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Review

Transcription factors involved in lens development from the preplacodal ectoderm

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ABSTRACT

Lens development is a stepwise process accompanied by the sequential activation of transcription factors. Transcription factor genes can be classified into three groups according to their functions: the first group comprises preplacodal genes, which are implicated in the formation of the preplacodal ectoderm that serves as a common primordium for cranial sensory tissues, including the lens. The second group comprises lens-specification genes, which establish the lens-field within the preplacodal ectoderm. The third group comprises lens-differentiation genes, which promote lens morphogenesis after the optic vesicle makes contact with the presumptive lens ectoderm. Analyses of the regulatory interactions between these genes have provided an overview of lens development, highlighting crucial roles for positive cross-regulation in fate specification and for feed-forward regulation in the execution of terminal differentiation. This overview also sheds light upon the mechanisms of how preplacodal gene activities lead to the activation of genes involved in lens-specification.

Introduction

The lens has been used as a very attractive model system for the study of tissue development in vertebrates. In the early 1900s, both Spemann and Lewis independently examined interactions between the retina and lens primordia in frog embryos. Using a hot needle, Spemann destroyed the presumptive retina region of the anterior neural plate in *Rana fusca* and found that the lens was missing on the manipulated side (Spemann, 1901). Thus, Spemann concluded that the retinal primordium is required for proper lens development. Lewis transplanted the retina primordium (optic vesicle) under the flank ectoderm in *Rana palustris* and found that an ectopic lens formed in the transplanted region (Lewis, 1904). Hence, Lewis proposed that stimuli from the optic vesicle were sufficient to convert the multipotent ectoderm into the lens. These studies are considered to be the first experimental documentation of embryonic induction, but it was not until the end of the 1980s that Grainger and colleagues showed that Lewis's conclusion provided an oversimplified view of events. Using a lineage tracing technique, they revealed that lenses formed ectopically on the flank in *R. palustris* and *Xenopus laevis* embryos were exclusively derived from contaminating donor cells carried along with the transplanted optic vesicles; thus, the optic vesicle was considered not sufficient to induce the lens (Grainger et al., 1988).

Grainger's group further investigated interactions between the retina and lens primordia in earlier stages of *Xenopus* development and found that the lens development is a successive process that begins in the ectoderm prior to its contact with the optic vesicle (Grainger, 1992; Henry and Grainger, 1987). According to their model, planar signals from the anterior margin of the developing neural plate and vertical signals from the anterior endomesoderm establish the lens-forming potential in the adjacent non-neural ectoderm by the neural plate stage. After neural tube formation, only the lateral part of this non-neural ectoderm makes contact with the developing optic vesicle and begins to differentiate into the lens. Interestingly, the anterior ectodermal region with lens-forming potential in Grainger's model appears to include the non-neural ectoderm known as the preplacodal ectoderm (PPE), which surrounds the anterior neural plate and includes the presumptive fields of lens, nasal, ear, adenohypophyseal, trigeminal and epibranchial placodes (Fig. 1A). Embryological studies have suggested that the PPE is formed as the pan-placodal ground state, which is then subdivided into the respective placodal tissues via local interactions with adjacent neural and mesodermal tissues (Baker and Bronner-Fraser, 2001; Jacobson, 1966).

After the classical embryological studies, molecular and genetic studies opened up a new era and significantly advanced our understanding of lens development. In 1991, a *paired* box gene, *Pax6*, was

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identified as the causal gene of the *Small eye* (*Sey*) mutation in mice; animals homozygous for the gene fail to develop lens placode (Hill et al., 1991; Hogan et al., 1986). *Pax6* was suggested to be implicated in the lens-forming potential identified in embryological studies, because of the *Sey* phenotype and *Pax6* expression that occurs in the presumptive lens ectoderm prior to contact with the optic vesicle in mice and chickens (Grindley et al., 1995; Li et al., 1994). The discovery of *Pax6* was followed by that of other transcription factor genes such as *Six1*, *Six3*, *FoxE3*, *Sox2*, *L-Maf*/*c-Maf* and *Prox1*, which are involved in PPE formation and/or subsequent lens differentiation (Brugmann and Moody, 2005; Cvekl and Duncan, 2007; Lang, 2004; Ogino and Yasuda, 2000; Schlosser, 2006; Streit, 2007). This review provides an overview of the sequential expression of these transcription factor genes, and then addresses their regulation and

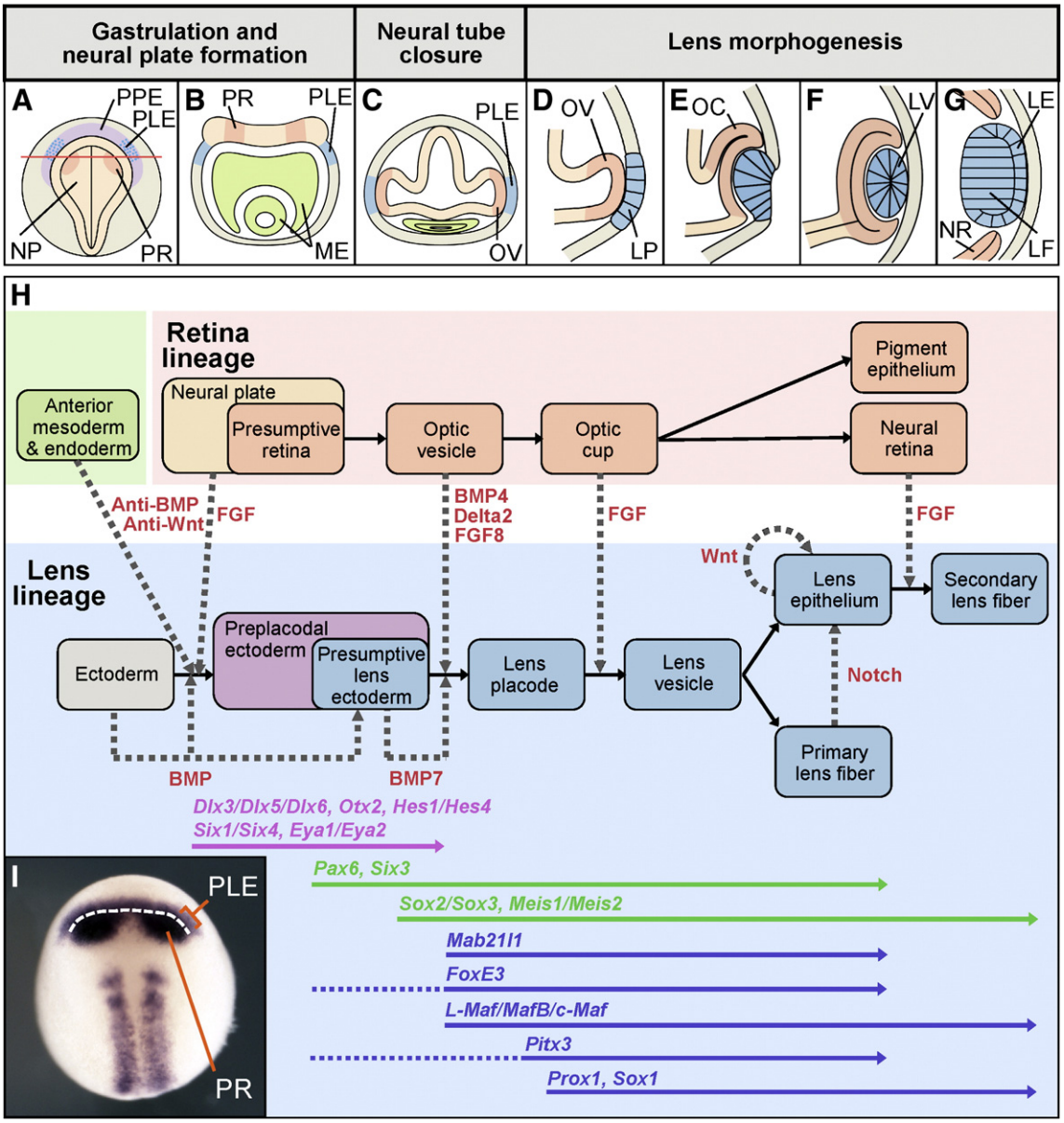

Fig. 1. Schematic illustration of vertebrate lens development, relationships between inductive interactions and sequential activation of transcription factors. (A–G) *Xenopus* was chosen as the vertebrate representative since its developmental lineages of lens, retina and other related tissues have been well studied (Eagleson and Harris, 1990; Eagleson et al., 1995). The developmental stages are indicated at the top of the figure. (A) Dorsal view of a neural plate-stage embryo (anterior at the top of the image) indicating the preplacodal ectoderm (PPE, purple), the presumptive lens ectoderm (PLE, dotted light blue), the neural plate (NP, light orange), and the presumptive retina field (PR, dark orange). (B) Transverse section of a neural plate-stage embryo through the PLE and PR. The red line in A indicates the plane of the section. Lens and retina lineages are shown in light blue and dark orange, respectively, in B-G, and mesoderm and endoderm (ME) are shown in light green. (C) Transverse section of a neural tube-stage embryo where the optic vesicle (OV), which develops from the PR, reaches the PLE. (D-F) Close-ups showing lens vesicle formation. The PLE overlying the OV becomes thickened to form the lens placode (LP), which subsequently separates from the head ectoderm to form the lens vesicle (LV). OC, optic cup. (G) Close-up of a maturating lens. LE, lens epithelium; LF, lens fiber; NR, neural retina. (H) Major signaling factors are indicated in red with dotted gray arrows. FGF signaling from the neural retina is responsible for the formation of the secondary lens fibers from the lens epithelium (Lovicu and McAvoy, 2005). The other signaling pathways are explained in the text. At the bottom, Expression profiles of preplacodal genes, lens-specification genes and lens-differentiation genes (pink, green, and blue arrows, respectively) studied in *Xenopus*, zebrafish, chicken and mouse embryos. The dotted blue lines of *FoxE3* and *Pitx3* represent species differences in initial expression profiles. Details and references are described in the text. (I) *In situ* hybridization analysis of *Pax6* expression in a neural plate-stage *Xenopus* embryo (dorsal view). The PLE and PR are indicated. The boundary between the neural plate and PPE is indicated by a white broken line. Note that preplacodal *Pax6* expression occurs broadly adjacent to the anterior margin of the neural plate.