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Research article

Novel roles for the lens in preserving overall ocular health

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ABSTRACT

Outside the traditional roles of the lens as an important refractive element and a UV filter, it was David Beebe's group that first demonstrated that the lens acts an oxygen sink that protects the tissues of the anterior segment of the eye from oxygen or oxygen metabolites. In this review, we follow on from this work, and present new evidence from our laboratory to demonstrate that the lens serves as a reservoir for the release of the antioxidant glutathione (GSH) into the aqueous humor to provide a source of GSH and/or its precursor amino acids to nearby tissues that interface with the aqueous humor, or to remove toxic metabolites from the eye via the aqueous outflow pathway. In addition to GSH release, our laboratory and others have shown that ATP is released from the lens under hyposmotic conditions to activate purinergic signalling pathways in an autocrine manner to alter lens function. In this review, we raise the idea that ATP and/or its subsequent degradation product adenosine may exert a paracrine function and influence purinergic signalling systems in other tissues to alter aqueous humor outflow. These new secondary roles indicate that the lens is not just a passive optical element, but a highly dynamic and active tissue that interacts with its neighbouring tissues, through modifying the environments in which these tissues function. We believe that the lens actively contributes to the ocular environment and as a consequence, removal of the lens would alter the functionality of neighbouring tissues. We speculate that a long term effect of lens removal may be to inadvertently increase the exposure of anterior tissues of the eye to oxidative stress due to elevated oxygen levels and a reduction in the availability of GSH and purinergic signalling molecules in the aqueous humor. Since cataract surgery is now being performed on younger patients due to our increasing diabetic population, over time, we predict these changes may increase the susceptibility of these tissues to oxidative stress and the incidence of subsequent ocular pathologies. If our view of the lens is correct, the actual loss of the biological lens may have longer term consequences for overall ocular health than currently appreciated.

1. Introduction

While it is generally acknowledged that for optimal visual acuity, all the optical elements that contribute to the passage of light through the eye need to be appropriately configured, little attention has been given to the cellular interactions between the major tissues in the eye, and how they might regulate their neighbouring tissues, or the environments in which these tissues function.

The role of this topical review therefore is to investigate whether ocular tissue interactions at the cellular level are involved in determining the integrated functionality of the eye, with a particular focus on the role played by the lens. This focus on the lens is for two principle reasons. Firstly, due to its size, position and avascular nature, the lens, via its need to accumulate nutrients from and to excrete wastes into the ocular humors, has the ability to modify the fluids that nourish the similarly avascular cornea and trabecular meshwork, thereby affecting their function. Secondly, the lens is routinely removed from the eye during cataract surgery allowing us to determine both the short and long term effects of its removal on the health of other ocular tissues in the eye. Indeed, the

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apparent success of cataract surgery has led to the view that the lens is merely a passive optical element that can be replaced by an intraocular implant, thereby limiting research into potential roles that the lens could be playing in determining overall ocular health. For these reasons in this review, we first present emerging evidence that the lens is not a passive optical element, but a dynamic and active tissue with a unique structure and function, before presenting some examples of how the lens could potentially interact with other ocular tissues. Finally, we speculate as to how removal of the lens could impact on the progression of other ocular diseases to highlight the potential importance of the lens to long term ocular health.

2. The ocular lens: more than a passive optical element

While the transparent properties of the lens are a direct result of its highly ordered tissue architecture, the lens is not a purely passive optical element. It has been proposed that the lens operates an internal microcirculation system which maintains lens transparency by delivering nutrients to the lens fiber cells faster than would occur by passive diffusion alone (Donaldson P, 2001; Mathias et al., 1997, 2007). Briefly, this model of lens transport states that a circulating current of Na^+ ions, primarily enters at the poles and travels into the lens via the extracellular spaces between fiber cells (Fig. 1). Na^+ crosses fiber cell membranes, and returns towards the surface via an intercellular pathway mediated by gap junction channels, where it is actively removed by Na^+ pumps concentrated at the lens equator (Candia and Zamudio, 2002). This circulating ionic current creates a net flux of ions that in turn generates fluid flow that has been shown to enter the lens at both poles (Candia et al., 2012; Vaghefi et al., 2011). The accompanying extracellular flow of water convects nutrients towards the deeper lying fiber cells, while the outward intercellular flow, driven by a hydrostatic pressure gradient (Gao et al., 2011), removes wastes and creates a well-stirred intracellular compartment. Thus active pumping of Na^+ by surface cells is able to not only regulate the ionic composition and water content of inner fiber cells to maintain the optical properties of the lens (Vaghefi et al., 2011, 2015), but also

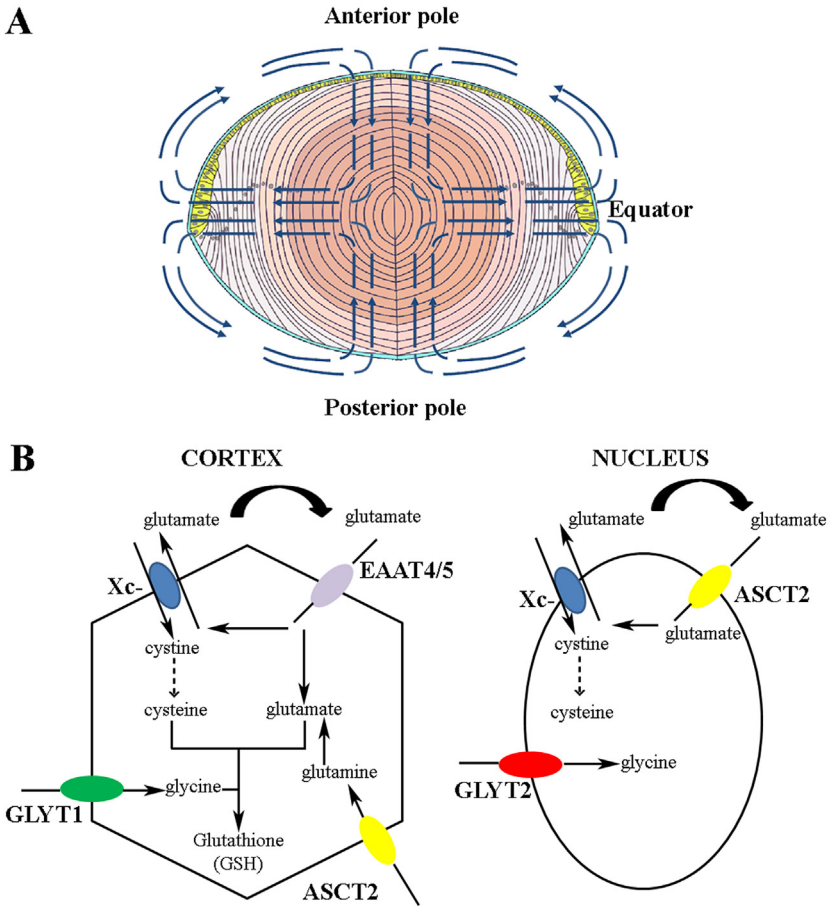

Fig. 1. Maintenance of lens transparency. (A) Current flow through the lens that underpins the internal microcirculation system. It has been proposed that the influx of ions at the anterior and posterior poles is accompanied by the convection of water, oxygen, nutrients, and antioxidants to the deeper-lying fiber cells, whereas the efflux of ions at the equator facilitates the removal of fiber cell waste products (Mathias et al., 1997). **(B)** Fiber cells of the lens cortex and nucleus express distinct transporter isoforms to mediate amino acid uptake in the different regions of the lens. In the outer cortex of the lens, the cystine/glutamate exchanger Xc- and the Excitatory Amino Acid Transporters EAAT4/5 are co-expressed, indicating that these transporters may work together to accumulate cystine (Lim et al., 2005). Xc-uses the high glutamate concentration to drive the exchange of extracellular cystine for intracellular glutamate. This cycle of exchange is maintained by EAAT4/5 which actively removes glutamate from the extracellular space. The primary source of glutamate for GSH synthesis is believed to be derived from glutamine uptake via the Alanine Serine Cysteine Transporter 2 (ASCT2) and its subsequent conversion to glutamate (Lim et al., 2006). Glycine, the third precursor amino acid required for GSH synthesis is likely to be mediated via the glycine transporter 1 (GLYT1) (Lim et al., 2006). In the nucleus, Xc- and ASCT2 are co-expressed and since ASCT2 is able to transport glutamate at low pH which coincides with the acidic environment of the lens center, Xc-is likely to work with ASCT2 to mediate cystine uptake (Lim et al., 2006). Cystine uptake in a region not capable of GSH synthesis may indicate that cysteine itself acts as a low-molecular-mass antioxidant (Li et al., 2007). Finally, the glycine transporter 2 (GLYT2) appears to be responsible for the accumulation of glycine in the lens nucleus (Lim et al., 2007), where it may act as an anti-glycating agent to protect against protein modifications.

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