HHS Public Access

Author manuscript

Prog Mol Biol Transl Sci. Author manuscript; available in PMC 2017 October 25.

Published in final edited form as:

Prog Mol Biol Transl Sci. 2015 ; 134: 119–127. doi:10.1016/bs.pmbts.2015.04.006.

Overview of the Lens

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Abstract

In order to accomplish its function of transmitting and focusing light, the crystalline lens of the vertebrate eye has evolved a unique cellular structure and protein complement. These distinct adaptations have provided a rich source of scientific discovery ranging from biochemistry and genetics to optics and physics. In addition, because of these adaptations, lens cells persist for the lifetime of an organism, providing an excellent model of the aging process. The chapters dealing with the lens will demonstrate how the different aspects of lens biology and biochemistry combine in this singular refractive organ to accomplish its critical role in the visual system.

1. INTRODUCTION

Like the lens in a camera, the basic function of the eye lens is to transmit and focus light onto the retina. To facilitate this, it contains one of the highest concentrations of proteins of any tissue. The lens has been studied scientifically for over a century, beginning in 1833 when Sir David Brewster deduced the fine structure of the cod lens using only a candle and a finely ruled steel bar.[1] In 1894, Mörner first described high concentrations of soluble structural proteins we now call crystallins,[2] and Spemann developed the concept of inductive interactions in development by studying the lens in 1901.[3] Renwick mapped a cataract locus, one of the first autosomal loci to be localized,[4] and chicken lens δ-crystallins were among the first mRNAs to be isolated and cloned.[5] Thus, in addition to being important in the study of inherited diseases, the lens has also been a model system invaluable for developmental and structural biology.

2. STRUCTURE AND CELLS OF THE LENS

Weighing about 65 mg at birth, the human lens increases in weight to about 160 mg by the age of 10 at which time growth slows substantially so that it weighs about 250 mg by the age of 90.[6,7] As much as 60% of the total mass of the lens can be made up of proteins, much higher than almost any other tissue.[8] The lens is surrounded by a collagenous capsule, on which the anterior-facing basal poles of the epithelial cells rest, as do the basal poles of the fiber cells facing posteriorly (Fig. 1).[9,10] The capsule acts as a barrier to diffusion and

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contributes to shaping the lens during accommodation.[11,12] Its main components are type IV collagen, laminin, entactin, perlecan, type XVIII collagen, heparin sulfate proteoglycan, and fibronectin,[13,14] of which the first four are major structural molecules that self-assemble to form a matrix. The capsular filaments, of uniform size and aligned in a parallel fashion, are thinnest at the posterior pole and thicken to a maximum at the equator, where the lens zonules insert.[14] Fibrillin and elastin fibers also integrate in the equatorial region, especially in the outer zonular.[15] The lens capsule is first detectable at 5–6 weeks of gestation in humans[16] and is produced continually throughout life[12] anteriorly by the cuboidal epithelium and more slowly posteriorly by the fiber cells.

Mitotic division in the lens occurs in the germinative zone of the anterior epithelium located just anterior to the equator. The anterior epithelial cells of the lens are connected by gap junctions,[17] allowing exchange of low-molecular-weight metabolites and ions. They have few or no tight junctions that would make the extracellular spaces impermeable to these molecules.[18,19] Anterior cuboidal epithelial cells also are rich in organelles and contain large amounts of cytoskeletal proteins such as microtubules, spectrin, α-actinin, actin, myosin, and vimentin, presumably to help stabilize the cell structures during accommodation.[20–22] Both lens epithelial and especially fiber cells contain large amounts of crystallins.

Fiber cells make up the lens nucleus. Layers of nucleated cortical fiber cells form highly ordered concentric shells around the nonnucleated central fiber cells which make up the fetal nucleus, with the ends of the peripheral fiber cells abutting in sutures anteriorly and posteriorly. Both the ordered arrangement of the fiber cells and their sutures as well as their intracellular structure are important for light transmission and lens transparency.[23–25] Also contributing to transparency is the presence of only minimal extracellular space between fiber cells, which have many interdigitations.[9,26] Junctional complexes between adjacent fiber cells allow for exchange of metabolites.[21,22] Lens crystallins, which make up about 90% of the water-soluble protein, are the main soluble components of fiber cells, along with cytoskeletal components, including actin, myosin, vimentin, α-actinin, and microtubules.[27]

The lens is composed of a single cell type that follows a developmental pattern, beginning as a member of the germinative zone in the single layer of anterior epithelial cells overlaying the fiber cell mass.[26] Epithelial cells then migrate laterally toward the equator, where they begin to elongate and invert to form secondary fibers. In order to increase light transmission, organelles such as mitochondria, Golgi bodies, and both rough and smooth ER are degraded in the differentiating lens fiber cells so that they are absent from nuclear fiber cells. The density of their cell membranes increases, approaching that of the cytoplasm, which also decreases light scattering.[28] As the cells elongate newer cortical fiber cells are layered over them so that they are moved toward the lens nucleus, stretching anteriorly from the cuboidal epithelial cells posteriorly to the posterior capsule. Transcriptional control plays a significant role in the differential synthesis of lens crystallins (see Ref. [29]). The distribution of β-crystallin mRNAs in chickens[30] and the β- and γ-crystallin proteins and mRNAs in rats[31,32] provides examples of the spatial and temporal control of crystallin gene expression during lens development.

3. TRANSPARENCY

The main optical function of the lens is to transmit light, focusing it on the retina. The cornea contributes about 80% of total refraction, while the lens fine-tunes the focusing of light onto the retina. Although the human lens is colorless at birth, there is a gradual increase in yellowish pigmentation with age[33] probably due to the production of 3-hydroxykynurenine and other metabolites of tryptophan that filter UV light.[34] The lens transmits light with wavelengths up to 1200 nm efficiently, but transmits very little light below 390 nm. 1200 nm is well above the limit of visual perception, about 720 nm. As discussed previously, the architecture and cellular contents of the lens are critical for its transparency. The transparency and high-refractive index of cells in the lens result from tight packing of their proteins, providing a constant refractive index over distances approximating the wavelength of the transmitted light.[24,25] In fact, as lens proteins are diluted to concentrations below that found in the lens, about 450 mg/ml, light scattering actually increases,[35,36] because dilution decreases the weak interactions between unlike proteins that occur at high concentrations and help to maintain lens transparency.[37,38] Finally, there is a gradual increase in the refractive index of the human lens from 1.38 (73–80% H_2O) in the cortex to 1.42 (68%H_2O) in the nucleus, in part due to an enrichment of tightly packed γ-crystallins.[39]

4. AGING

The inability of cells to be replaced in the encapsulated lens combined with the inability of lens cell proteins to turn over in the nonnucleated fiber cells makes the lens particularly susceptible to damage with aging and environmental insults such as UV light and other oxidative stresses.[40] This results in a decrease in transmission of light and focusing even in the normal aged lens so that the intensity of light reaching the retina is reduced by about 10-fold by 80 years of age.[41] It also increases susceptibility to senescent cataract and presbyopia, especially in individuals exposed to environmental insults or having a genetic proclivity.[42] With increasing age, vacuoles and multilamellar bodies develop between lens fiber cells, occasionally disrupting the fiber plasma membrane.[43] In addition, most of the elaborate cytoskeletal structure found in lens cells disappears with age,[44] so that by the fifth decade presbyopia develops with loss of the ability to accommodate.[45,46]

Enzymatic activity in the lens decreases with age, especially in the central cells of the lens nucleus where the cells are older than those in the cortical nucleus and especially the anterior epithelial cells.[47] This compromised intracellular homeostasis might be exacerbated by the decreased metabolic coupling of the active cortex and the inactive nucleus that occurs in older lenses, in part associated with decreased gap junction coupling.[48,49] This is particularly relevant for the enzymes that produce a reducing environment by maintaining high levels of reduced glutathione, such as glutathione reductase and glucose-6-phosphate dehydrogenase.[50] Decreases in the activity of these and other reducing enzymes decrease defenses against oxidative damage in the lens and exacerbate damage to crystallins and other metabolic support systems.[51] Finally, as the lens ages intracellular Na^+ and Ca^{2+} concentrations rise, probably due to an increase in lens permeability or decrease in ion channel pumping efficiency.[52]

Lens crystallins also show age-related changes that might interfere with lens transparency.[37] Between 10 and 50 years of age crystallin modification increases,[53] as does the level of high-molecular-weight aggregates and water-insoluble protein.[54] Because of their chaperone activity, this is especially notable in the α-crystallins, but is also seen in the β- and γ-crystallins.[55,56] Crystallins, membranes, and enzymes are also cleaved and partially degraded, including the nonenzymatic cleavage of αA-crystallin at the bond between Asn101 and Glu102.[57] In what might be a positive feedback effect, cleavage products of βA3-crystallin appear to inhibit the chaperone activity of α-crystallin chaperone.[58] γ-Crystallins, and particularly γS-crystallin, are often subject to proteolysis, degradation, and modification in age-dependent cataracts, being broken down to low-molecular-weight peptides.[59–61]

As the lens ages both the amino- and carboxyl-terminal arms of up to half of the intrinsic membrane protein AQP0 (MP26) molecules undergo proteolysis, forming MP22.[62] Other posttranslational modifications of AQP0 also occur with aging including C-terminal phosphorylation, possibly involved in intercellular trafficking, and glycation, which influences AQP0 interaction with calmodulin. However, the precise functional significance of these remains unclear.[63,64] The lens contains proteasomes, which preferentially degrade oxidized proteins[65] tagged with the protease cofactor ubiquitin,[66] whose activity is increased by oxidative stress.[67] These proteinases are balanced during aging by inhibitors including the chaperones HSP90 and α-crystallin.[59]

Covalent modifications of crystallins and other lens proteins also increase with aging, with increases in oxidation of methionine, deamidation of asparagine and glutamine residues, disulfide bridges, backbone cleavage, and racemization of aspartic acid residues.[59,68,69] Deamidation can destabilize βA3-crystallin, causing it to aggregate,[70] while deamidation of glutamines at the interface of γD-crystallin can also destabilize it.[71] Asp151 in αA-crystallin is especially susceptible to racemization because it forms a succinimide intermediate easily.[72] Racemization at both Asp58 and Asp151 can lead to increased aggregation and decreased chaperone activity and is enhanced by mutations of nearby residues.[73] Finally, phosphorylation and nonenzymatic glycosylation (glycation) also occur, especially affecting the ε-amino groups of lysine residues.[57,74,75] These can participate in the Maillard reaction, resulting in nondisulfide covalent cross-links, increased pigmentation, and nontryptophan fluorescence.[76] Glycation of α-crystallin can also decrease its chaperone function, eventually resulting in aggregation. [77] Lens proteins can also undergo carbamylation with aging or other insult, and this can induce cataract,[78] which has been proposed to be the mechanism of cataract associated with chronic diarrhea and its resultant uremia.[79] Thus, the development and biology of the lens is directed at establishing transparency and focusing of light, and then defending this highly specialized system against damage by age and environmental insults.

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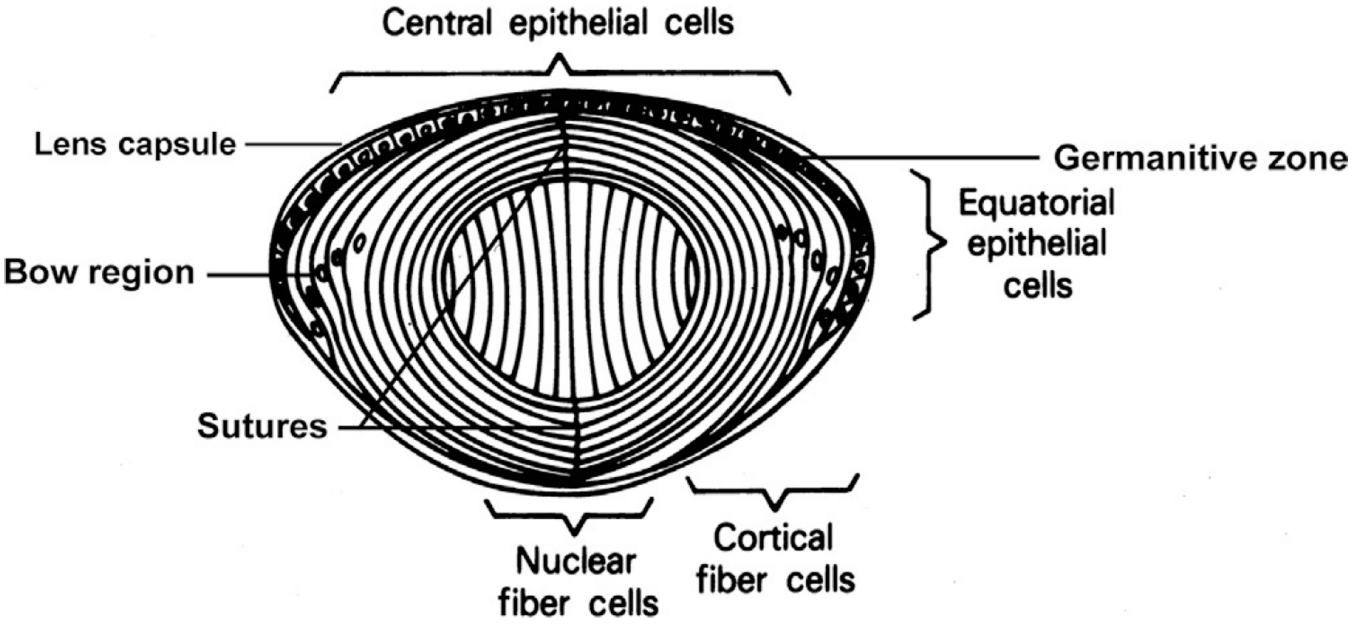

Figure 1.

Human lens structure. Anterior epithelial cells divide at the 10 and 2 o'clock positions. Cells then move laterally, eventually inverting in the bow region, at which time they elongate and begin degrading their organelles to form cortical fiber cells. Central nuclear fiber cells elongate from the posterior epithelia early in development. The ends of the more peripheral secondary fiber cells abut at the sutures, which are shown here as vertical lines but are seen clinically as the anterior and posterior Y structures.