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Review

Lens induction in vertebrates: Variations on a conserved theme of signaling events

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Abstract

This review provides an overview of our current understanding of signaling mechanisms involved in lens induction, which are presented in context of the major stages of lens induction (competence, bias, inhibition and specification). Although the process of lens induction is generally well conserved, we highlight aspects of induction that vary among species. Finally, this review identifies future challenges in forming an integrated network of signaling pathways involved in lens induction.

Keywords: Lens; Placode; *Six*1; *Pax*6; *Sox*2

Contents

Abbreviations: ANP, anterior neural plate; BMP, bone morphogenetic protein; ERK, extracellular signal related kinase; FGF, fibroblast growth factor; Hh, hedgehog; HH, Hamburger and Hamilton stage; NCC, neural crest cell; OV, optic vesicle; PLE, presumptive lens ectoderm; PPR, pre-placodal region; RTK, receptor tyrosine kinase; sFRP, secreted frizzled-related protein

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1. Introduction

In vertebrates, the lens is derived from a thickened epithelial structure called a placode, which is one of two innovations unique to the vertebrate lineage that evolved as organisms shifted from filter feeding to active predation [1]. Experimental evidence largely supports the induction of a common pre-placodal region (PPR) from which all sensory and neurogenic placodes are derived [2–4]. PPR induction is a multi-step process that is spatially and temporally associated with both patterning of the neural plate and induction of the neural crest (NCC) [2–4].

Lens induction was originally mis-characterized as a simple one-step process dependent upon close association of the surface ectoderm with the optic vesicle (OV) [5,6]. The combination of tissue transplant experiments incorporating reliable host/donor marking strategies [7] and the formation of 'free lenses' (lenses forming in the absence of a retina) in a high percentage of species including anurans, urodeles, fishes, birds and mammals [5] forced a re-evaluation of this model. Current lens induction models encompass discrete developmental stages including competence, bias, inhibition, specification and differentiation that span from mid to late gastrulation through neural tube stages. Ultimately, repressive signals play an essential role in the appropriate placement of a single lens associated with each OV.

In this review, we will highlight the known signaling events that control the stages of competence and bias, which are tightly linked to patterning of the neural plate border and induction of the PPR. We will highlight evidence that inhibitory signals ensure that lens specification occurs in a restricted region of the head ectoderm and address lens specification with particular focus on OV-dependent signaling. By necessity this review will also discuss stage-specific genetic markers and how they help define inductive signals.

While lens induction is generally well conserved, species-specific differences in the expression of stage-specific marker genes, tissues required for induction and the timing of lens specification have been uncovered. Thus, we will discuss experiments and their implications from a broad perspective particularly when data supporting similar conclusions are available in multiple model organisms and highlight areas of species-specific variation.

2. Definitions

2.1. Competence

Competence is defined as the ability to respond to an inducing signal and to adopt a particular fate [5,8]. Competence indicates developmental potency rather than fate specification and is a transient property that initially encompasses a broad domain. Subsequent inductive events restrict competence as a tissue becomes more or less likely to adopt a particular fate.

In *Xenopus*, lens-forming competence is operationally defined as the ability of a tissue to form a lens when transplanted to the lens-forming region of neural plate stage embryos [9] and is acquired in all non-neural ectoderm autonomously, peaking in mid to late gastrulation (Fig. 1) [9,10]. By the time of neurulation, lens-forming competence is restricted to the peri-lens ectoderm.

In chick embryos, generic placode-forming competence is acquired by late gastrulation when non-neural ectoderm can be induced to express the placodal markers, *Six*1 and *Eya*1 (Fig. 1) [11]. Unlike amphibian embryos, however, the domain of lens competence in birds remains broad throughout neurulation, encompassing much of the anterior ectoderm. Indeed, at the time that the OV apposes the head surface ectoderm, both presumptive lens ectoderm (PLE) and ventral ectoderm are competent to express the lens marker, *δ-crystallin*, when cultured in isolation [12].

While the acquisition of competence in fish and mice has not been rigorously assessed, abundant evidence for a multi-step lens induction process exists. In fish, the existence of a broad lens-competent domain is indicated by the formation of lenses in place of the adenohypophysis in hedgehog (Hh) pathway mutants [13–17]. Furthermore, conversion of the adenohypophysis to lens only occurs if Hh signaling is altered prior to 10 h of development [16]. This suggests that, as in amphibians, the lens-forming competence domain in zebrafish is temporally restricted. Furthermore, in medaka fish, ectopic lenses have been observed in place of the otic vesicle or in lateral/ventral head ectoderm in response to ectopic *Six*3 or *Sox*3, respectively [18,19]. Experiments in the salamander, *Taricha torosa*, support a sequential and cumulative lens induction process, that is initially dependent upon dorsolateral endoderm at late gastrula stages and then on presumptive cardiac mesoderm [5]. In mice, lens-forming competence also exceeds the lens placode domain, as ectopic lens tissue forms in nasal peri-ocular tissue to the nasal extremity and on the upper lip in mice bearing conditional deletion of *β-catenin* (*lens-cre*, *Catnb*$^{tn2Kem/tn2Kem}$) [20].

2.2. Bias

Lens-forming bias, a term coined by Grainger and colleauges in *Xenopus* specifically refers to the strong inductive events associated with neural plate stage embryos. In *Xenopus*, bias is acquired from the anterior neural plate (ANP) and is distinct from signaling associated with the OV (Fig. 1) [8,21]. The