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The molecular mechanisms underlying lens fiber elongation

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ABSTRACT

Lens fiber cells are highly elongated cells with complex membrane morphologies that are critical for the transparency of the ocular lens. Investigations into the molecular mechanisms underlying lens fiber cell elongation were first reported in the 1960s, however, our understanding of the process is still poor nearly 50 years later. This review summarizes what is currently hypothesized about the regulation of lens fiber cell elongation along with the available experimental evidence, and how this information relates to what is known about the regulation of cell shape/elongation in other cell types, particularly neurons.

1. Introduction

1.1. Lens fiber cell morphology

The ocular lens is a remarkable structure. It is a transparent, cellular tissue which has numerous biochemical and structural specializations that form an exquisitely tuned refractive index gradient which efficiently refracts light (Fig. 1A) (Bassnett et al., 2011). The earliest histological investigations of the lens noted that it is comprised of two morphologically distinct cell types surrounded by a thickened basement membrane, the lens capsule (Thin and Ewart, 1876). Lens epithelial cells are found on the anterior surface closest to the cornea, while the profoundly elongated lens fibers form the bulk of the lens (Fig. 1B) (Zampighi et al., 2000). There is considerable species and developmental variation in the length of lens fibers. Chicken primary lens fibers are 200–400 μm long measured from their apical tip to their basal attachment site on the lens capsule (Shestopalov and Bassnett, 2000), while adult bovine secondary lens fibers are up to 20 mm in length (Kuszak et al., 2004a).

Lens fiber cells are organized into radial cell columns whose packing is optimized by their hexagonal cross sectional profile with two parallel sides ranging from 5 to 15 μm wide and four shorter sides ranging from 1 to 5 μm (Fig. 2A) (Bassnett et al., 2011). The advent of electron microscopy revealed that lens fiber cell structure is even more complex, and can vary both between species and at different locations within the same lens (Kuszak et al., 2004a; Shestopalov and Bassnett, 2000). The straight sides of newly forming cortical fiber cells have “ball and socket” membrane specializations which are rich in gap junctions to allow for efficient cell communication in an avascular lens (Fig. 3 A, B) (Bassnett et al., 2011; Kistler et al., 1986; Zhou and Lo, 2003). Each vertex at the intersection between these straight sides exhibits a very elaborate membrane structure, the membrane protrusion, which also greatly increases the surface area between cells, and may be critical for lens transparency (Fig. 2B) (Kuszak et al., 1980, 2004a). In mice, fiber cells lose obvious ball and socket junctions and develop more elaborate membrane protrusions as they mature (Fig. 3 C, D; Fig. 4A). Overall, lens fibers at different depths within the lens have obvious differences in membrane architecture, and can develop even more complex membrane architectures, which can include the larger scale deformations of the lateral fiber cell membrane known as paddles and undulations (Fig. 4) (Kuwabara, 1975). In contrast, lens fibers found in the center (the nucleus) of adult lenses tend to have only small membrane protrusions, but in many species, the straight sides develop a highly ordered membrane structure, the furrowed membrane (Fig. 5), which allows lens fibers to tightly pack by reducing extracellular space, a process that may be critical to form the refractive index gradient (Al-Ghoul et al., 2001; Costello et al., 2008, 1989; Lo and Harding, 1984).

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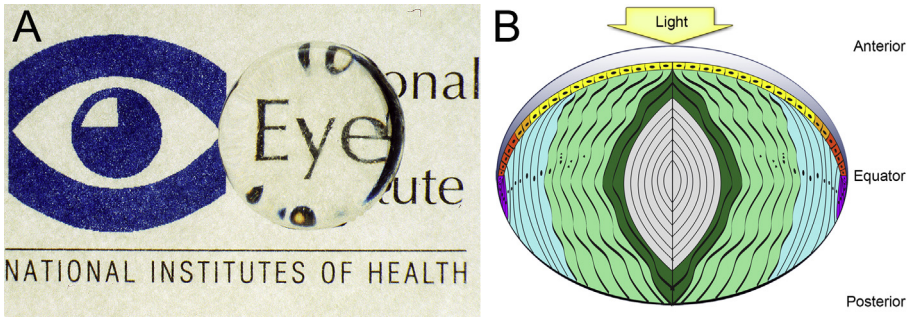

Fig. 1. A) A cow lens placed over the National Eye Institute logo showing both the clarity and refractive properties of the ocular lens. B) Parts of the lens. The lens is composed of two cell types: a monolayer of epithelial cells seen on the anterior surface, which proliferate and differentiate to fiber cells which make up the majority of the lens. Light yellow– light; dark grey– lens capsule; yellow– central epithelium; orange– germinative zone; red– transition zone; purple– meridional row region/bow region; light blue– outer cortical fiber cells; light green-inner cortical fiber cells; dark green– beginning nuclear fiber cells; light gray– nuclear fiber cells including the primary fiber cells which are found at the very center. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

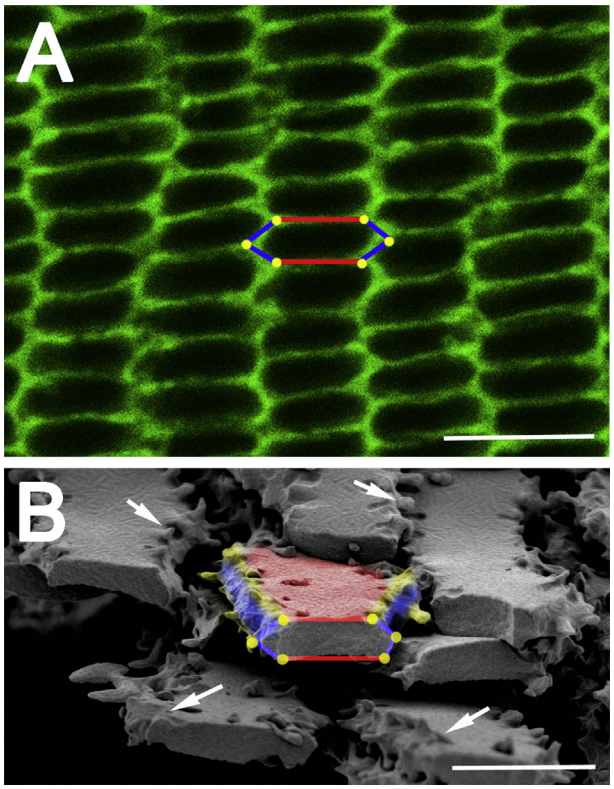

Fig. 2. Lens fiber cells have a hexagonal geometry when viewed in cross section. (A) An equatorial cross section of a mouse lens stained with fluorescent wheat germ agglutinin and viewed with a confocal microscope. The hexagonal geometry of cells is highlighted in the center of the image showing the two broad sides of the cell labeled in red, the four short sides labeled in blue and the six vertices represented as yellow dots. Scale bar = 7.5 μm (B) A scanning electron micrograph showing lens fiber cells cut across their major axis allowing for viewing of their hexagonal geometry. The yellow vertices and white arrows show that there are membrane protrusions seen along these edges. Red– broad side; blue– short side; yellow– vertices/membrane protrusions; Scale bar = 5 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

1.1.1. Lens differentiation

The lens derives exclusively from the head ectoderm which receives signals produced by the optic vesicle (an outpouching of the neural tube) (Chow and Lang, 2001; Donner et al., 2006; Grainger, 1992), to form the lens placode. This structure then invaginates to form the lens pit, and closes to form the lens vesicle (Cvekl and Piatigorsky, 1996). At this point, the lens vesicle is a hollow structure comprised of a basement membrane lined with polarized epithelial cells whose apical surfaces face the vesicle interior. The cells in the anterior portion of the lens vesicle (which faces the developing cornea) are fated to become the lens epithelium which will form the proliferative cell population solely responsible for any further lens cells that form throughout life (Bhat, 2001). In contrast, the lens cells in the posterior aspect of the lens vesicle (those closest to the developing retina), terminally leave the cell cycle (Griep, 2006), downregulate the expression of a subset of genes that are active in head ectoderm/lens epithelial cells (Manthey et al., 2014; Pontoriero et al., 2009; West-Mays et al., 1999), and turn on high level expression of numerous genes that will establish the lens fiber cell proteome that is necessary for lens transparency and its refractive index gradient (Duncan et al., 2004; Hawse et al., 2005; Hoang et al., 2014; Pierscionek and Regini, 2012). Simultaneously, these cells undergo a massive cell shape change where the cuboidal/flattened epithelial cell is remodeled into the elongated lens fiber cell (Bassnett and Winzenburger, 2003; Bassnett, 2005; Shestopalov and Bassnett, 2000). These “primary” lens fibers are the shortest mature lens fibers and are found in the center of adult lenses as there is little to no lens fiber cell turnover across the lifespan (Augusteyn, 2010; Bassnett and Winzenburger, 2003; Stewart et al., 2013). Further growth of the lens occurs as lens cells formed via lens epithelial cell proliferation are crowded out of the epithelium proper towards the lens equator (Shi et al., 2015). Upon reaching the lens equator, these nascent secondary lens fiber cells come into contact with differentiation promoting FGF ligands, likely similar to those that drove primary fiber formation (Lovicu et al., 2011; de Iongh and Duncan, 2014). However, unlike primary fiber cell differentiation, secondary fiber differentiation does not appear to be as dependent on BMP (Faber et al., 2002) and Wnt/β-catenin signaling (Lovicu et al., 2011). While secondary lens fiber morphology appears more complex and tightly regulated than that of primary fibers (Bassnett et al., 2011), these cells do undergo many of the same molecular and morphological changes, leading to the formation of new fiber layers over the lens core which initially consists of only primary lens fibers (Bassnett, 2005). This process continues throughout the life span, with new lens fiber cells being added over those formerly produced to create a functional lens (Augusteyn, 2010).

Despite these significant changes in morphology during their differentiation, lens fibers initially maintain the classical apical/basal polarity characteristic of epithelial cells, maintaining a basal attachment to a basement membrane (the lens capsule) while making apical contacts with the apical side of lens epithelial cells (Zampighi et al., 2000). In primary lens fibers, this apical contact is

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