transformation are probably Dickkopf proteins that inhibit Wnts and the Wnt-induced β -catenins. In mice with loss-of-function mutations in their *Dickkopf-2* genes, the corneal epithelium becomes head epidermal tissue (Mukhopadhyay et al. 2006). The presumptive corneal cells secrete layers of collagen into which neural crest cells migrate and make new cell layers while secreting a corneal-specific extracellular matrix (Meier and Hay 1974; Johnston et al. 1979; Kanakubo et al. 2006). These cells condense to form several flat layers of cells, eventually becoming the corneal precursor cells (see Figure 1a; Cvekl and Tamm 2004). As these cells mature, they dehydrate and form tight junctions among the cells, uniting with the surface ectoderm (Kurpakus et al. 1994; Gage et al. 2005) to become the cornea. Intraocular fluid pressure (from the aqueous humor) is necessary for the correct curvature of the cornea, allowing light to be focused on the retina (Coulombre 1956, 1965).

Repair and regeneration are critical to the cornea since, like the epidermis, it is exposed to the outside world. The main problem for the cornea is reactive oxygen species (ROS) that damage DNA and proteins. The major sources of ROS are the amniotic fluid (as an embryo) and ultraviolet light (as an adult). One protective mechanism is the production of the iron-binding protein ferritin (Linsenmeyer et al. 2005; Beazley et al. 2009). The second mode of protection is a layer of basal cells that continually renew the corneal epithelial cells throughout the life of the individual. Long-lived stem cells found at the edge of the cornea contribute to corneal repair and can regenerate the cornea in humans (Cotsarelis et al. 1989; Tsai et al. 2000; Majo et al. 2008). The cells in this region also secrete Dickkopf to prevent their becoming epidermal cells (Mukhopadhyay et al. 2006).

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