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Review

Tools to fight the cataract epidemic: A review of experimental animal models that mimic age related nuclear cataract

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ABSTRACT

Cataract is the leading cause of blindness worldwide and accounts for approximately half of all forms of vision loss. Currently, the only way to treat cataracts is by surgery. However, with an ageing population, the demand for surgery and the need for cost effective alternative solutions grows exponentially. To reduce the need for cataract surgery, alternative medical therapies to delay cataracts are urgently required. However, given the difficulty in accessing human cataract lenses, investigating the process of cataract formation and testing the efficacy of potential therapies in humans is problematic. Therefore, researchers have looked to create suitable animal models of cataractogenesis to identify therapeutic options. This review will provide an overview of the cataract specific changes previously reported in human cataract lenses, before focussing on the specific changes that occur in age related nuclear (ARN) cataract, the most common form of cataract in humans. This will be followed by a discussion of a range of existing animal cataract models and their respective suitability for mimicking the processes associated with the development of ARN cataract, and therefore their utility as models to test anti-cataract therapies for future use in humans.

Contents

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1. Introduction

Cataract is the leading cause of blindness worldwide and accounts for approximately half of all forms of vision loss (Bourne et al., 2013). The main risk factors associated with cataract are predominantly age and diabetes, but others include nutrition (malnutrition and obesity), exposure to sunlight, genetics, gender, smoking and alcohol (Chatterjee et al., 1982; Brian and Taylor, 2001; Weintraub et al., 2002; Kelly et al., 2005; Truscott, 2005; Olafsdottir et al., 2012; Ye et al., 2012; Pan and Lin, 2014). Currently, the only way to treat cataracts is by surgery. However, with an ageing population, the demand for surgery and the need for cost effective alternative solutions grows (Semmens et al., 2003). It has been predicted that delaying the onset of cataract by ten years will halve its incidence (Brian and Taylor, 2001). However, developing anti-cataract strategies using human donor lenses is fraught with difficulties. Barriers to this include the limited availability of human donor lenses and intact cataractous lenses, the narrow age range (since lenses are typically from older donors), post-mortem delay between death and tissue processing, and the inherent variability between donors (genetic variation, systemic disease, cause of death, exposure to environmental risk factors). While not ideal, this has led investigators to turn to animal models of lens cataract.

There is a large number of animal models currently in use and with the uptake of transgenic technologies this number is increasing. These models have been used to either study the pathogenesis of cataract, or to trial anti-cataract therapies with the long term view to reduce the incidence of cataract in humans. While one experimental system cannot entirely replicate the cataract process in humans, investigators need to be mindful of selecting an appropriate animal model. However, it is often unclear what form of human cataract these animal models are trying to model. Clinically four main forms of lens cataract are recognised in humans. Three of these, sub-capsular, cortical and nuclear are named after the regions in the lens where the light scattering cataract first originates (see Table 1). In general, a cataract will start as one of these three regional types of cataract, but over time the cataract may spread to other lens regions to produce a mixed cataract phenotype, the fourth major class of cataract. Of the four major sub-types nuclear cataract is the most common (Age-Related Eye Disease Study Research, 2001). Its onset is associated with advancing age and is characterised by light scattering induced by protein aggregation specifically in the lens nucleus in the absence of overt changes to fibre cell morphology (Harding, 1991). In contrast, cortical and posterior subcapsular cataract is more strongly associated with diabetes and is associated with changes to the morphology of the fibre cells in the outer regions of the lens (Jeganathan et al., 2008; Olafsdottir et al., 2011). UV light is also considered a major risk factor for cortical cataract, with epidemiological studies linking UV-B exposure to sunlight induced cataract (Taylor et al., 1988; Cruickshanks et al., 1992; West et al., 2005), but for which UV-A light cannot be altogether excluded (Dillon, 1999) (see Table 1). Interestingly, many of these cortical cataracts form in the lower nasal region of the lens (Schein et al., 1994; Sasaki et al., 2003; Abraham et al., 2010), where it has been shown that light coming in from the side of the eye can focus 20 times stronger in the germinative region of the nasal side of the lens (Coroneo et al., 1991; Kwok and Coroneo, 2000), possibly causing cortical cataract in this region.

The focus of this review is to assess the relative ability of animal models to mimic the specific changes to the lens that occur in age related nuclear (ARN) cataract. To facilitate this comparison, we will first provide an overview of the morphological, biochemical and physiological changes that have been reported in human ARN cataract in order to develop a set of parameters to assess the relative merits of animal models to mimic ARN cataract in humans. This will then be followed by descriptions of animal models currently in

Table 1
Summary of cataract types, risk factors and mechanism of cataract formation.

Type of cataract	Major risk factors	Appearance of opacification	Mechanism of cataract formation	References
Subcapsular	■ Diabetes ■ Ageing ■ Retinitis pigmentosa ■ Intraocular corticosteroid use	■ Below the lens capsule ■ Predominantly posterior location	■ Swelling and breakdown of lens fibres ■ Abnormal migration of epithelial cells from the equator towards the posterior pole ■ Production of extracellular granular and fibrillary material	(Eshaghian and Streeten, 1980; Eshagian, 1982)
Cortical	■ Diabetes ■ UV exposure	■ Wedge shaped or radial spoke opacification in the lens cortex	■ Loss of ionic balance: increase in Ca^{2+} and Na^{+} concentrations. ■ Activation of Ca^{2+} dependent proteases that cause cleavage of cytoskeleton proteins ■ Distinct localized zone of cell swelling in the lens cortex	(Duncan and Bushell, 1975; Bond et al., 1996; Jacob, 1999; Sanderson et al., 2000)
Nuclear	■ Ageing ■ Smoking	■ Increased yellowing of the lens nucleus	■ No major changes in ionic content in the lens centre ■ No major morphological disruption of nuclear fibre cells ■ Significant oxidation of lens protein SH groups as a result of GSH depletion ■ Loss of protein SH groups ■ Increase in protein mixed disulfides ■ Formation of high molecular weight aggregates	(Duncan and Bushell, 1975; Takemoto et al., 1984; Costello et al., 1992; Lou and Dickerson, 1992; Al-Ghoul et al., 1996; Truscott, 2005)