The ocular lens: a classic model for development, physiology and disease

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Millions are rendered blind or exhibit visual impairment due to pathologies of the lens of the eye. Lens research therefore addresses the direct need to gain insights into the cellular and molecular basis of disease, but, moreover, serves as a valuable experimental system to answer fundamental biological questions. This themed issue showcases the scientific knowledge of the processes involved in the development, structure, ultrastructure, physiology and pathology of the lens and how this information has the potential to significantly further knowledge in various fields of research. The issue is divided into three main areas. Firstly, the lens is discussed as a developmental model for embryonic induction, as an elegant system for studying the role of growth factors in development, and for analysis of the molecular control and cellular basis of cellular differentiation. The genetic basis of disorders of lens development, including paediatric cataract (lens opacity), are also discussed in this section. Secondly, adult lens structure and ultrastructure are covered, as well as the lens as a model for homeostasis and solute exchange. Finally, the papers in the latter part of the special issue review lens pathology, including the lens as a model for normal and pathological ageing, vitreoretinal influences on lens function and cataract and the lens as a model for fibrotic disease. Overall, the articles highlight the lens as a continuing, very important and attractive model system for biologists working in many different research areas.

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1. INTRODUCTION

The lens is a uniquely transparent structure with many interesting properties, which has been referred to as the ‘sparkling jewel’ of anatomy [1]. The lens is derived from the surface ectoderm. Following the formation of the lens vesicle, cells lying on the posterior surface elongate towards the epithelial cells covering the anterior surface to form the primary fibre cell population. The adult lens is isolated from other tissues, has neither neural innervation nor a vascular system and therefore receives all required nutrients from the aqueous and vitreous humours with which it is bathed. As cell death in the normal lens is restricted, overall growth is fundamentally regulated by cell division rates. Proliferation occurs exclusively at the equatorial region in the adult lens from a putative stem cell population [2], while cells of the central anterior epithelium are quiescent. In addition, the lens equator is the site at which fibre cell differentiation begins, involving massive cellular elongation and degradation of all intracellular organelles, including the nucleus. The discrete organization of cells within the lens, together with the expression and ordered packing of crystallin proteins, permits lens transparency to be maintained for significant periods of life.

Multiple factors can lead to cataract, which is defined as any opacity of the lens resulting in significant variations in the refractive index of the lens over distances similar to the wavelength of transmitted light. According to the latest estimates, 18 million people are blind from cataract as identified by the World Health Organisation (WHO) (http://www.who.int/blindness/causes/priority/en/index1.html). Cataract is defined by its age of onset and can be classified as congenital, juvenile, pre-senile or senile (age-related) with different proportions of genetic and environmental influences on the aetiology of these various classifications. Furthermore, there are a number of different types of cataract, which have different phenotypes and occur via different cellular and molecular mechanisms. Thus, in order to understand the reasons for cataract, it is necessary to investigate the cellular and molecular basis of lens development and physiology.

Indeed, the lens has long been used as a tractable model system in which to investigate fundamentally important biological processes and principles. Therefore, this themed issue comprises articles about wide ranging aspects of lens biology that are of relevance to many other fields.

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One contribution of 10 to a Theme Issue ‘The ocular lens: a classic model for development, physiology and disease’.
The lens has been used as a classical developmental model system for many years. Hans Spemann was awarded the Nobel Prize for Physiology or Medicine in 1936 for his work on the organizer-effect in embryonic development and embryonic induction (http://nobelprize.org/nobel_prizes/medicine/laureates/1935/spemann-lecture.html). Many of Spemann’s key observations and insights about embryonic and tissue-specific inductive processes were obtained from investigating the induction of the lens in the ectoderm during very early embryonic development resulting in formation of a lens placode. Currently, striking advances are being made in the field of lens induction, particularly its molecular basis (e.g. the role of specific growth factors and tissue interactions in developmental determination and patterning events) and these are providing fundamentally important insights into inductive processes in development in general. The article here by Lena Gunhaga addresses these issues, specifically focusing on how individual signalling molecules, including bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), Wnts and Shh, regulate the initial specification of lens placodal cells and the progressive development of the lens via the coordination of both molecular and tissue interactions [3].

The lens has also been an important model system for studying the mechanisms that govern cellular differentiation following exposure to growth factors, and in the article by Lovicu and colleagues these issues are addressed, focusing on the lens as a wonderful tool to dissect out these processes in time and space using various animal models [4]. The use of transgenic and gene knockout techniques in the lens is a rapidly advancing area of research that provides important new insights into the role of growth factors and their receptors in developmental patterning events and this area is discussed in this article. In particular, the recent development of crystallin-cre mice is allowing lens-epithelial and fibre-cell-specific deletion of selected genes in particular compartments of the lens when these mice are crossed with mice possessing floxed genes. Several of these studies, using the lens as a tractable model system, have provided important insights into the roles of Wnt, BMP and FGF signalling in proliferation, migration and differentiation during embryonic development in general, which are also discussed in this article.

Degradation processes occurring during lens fibre cell differentiation are essential for lens clarity. Michael Wride addresses this area in which rapid advances are currently being made in parallel with improved understanding of the intracellular signalling and proteolytic pathways involved [5]. In this context, the lens is being used to investigate aspects of cell survival and the emerging insights being obtained into the use of apoptosis signalling pathways for differentiation rather than cell death per se, although controversies and doubts remain about the relative roles of effector and initiator caspases in this process, for example. Further work reveals that other proteolytic enzymes such as cathepsins and calpains as well as the ubiquitin proteasome (UPP) system are also important in this process, and the interactions and importance of these pathways is reviewed. Furthermore, the point is made that multiple, parallel and redundant signalling and proteolytic pathways are emerging as players in lens fibre cell differentiation and that these pathways often form interacting networks. Therefore, it is argued in this article that the various signalling pathways employed during lens fibre cell differentiation and organelle loss may functionally compensate for each other in response to mutations in or knockouts of certain genes involved in this process. This is highly important given the importance of lens clarity for correct vision.

Indeed, the lens is pivotal for the development of the eye and mutations in genes important in lens development can have serious consequences for vision. Amanda Churchill and Jochen Graw highlight clinical and experimental advances in congenital and paediatric cataracts in their article [6]. These authors cover the genetic analysis of families with vision defects, including discussion of various mutations in genes coding for transcription factors, for example FoxE3, Maf and Pitx3, structural proteins such as crystallins and connexins, metabolic pathways including enzymes involved in sugar metabolism, such as galactose, and, intriguingly, axon guidance molecules. Furthermore, mouse cataract mutants are reviewed and the point is made that, since many of the genes mutated in lens defects are also expressed outside the eye, cataracts may act as early and readily detectable biomarkers for a number of systemic syndromes.

As revealed by advances in laser scanning confocal microscopy and electron microscopy, the lens has a unique structure and ultrastructure, which can appear deceptively simple, but is essential for its efficient function. Indeed, the lens has been something of a test organ for techniques in laser scanning confocal microscopy. Steve Bassnett and colleagues discuss the structure and ultrastructure of the lens and make the point that various structural adaptations serve to minimize light scatter, enabling the lens to function as ‘biological glass’ [7]. The lens must remain transparent to maintain its function and therefore provides valuable information relating to tissue construction and design. An important aspect in maintaining lens transparency is regulation of solutes. Ralf Dahm and colleagues address this issue and draw light upon the mechanisms controlling transport and exchange in the vertebrate lens, which include: paracellular transport, membrane transport by specific carriers and transporters, gap junctional transport and transcellular transport by coated vesicles [8].

The ability of the lens to remain transparent for so long is a considerable biological achievement. However, when the exquisite order of the lens is disrupted, or cannot be maintained effectively, cataract results. Age is the major risk factor associated with cataract and the relationship between ageing and age-related cataract is addressed by Ralph Michael and Tony Bron [9]. In this article, three forms of cataract that have different aetiology are discussed. Nuclear cataract affects the central fibre cells (the lens nucleus) and is associated with post-translational modification of proteins in this region. This results in accumulation of fluorescent chromophores and greater potential oxidation, which, in turn, causes cross-linking of proteins and light scatter. In many ways, nuclear cataract is

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believed to be an acceleration of the natural ageing process. Cortical cataract affects the peripheral lens fibre cells and is associated with changes in membrane permeability and ion imbalance. For example, cortical cataracts exhibit very high intracellular calcium concentrations. Age-related mechanisms that can influence the onset of cortical cataract are also discussed. Posterior subcapsular cataract results from an inability of lens epithelial cells to form new fibre cells. Subsequently, these cells grow across the posterior capsule and form subcapsular plaques, thereby giving rise to light scatter. The cellular basis for this condition is fascinating and provides valuable information relating to biological cues within an organ, and is therefore highlighted. It is also evident that modification to the local environment can influence lens cell function.

David Beebe and colleagues address this issue in relation to the vitreous humour [10]. The oxygen levels at the posterior surface of the lens are low, but it is argued that breakdown of the vitreous will increase the level of oxygen available at the posterior lens surface and render the tissue more susceptible to oxidative stress. This problem is magnified during vitrectomy (removal of the vitreous humour) and explains the basis for rapid nuclear cataract formation in these patients following surgery.

Fibrosis affects multiple organs including the lens and is associated with hyper-proliferation, cell trans-differentiation, matrix modification and contraction. Anterior subcapsular cataract results from modified lens epithelial cells giving rise to a light scattering plaque. Posterior capsule opacification is the major complication of cataract surgery and is a consequence of a robust wound-healing response. In the final paper in the issue, Julie Eldred et al. discuss the value of the lens as an experimental model to study the processes that give rise to fibrosis [11]. The molecular and cellular organization of the lens is well defined and consequently modifications associated with fibrosis can be clearly assessed. Moreover, the avascular and non-innervated properties of the lens allow effective in vitro studies to be employed that complement in vivo systems and relate to clinical data. Using the lens as a model for fibrosis has direct relevance to millions affected by lens disorders, but also serves as a valuable experimental tool to understand fibrosis per se.

2. CONCLUSIONS AND SUMMARY
The unique aspect of this collection of articles is the fact that they combine both basic and clinical recent work on the developmental genetics and cellular basis of early lens development and cellular differentiation, the molecular basis of congenital and age-onset cataract, lens physiology and structure and the causes of cataract and complications associated with cataract surgery. Overall, the articles highlight the lens as a continuing, very important and attractive model system for biologists working in many different research areas and also highlight that clinical solutions to cataract are dependent on gaining insights into the basic cellular and molecular mechanisms employed during lens development and homeostasis.

We therefore hope that this themed issue will act as an inspiration to new generations of scientists to become engaged by the unique and fascinating properties of the lens. We are passionate that such further engagement with the lens will facilitate scientists in answering important questions in their own particular fields of biological/clinical interest.

We would like to wholeheartedly thank all of the authors for agreeing to contribute to this issue and for providing an excellent set of articles that will no doubt stand the test of time. We would also like to extend our deep appreciation to all the reviewers of the articles, who freely gave of their time and energy and who always provided timely, excellent and constructive comments on the manuscripts.

REFERENCES