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Experimental models for posterior capsule opacification research

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ABSTRACT

Millions of people worldwide are blinded due to cataract formation. At present the only means of treating a cataract is through surgical intervention. A modern cataract operation involves the creation of an opening in the anterior lens capsule to allow access to the fibre cells, which are then removed. This leaves in place a capsular bag that comprises the remaining anterior capsule and the entire posterior capsule. In most cases, an intraocular lens is implanted into the capsular bag during surgery. This procedure initially generates good visual restoration, but unfortunately, residual lens epithelial cells undergo a wound-healing response invoked by surgery, which in time commonly results in a secondary loss of vision. This condition is known as posterior capsule opacification (PCO) and exhibits classical features of fibrosis, including hyperproliferation, migration, matrix deposition, matrix contraction and transdifferentiation into myofibroblasts. These changes alone can cause visual deterioration, but in a significant number of cases, fibre differentiation is also observed, which gives rise to Soemmering's ring and Elschnig's pearl formation. Elucidating the regulatory factors that govern these events is fundamental in the drive to develop future strategies to prevent or delay visual deterioration resulting from PCO. A range of experimental platforms are available for the study of PCO that range from in vivo animal models to in vitro human cell and tissue culture models. In the current review, we will highlight some of the experimental models used in PCO research and provide examples of key findings that have resulted from these approaches.

1. Introduction

Fibrosis is a condition that affects multiple organs and is associated with hyperproliferation, migration, matrix deposition, matrix contraction and transdifferentiation into myofibroblasts (Leask and Abraham, 2004). Posterior Capsule Opacification (PCO) is a disorder that results following cataract surgery (Fig. 1) and presents some fibrotic features in virtually all cases (Eldred et al., 2011; Wormstone, 2002; Wormstone et al., 2009). In a number of patients, fibre differentiation is also evident, which gives rise to Soemmering's ring and Elschnig's pearls that can cause further visual deterioration (Findl et al., 2010; van Bree et al., 2013a, 2012). PCO affects millions of individuals (Eldred et al., 2011; Wormstone, 2002; Wormstone et al., 2009). Understanding the regulatory mechanisms that underpin this condition is crucial if we are to advance treatment strategies that will prevent or delay visual deterioration resulting from PCO. In order to make significant breakthroughs, good experimental systems are required. In the current review, we will introduce the problem of PCO and highlight some of the experimental platforms available for PCO research and provide examples of key findings that have resulted from these approaches.

Cataract is the major priority in the global initiative to eliminate avoidable blindness by the year 2020 (McCarty and Taylor, 2001). Due to medical and sociological advances we are in a time where longevity has been significantly extended and our ageing population is increasing (http://www.worldometers.info/world-population/). Consequently, the incidence of cataract will rise. Cataract surgery is already the most common operative procedure in the world and is expected to reach a rate of 30 million per annum by the year 2020. While cataract surgery initially provides excellent results, it is blighted by a secondary loss of vision caused by PCO, which requires further surgical intervention to restore vision in a patient. This affects the wellbeing of the individual and places a great financial burden on health care providers (Wormstone et al., 2009).

A modern cataract operation involves making a small incision in the sclera or cornea to permit introduction of surgical tools with

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minimal physical disruption to the eye. An opening in the lens is made by creating a continuous curvilinear capsulorhexis (capsular tear) in the anterior capsule using a capsulotome; an alternative practice is to use a femtosecond laser, which theoretically provides a consistent size and position of the rhexis (Abouzeid and Ferrini, 2014). This circular window in the anterior capsule allows access to the central regions of the lens that are typically associated with cataractous change. The lens fibres are usually removed by phacoemulsification, but in some cases this is assisted by femtosecond laser treatment of the fibre cells and on rare occasions traditional hydrodissection methods are required. Residual fibre cells are removed by irrigation/aspiration techniques. The product of cataract surgery is a capsular bag; which comprises a portion of the anterior and the entire posterior capsule. The bag remains within the eye and is supported by the zonules, which allows a continued partition of the aqueous and vitreous humours. In the vast majority of patients, an intraocular lens (IOL) is placed within the capsular bag and in doing so restores refractive power. Following surgery light can pass freely along the visual axis through the transparent IOL and thin acellular posterior capsule. However, lens epithelial cells can resist the trauma of surgery and these robust cells in time re-colonise regions of the anterior capsule denuded by surgical abrasion. Most importantly cells colonise the previously cell-free posterior capsule and encroach upon the visual axis. Modifications to cell organisation and the underlying matrix can cause light scatter (van Bree et al., 2013b, 2012). These changes can ultimately cause visual deterioration, which requires corrective

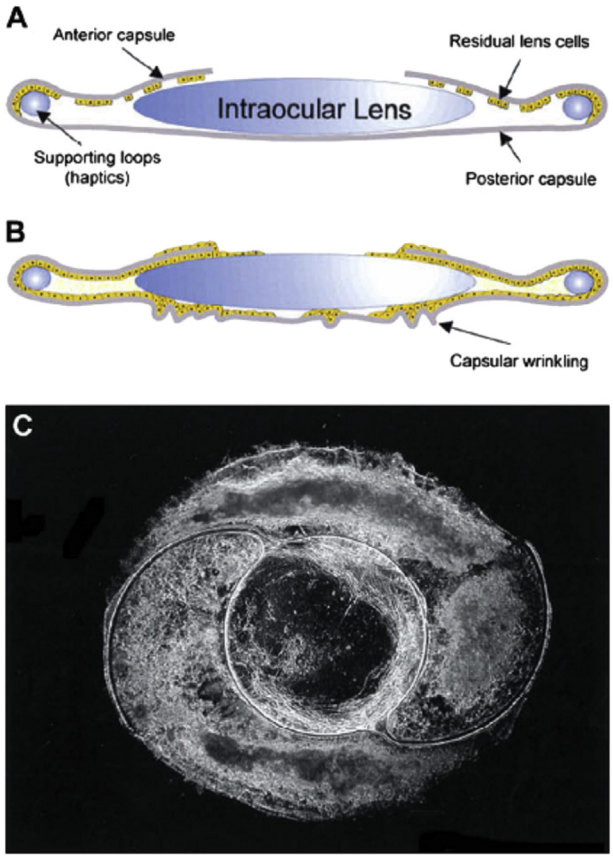

Fig. 1. A schematic representation of (A) the post-surgical capsular bag and (B) the extensive growth and modification that gives rise to Posterior capsule opacification following cataract surgery. (C) A dark-field micrograph of a capsular bag removed from a donor eye that had undergone cataract surgery prior to death that exhibits light scattering regions beneath an intraocular lens. First published in Wormstone (2002) with permission from Experimental Eye Research (Elsevier).

Nd:YAG laser treatment to ablate the central posterior capsule and associated cells, in order to permit an uninterrupted path through the visual axis (Wormstone et al., 2009); however this is both expensive, logistically difficult with elderly patients and has associated medical risk, such as increased likelihood of retinal detachment (Ranta and Kivela, 1998).

There are a number of factors that can increase the incidence of PCO, for example young age, intraocular inflammation and surgical factors (Wormstone et al., 2009). Many studies have shown that PCO rates can be diminished by improved IOL design (Hayashi et al., 2001; Nishi et al., 2001), especially a square edge profile, which produces a barrier to LEC migration. However, in spite of these improvements about 10% of patients still require a Nd:YAG laser capsulotomy within 2 years of surgery (Li et al., 2013) and these numbers continue to rise with greater post-surgical time (Vock et al., 2009). This places a strain on healthcare resources, medical time and the quality of a patient's life (Cleary et al., 2007). These problems are exacerbated in paediatric eyes, eyes with inflammation or with multifocal IOLs. Reducing the impact of PCO on patients is therefore of great practical importance and novel approaches need to be developed.

Our understanding of the biological processes governing PCO formation (Fig. 2) and how surgical procedures can be developed to improve patient outcomes has grown over the past 20–30 years. However, the problem is far from resolved and thus scientists and clinicians need to gather, interpret and apply information that furthers our understanding of PCO and its management. In order to achieve this, a body of experimental systems are required and should be viewed as a collection of tools that together can best answer key questions. PCO research is well served by a variety of experimental systems (Table 1). We will therefore go on to discuss developments with in vivo models, cell culture systems and tissue culture models. With respect to any model it is vital that the experimental design and objectives are ultimately directed to the improvement in patient health. In the majority of cases this will relate to human wellbeing, but we should also consider that cataract surgeries are performed in veterinary practices and again PCO is a major problem in these patients. With respect to guiding our research programmes and specific experiments it is important to examine the information provided through post-mortem analysis (Marcantonio et al., 2000; Saika et al., 2002; Wormstone et al., 2002a) and patient imaging systems (Grewal et al., 2008; Ursell et al., 1998). Cell organisation, modifications, expression of genes or proteins provide a snap-shot at the scene of the crime. It is, however, difficult to garner the processes that lead to these changes directly from such data. It is therefore the skill of the scientist to discern how such changes can occur and then experimentally test that hypothesis using existing models or through development of novel tools.

2. Experimental model systems

2.1. In vivo

A number of animal in vivo models have been developed that permit investigations into the mechanisms driving PCO and in some cases to evaluate IOLs. These models have the benefit of a complete inflammatory response, but this still needs to be considered with care as the inflammatory response in species can differ markedly (Bito 1984). Another limitation is the difficulty assessing ongoing progression of PCO in these systems with much of the information obtained from detailed end-point examinations. Another consideration relating to species difference, which is perhaps most pertinent to therapeutic target identification, relates to different receptor expressions and signalling profiles. For