Human Development
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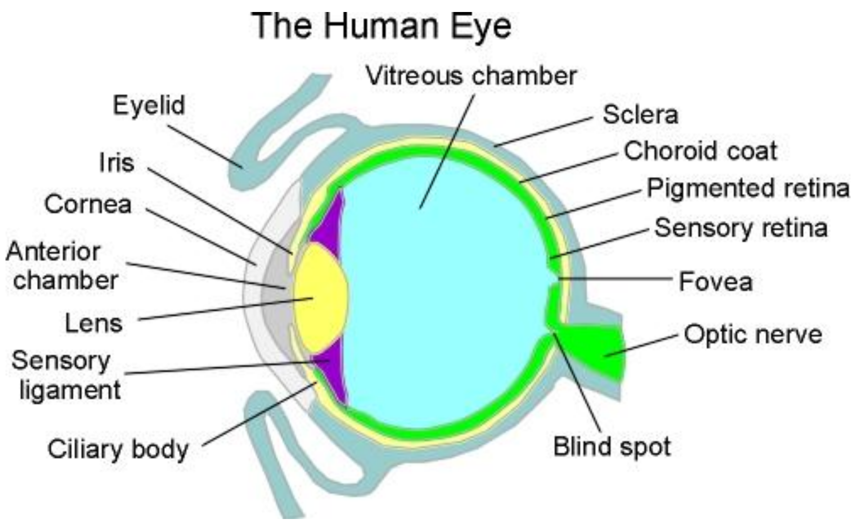
Development of the Eye: A Series of Inductive Interactions

The Human Eye

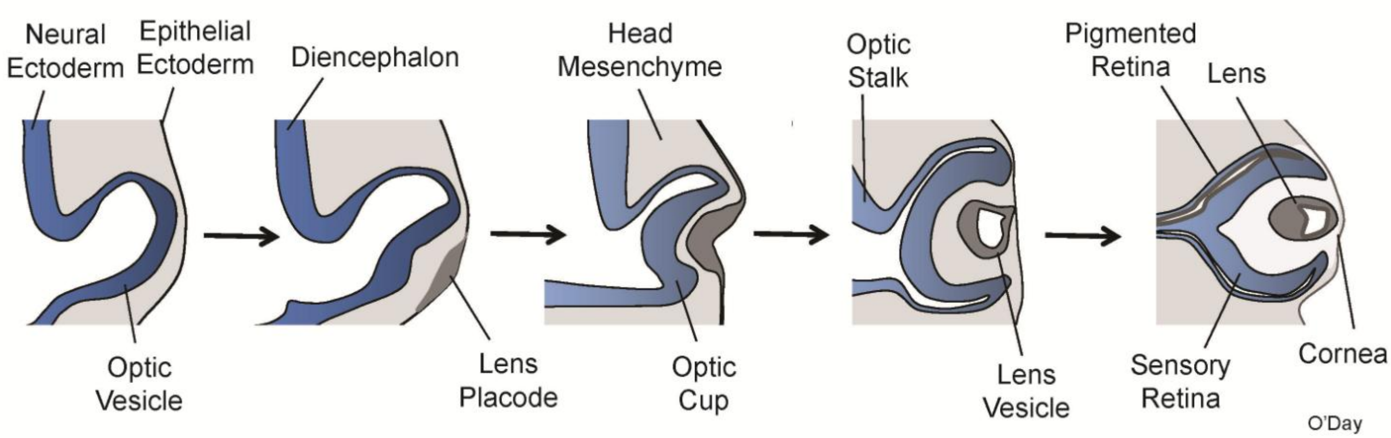
The eye is a complex structure and was one of the organs that was experimentally studied by the earliest embryologists. Let's look at the overall structure of the eye and then at its early embryology. We'll then discuss the control of eye development and some of the information that is known about the differentiation of some of its component cells.



Development of the Human Eye

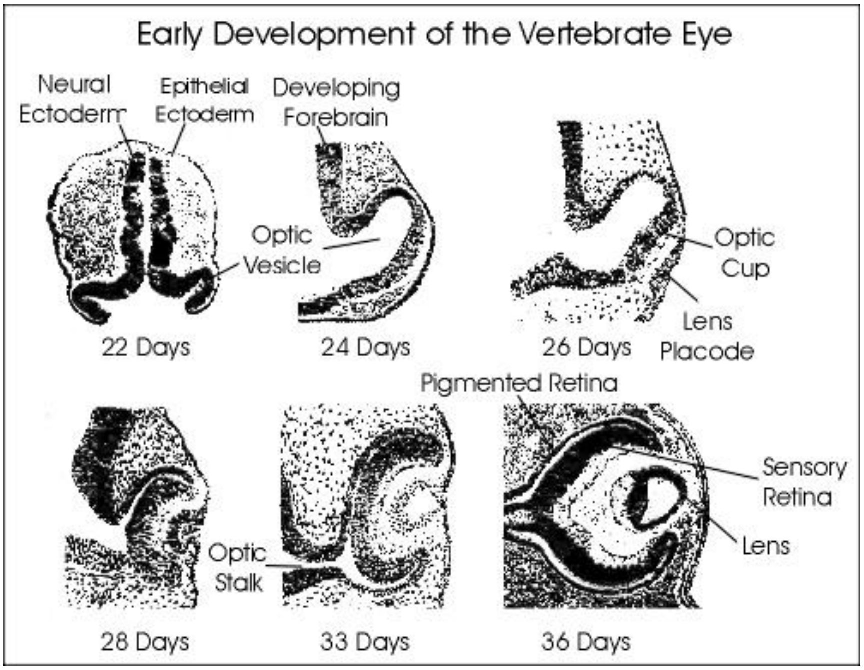
Cross-Sections through head region of embryo revealing changes in optic cup, lens formation and brain:

- The optic vesicles extend from the Diencephalon
- Optic vesicles come into close proximity to epithelial ectoderm
- Optic vesicle thickens & folds as optic cup
- Lens placode forms from epithelial ectoderm
- Lens placode infolds as future lens



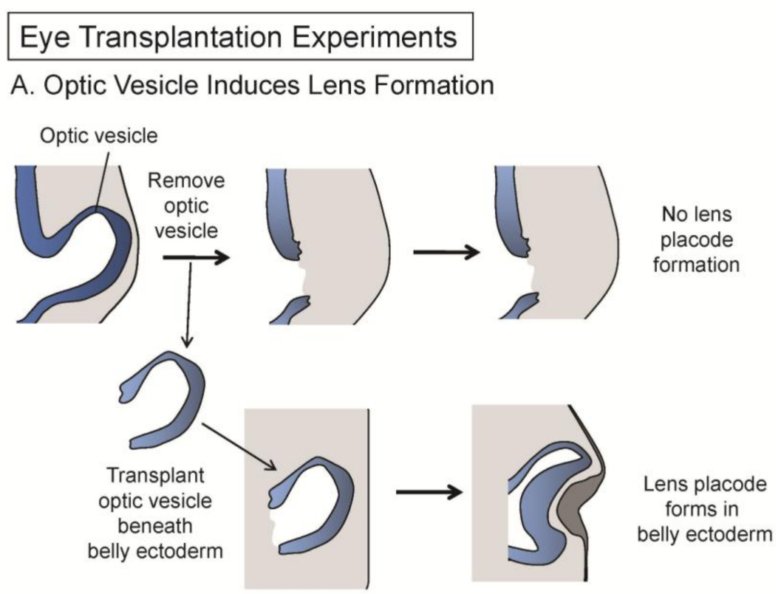
The following events are shown in the series of embryonic cross-sections below:

- 22 Days--Eye formation begins
- 22-24 Days--Optic Vesicle forms
- 26 Days --Optic Cup & Lens Placode are present
- 28 Days-- Optic Cup & Lens Placode infolding continues
- 33 Days--Sensory & Pigmented Retina development begins
- 33-36 Days--Lens pinches off as a separate entity

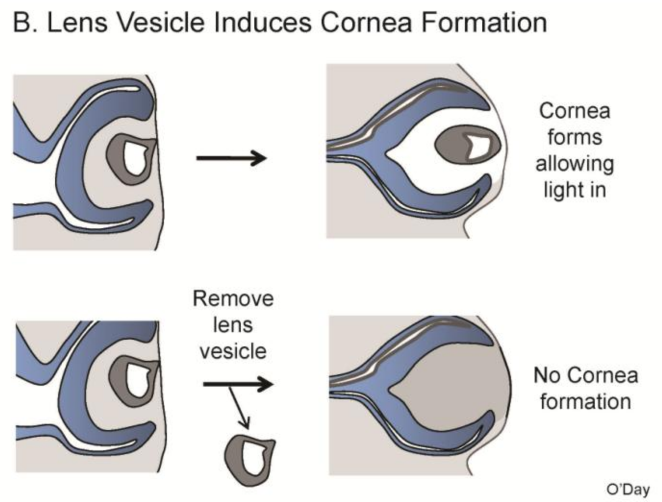


Induction & Eye Development: Early Experiments

The following diagram presents a summary of many different types of experiments that were done first on frog and chick embryos and more recently on mouse embryos. Such experiments have not been performed with human embryos but it is assumed similar results would be found.



- Remove Optic Cup = No Lens
- Transplant Optic Cup below non-head epidermis (e.g., belly ectoderm) and lens forms



- Remove lens vesicle and cornea doesn't develop
- Other variations on transplants led to understanding of "Chain of Inductions" in eye development

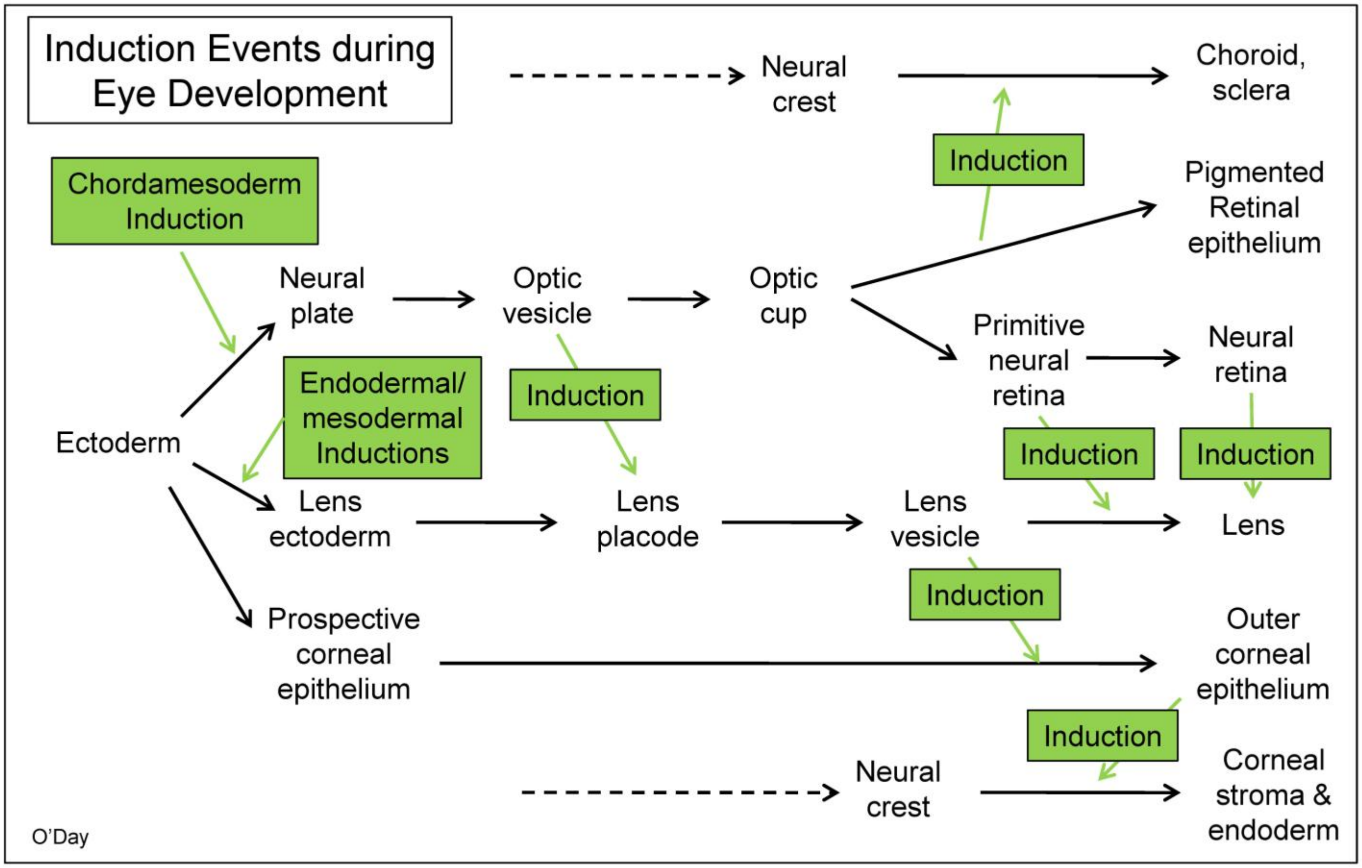
A Chain of Inductions Mediates Eye Development

These types of tissue transplantation experiments were performed by dozens of different labs over many years. Tissues of various ages and types were combined to reveal the following inductive interactions and results during eye development:

- Chordamesoderm Induces Neural Tube
- Optic Cup Induces Lens
- Lens with or without the Optic Cup Induces Cornea
- Other combinations induce other components

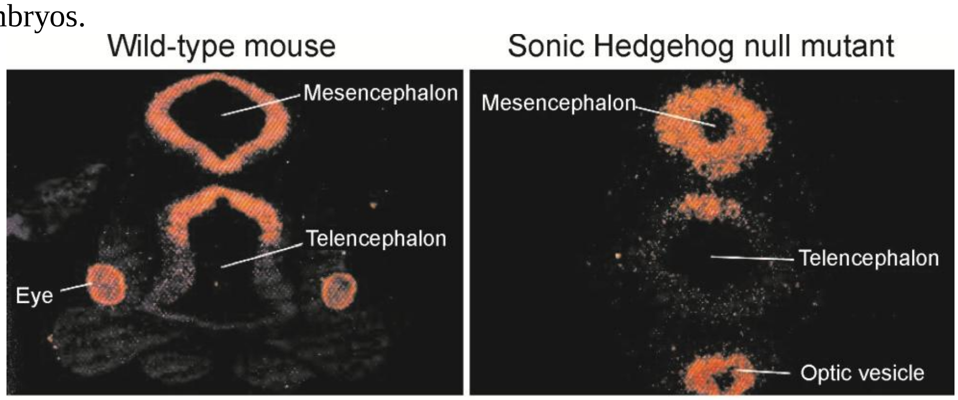
Result: eyes form at proper place & time; components appear in proper position & orientation
These results are further clarified in the following diagram which presents a summary of a large number of independent experiments by many different researchers. Even before the optic vesicle appears, at least two critical inductive events have occurred. The induction of the neural tube by chordamesoderm defines the anterior regions (diencephalon) where the optic vesicles will form. Endodermal-Mesodermal induction specifies the lens ectoderm which will subsequently be induced by the optic vesicle to become the lens placode.

Subsequent products of the optic vesicle, the optic cup and the future neural retina induce the formation of the choroid & sclera and the lens, respectively. The lens interacts with the future corneal epithelium to induce the outer corneal epithelium which, in turn, induces the neural crest to form the corneal stroma and endoderm. Clearly one stage influences the next resulting in a functional structure in which each of the components is present in the proper position relative to the other eye components.



Sonic Hedgehog & Eye Development

Many factors have been characterized that regulate eye development. For example the transcription factors Six3, Pax6 and Rx1 are expressed at the anterior tip of the neural plate with Pax6 playing a critical role in lens and retina development. Studies on families with congenital eye defects have shown that the absence of Pax6 in humans leads to the complete absence of eyes while other defects are associated with heterozygous conditions. Cyclopia refers to the formation of a single eye in the center of the face. Sonic hedgehog mediates the division of the original single eye field into two. As shown in the following figure, the expression of an eye-specific gene called otx-2 (false reddish colour) is defective in null sonic hedgehog mutant mouse embryos.

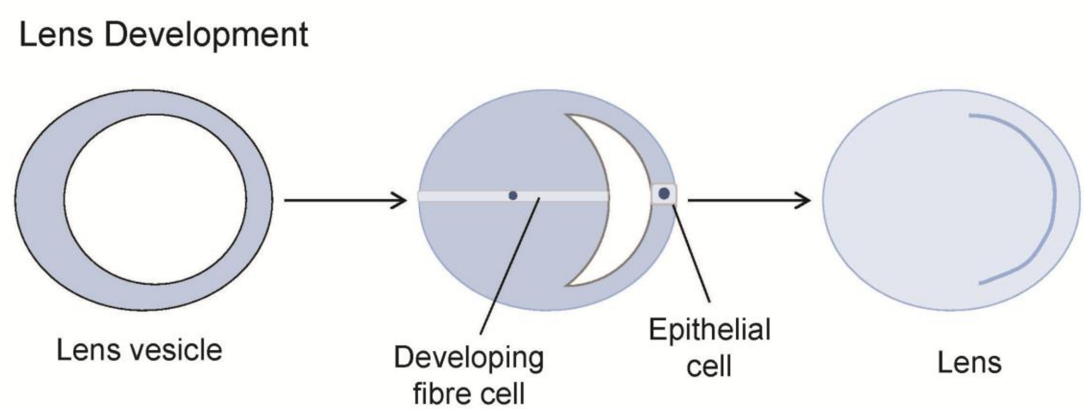


Chiang et al, 1996. Nature 383: 407-413.

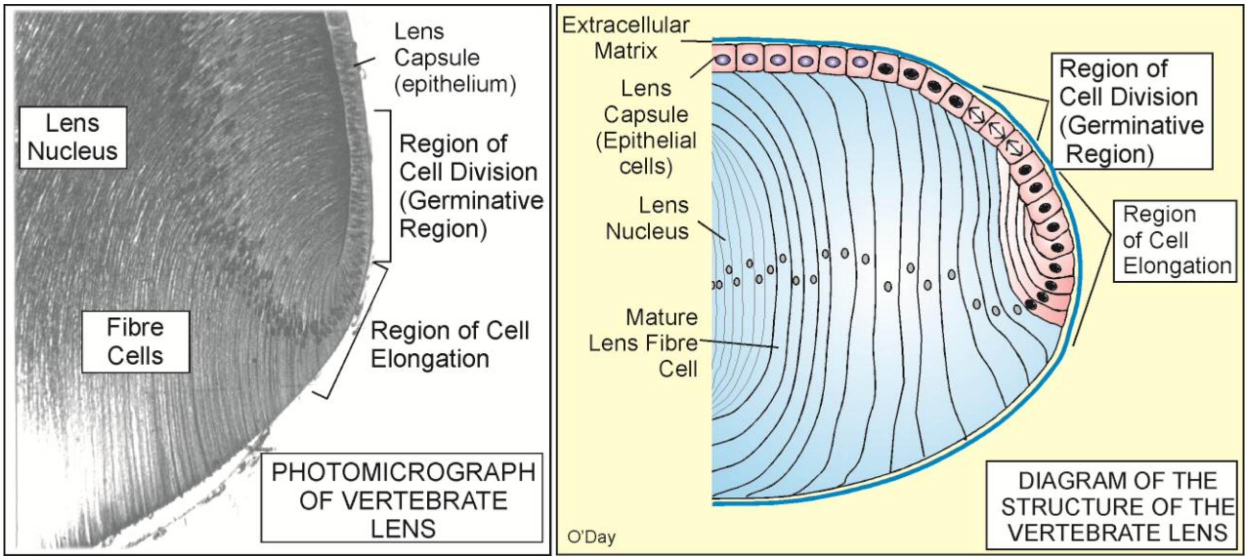
Notice in the normal mouse, the expression of otx-2 occurs in the mesencephalon, diencephalon and optic vesicles. In the null hedgehog mutants, the eye fields have not separated and the expression of otx-2 is seen in the single (cyclopic) optic vesicle plus the brain regions.

Lens Differentiation & Crystallin Proteins

- Lens needs to clarify to allow light to pass
- Lens needs to be proper shape to focus light
- Cells at posterior side elongate (compare epithelial cells with developing fibre cells in figures)
- Cells need to multiply to fill in this space (not detailed here)
- Fibre cells fill with clear crystallin proteins so light can pass through as well as be focused by the lens
- Two main crystalline gene families: α- and βγ-crystallins
- Crystallin proteins are clear, stable, water-soluble proteins
- α-crystallin synthesis begins in lens placode and is important for lens epithelial development
- α-crystallin gene knockouts in mice lead to lens that are 50% smaller than control mice
- βγ-crystallins are predominantly found in lens fibre cells
- Crystallin proteins are also found in other tissues, with many other functions



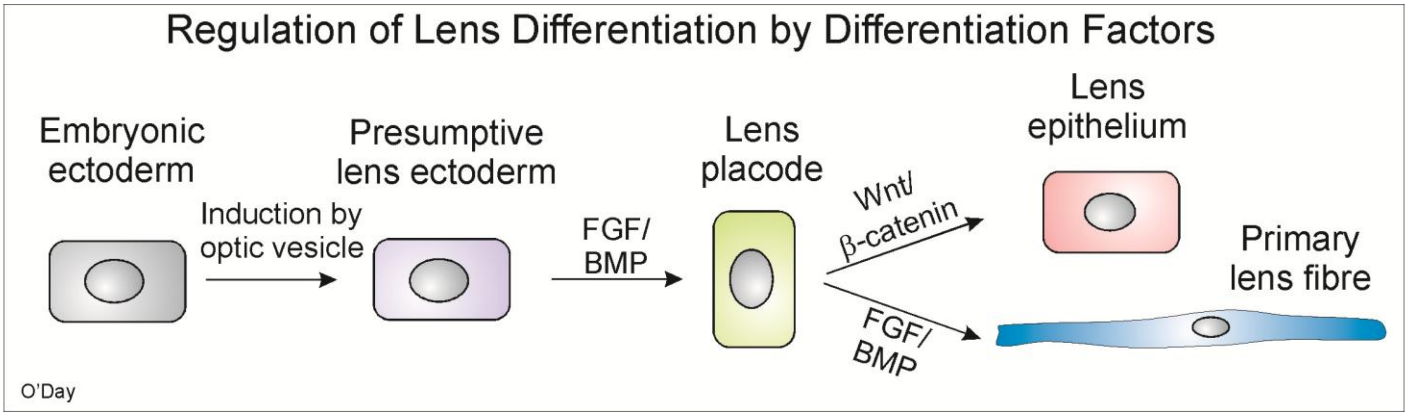
Let's take a more detailed look at the structure of the lens before analyzing some molecular events underlying its development.



- Germinative Region: cells are actively dividing
- Region of Cell Elongation: cells are beginning to change shape & differentiate
- Cells differentiate into fibre cells
- Fibre cells densely packed in centre as lens nucleus

Differentiation Factors Regulate Lens Cell Differentiation

Some of the factors that regulate lens cell differentiation are being elucidated. The following figure summarizes current knowledge.



While the specific factors that underlie the transformation of embryonic ectoderm to presumptive lens ectoderm remain to be identified, FGF and BMP are required for the transformation of presumptive lens ectoderm into the determined cells present in the lens placode. As seen above, the development of the lens placode into the mature lens required the regular division of cells of the lens epithelium that supply the cells that will differentiate into the elongated fiber cells of the lens body. Lens epithelial cell function is maintained by the factors Wnt and β-catenin. These factors likely function to maintain the cell polarity of the epithelial cells as well as to co-ordinate the cellular rearrangements involved in lens differentiation. Epithelial cell adhesion is mediated by cadherins which interact with the cytoskeleton via β-catenin. On the other hand, adhesion via cadherins is lost in fibre cells (and hence so is the need for β-catenin). The final conversion of lens epithelial cells to lens fiber cells is induced by the further action of FGF and BMP. Slowly we are gaining insight into the factors and signal transduction mechanisms that regulate eye development which in future will guide research into correcting developmental defects in this organ.

The loss of opacity in the eye is often due to cataracts. Cataracts are a result of degeneration in the crystalline proteins of the eyes caused by cross-linking, aggregation and proteolytic digestion among other things. This leads to “cloudy” vision or what is more properly termed age-related opacity.

References

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