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Review

An essential role for FGF receptor signaling in lens development

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Abstract

Since the days of Hans Spemann, the ocular lens has served as one of the most important developmental systems for elucidating fundamental processes of induction and differentiation. More recently, studies in the lens have contributed significantly to our understanding of cell cycle regulation and apoptosis. Over 20 years of accumulated evidence using several different vertebrate species has suggested that fibroblast growth factors (FGFs) and/or fibroblast growth factor receptors (FGFRs) play a key role in lens development. FGFR signaling has been implicated in lens induction, lens cell proliferation and survival, lens fiber differentiation and lens regeneration. Here we will review and discuss historical and recent evidence suggesting that (FGFR) signaling plays a vital and universal role in multiple aspects of lens development.

Keywords: FGFR; FGF; Lens; Development; Eye

Contents

1. Introduction

The focus of this review is to examine what is known about the role of FGFs and FGFRs in the development of the vertebrate ocular lens. As this topic has been addressed using many different model systems, lens development will largely be considered in aggregate, and species differences will be highlighted when necessary. This is not meant to suggest that there are no differences between lenses of different species. In fact, we know that there are significant species differences in the size and shape of lenses as well as in the arrangement of suture patterns (reviewed in [1]). Lenses of different species also differ in major crystallin proteins (reviewed in [2]). Nonetheless, a strong argument can be made that the major genetic pathways and signaling molecules involved in vertebrate embryonic lens development are largely, if not entirely, conserved. With that being said, we will first launch into a brief overview of the major events in vertebrate lens development that transform a layer of

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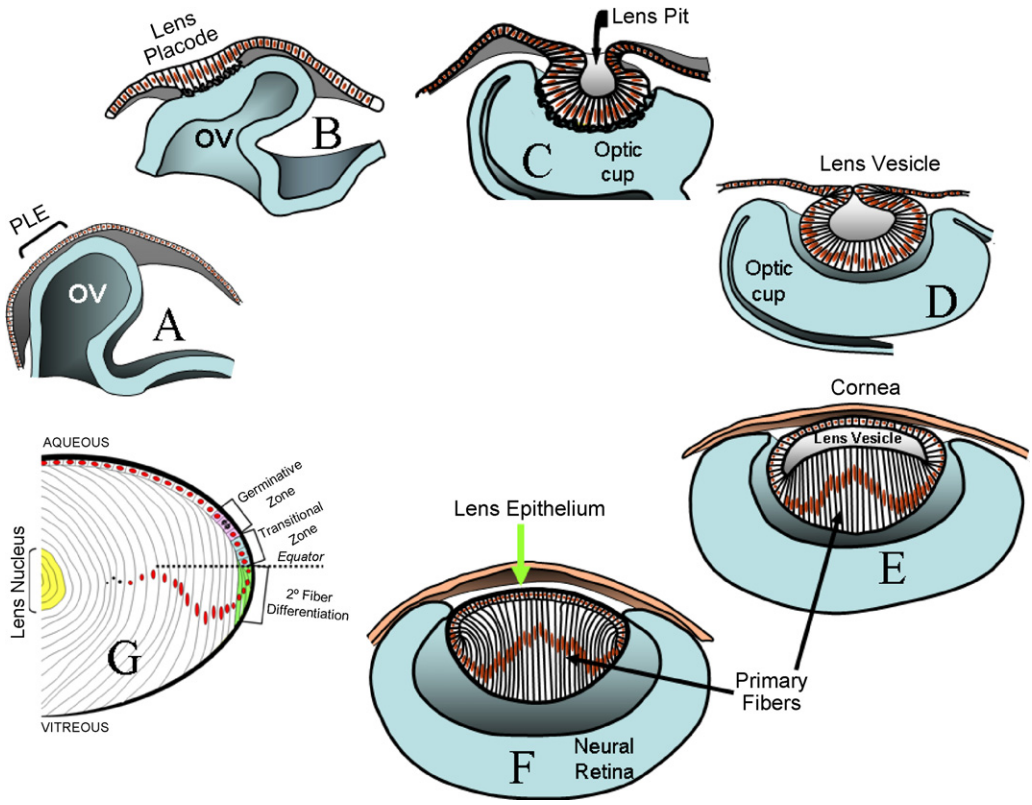

Fig. 1. (A) Morphological development of the lens begins as the optic vesicle (OV) approaches the presumptive lens ectoderm (PLE). (B) Upon physical contact of the OV with the PLE, cells within the PLE elongate forming the lens placode. (C) The lens placode invaginates forming the lens pit and the OV invaginates forming the optic cup. (D) The lens pit deepens and the connection of the lens pit and overlying surface ectoderm is lost forming the lens vesicle. (E) The overlying surface ectoderm differentiates into the corneal epithelium and the cells at the posterior of the lens vesicle elongate forming the primary fiber cells. (F) The primary fiber cells fill the lumen of the lens vesicle as they reach the anterior lens cells making up the lens epithelium. The inner layer of the optic cup differentiates into the neural retina. (G) The mature lens consists of an anterior epithelial layer composed of non-proliferating central lens epithelial cells (cuboidal cells with white cytoplasm) and a narrow band of proliferating cells known as the germinative zone (pink cells). Just posterior to the germinative zone is the transitional zone (blue cells) where many genes important for fiber cell differentiation are initially expressed. Just posterior to the lens equator (dotted line) transitional zone epithelial cells begin elongating forming secondary fiber cells (green cells). As secondary fiber cells progress through later stages of differentiation, they lose their intracellular organelles (represented by the shrinkage and loss of red nuclei). The lens nucleus (yellow) is composed of fiber cells that were present in the embryonic lens. The mature lens is bathed on the anterior surface by the aqueous humor and on the posterior surface by the vitreous humor. Adapted from Lovicu and McAvoy [170].

surface ectoderm in the early embryo into the transparent organ responsible (in collaboration with the cornea) for gathering and focusing light onto the retina. This will be followed by a brief review of the FGF and FGFR family, focused on those members of the family that are present in the developing or mature eye. The remainder of our discussion will focus on what we have learned about the role of FGFR signaling in different aspects of lens development and what questions remain to be answered.

1.1. Overview of embryonic lens development

Although detailed reviews of numerous aspects of lens development can be found elsewhere [3] here we will focus on the major events that are common to vertebrate lens development and result in the major structural features of the lens. In vertebrates, the lens begins development as a sheet of surface ectoderm that is exposed to multiple inductive influences during embryogenesis starting around late gastrulation and culminating when the presumptive lens ectoderm (PLE) overlies the embryonic optic vesicle (OV) (Fig. 1A). Shortly after physical contact between the PLE and OV is established, the lens ectoderm begins to thicken forming the lens placode (Fig. 1B). The lens placode subsequently invaginates forming the lens pit as the OV invaginates to form the optic cup (Fig. 1C). As the lens pit deepens, the connection to the surface ectoderm narrows forming the lens stalk. The lens stalk is a transient structure that eventually degenerates, by mechanisms that are currently unclear, separating the initially hollow lens vesicle from the overlying surface ectoderm that will differentiate into the corneal epithelium (Fig. 1D). The cells that were at center of the lens placode form the posterior half of the lens vesicle and continue to elongate toward the anterior, eventually filling the lumen of the vesicle as they form the primary lens fiber cells (Fig. 1E and F). The peripheral invaginating cells of the lens placode develop into the anterior half of the lens vesicle forming the lens epithelium. Initially all of the cells of the lens vesicle are capable of proliferation, but the primary fiber cells quickly lose their ability to proliferate as fiber differentiation progresses. While all lens epithelial cells retain the ability to undergo proliferation, lens cell proliferation normally becomes largely restricted, as development progresses, to