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Regulation of scleral metabolism in myopia and the role of transforming growth factor-beta

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ABSTRACT

Myopia is one of the most prevalent ocular conditions and is the result of a mismatch between the power of the eye and axial length of the eye. In the vast majority of cases the structural cause of myopia is an excessive axial length of the eye, or more specifically the vitreous chamber depth. In about 3% of the general population in Europe, USA and Australia, the degree of myopia is above 6 dioptres and is termed high myopia. In South East Asia the figure is closer to 20% of the general population with high myopia. The prevalence of sight threatening ocular pathology is markedly increased in eyes with high degrees of myopia (>−6 D). This results from the excessive axial elongation of the eye which, by necessity, must involve the outer coat of the eye, the sclera. Current theories of refractive development acknowledge the pivotal role of the sclera in the control of eye size and the development of myopia. This review details the major structural, biochemical and biomechanical changes that underlie abnormal development of the mammalian sclera in myopia. In describing the changes in regulation of sclera metabolism in myopia, the pivotal role of transforming growth factor-β signalling is highlighted as the responsible factor for certain critical events in myopia development that ultimately result in the scleral pathology observed in high myopia.

1. Introduction

Postnatal eye growth is constrained by the properties of the outer coat of the eye. The sclera comprises by far the major component of the ocular coat. Although historically the sclera has been considered a relatively inert tissue in metabolic terms, more recent research has shown it to undergo constant remodelling during eye growth, continuing throughout life, albeit at a lesser degree (Rada et al., 2000a). In common with other specialised connective tissues, the sclera is highly organised, enabling it to perform its roles. A major functional role of the sclera is the protection of the delicate intraocular structures. However, the sclera plays important roles in accommodation, by providing a stable base for the contraction of the ciliary muscle, in promoting accurate eye movements, by providing a stable base for extra-ocular muscle contractions and in allowing vascular and neural access to adjacent intraocular structures. Most importantly, from the perspective of this review, the sclera is critical in determining the absolute size of the eye and thus plays an important role in determining the refractive state of the eye.

The context of this review is the regulation of scleral metabolism during the development of myopia with particular focus on the role transforming growth factor-beta plays in these processes. The discussion will concentrate on the well characterised mammalian models of myopia, namely the tree shrew (McBrien and Gentle, 2003), marmoset (Rada et al., 2000b) and monkey (Wiesel and Raviola, 1977), whose scleral structure is known to be similar to human. In particular, as the most detailed studies of the role of the sclera in myopia have been conducted on the tree shrew model, results from this model will feature strongly. The tree shrew has been shown to be a reliable model of scleral changes in myopia in that it has the same scleral structure and undergoes similar changes to those found in human myopes (McBrien et al., 2001). Firstly, the structural and biochemical changes to the sclera in myopia will be briefly reviewed.

2. Sclera structure and metabolism in myopia

Scleral pathology in high myopia is a major cause, if not the most significant factor, in the chorioretinal damage that results in the permanent vision loss experienced by a substantial proportion of high myopes (Curtin and Karlin, 1970; Celorio and Pruett, 1991; Grossniklaus and Green, 1992; Morgan et al., 2012). The sclera undergoes a number of structural changes that include marked

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thinning, reduction in collagen fibril diameter and fibre dysregulation that are the result of altered metabolism and ultimately lead to excessive axial elongation of the eye resulting in visual impairment.

Thinning of the sclera, particularly at the posterior pole of the eye, is an important feature of the development of high myopia in humans. One of the most important clinical consequences of such thinning is the formation of posterior staphyloma, a condition in which the thinned sclera becomes ectatic (Curtin, 1977). Staphyloma formation occurs almost exclusively in the region of the posterior pole of the eye and thus can have a catastrophic affect on vision. When compared with the scleral thickness of age-matched emmetropic eyes, high myopes show a greatly reduced thickness (up to 50% thinner) at the posterior pole of the eye, regardless of the presence of staphyloma. Scleral thinning also occurs in the equatorial and anterior regions of highly myopic human eyes, however, these changes are less marked than those encountered around the posterior pole (Curtin and Teng, 1957; McBrien et al., 2000).

Early theories of scleral thinning hypothesised that the existing scleral tissue was re-distributed to cover the surface of the eye as the eye enlarged, suggesting that the sclera stretched passively to accommodate the expanding eye (Bell, 1978). However, early histological observations also showed that profound morphological changes, in addition to the thinning, were apparent in the scleral extracellular matrix. For example, scleral collagen fibril morphology was altered, particularly at the posterior pole of highly myopic eyes, with a characteristic shift in the fibril diameter distribution, resulting in an increased number of small diameter collagen fibrils (Curtin et al., 1979).

A major feature of scleral thinning in human myopia is that it is largely confined to the posterior pole of the eye, this regional effect of thinning is also observed in the tree shrew model of myopia (Fig. 1A) (McBrien et al., 2001; McBrien and Gentle, 2003). Scleral thinning occurs very rapidly in response to the onset of myopia development. Indeed, it has been found that the posterior sclera thins by some 20% over the first 12 days of myopia development in young tree shrews (Fig. 1B).

Analysis of the dry tissue weight of the sclera has demonstrated that the cause of scleral thinning in myopia is due to actual loss of scleral tissue as opposed to simply passive stretch of the sclera. The rate of loss of scleral tissue corresponds closely with the time course of scleral thickness changes at the posterior pole of the myopic tree shrew eye and demonstrates that posterior scleral tissue is lost rapidly. Significant decreases in scleral dry weight are apparent at the posterior pole (>5%, $p < 0.05$) after only 5 days of myopia induction in young tree shrews (Fig. 2A and B), representing the initial stages of myopia development (McBrien et al., 2000). This tissue loss continues to occur rapidly over the first 12 days of myopia development, accounting for a 17% reduction of scleral dry weight at the posterior pole region (Fig. 2B). Over the next 3–8 months of myopia progression the continued loss of scleral tissue is less marked (Fig. 2C) (McBrien et al., 2000). These studies demonstrate there is a net tissue loss from the whole sclera of up to 7% of dry weight in long-term form-deprived animals (>6 months), demonstrating that tissue is lost, rather than just re-distributed, during the development of myopia (Fig. 2B).

In conjunction with the loss of scleral tissue observed in the tree shrew model, characteristic changes in collagen fibril diameter are also apparent in the sclera of highly myopic eyes, consistent with the findings in human (Curtin and Teng, 1957) and monkey (Funata and Tokoro, 1990). However, fibril diameter changes occur on a slower timescale than the significant changes in scleral thickness and tissue loss occur. Studies demonstrate that the scleral fibril diameter profiles are similar in myopic eyes to those in the sclera of normal eyes during the early phases of myopia development. This is despite major changes in scleral thickness and dry weight having occurred in those same eyes (McBrien et al., 2001). However, after longer periods of myopia development, a reduction in median collagen fibril diameter is found at the posterior pole of myopic eyes. The fibril diameter change is most marked in the outer scleral fibre bundles (see Fig. 3A), which is consistent with the embryological observation that the outer fibre bundles are the last to mature (Sellheyer and Spitznas, 1988; Kuc and Scott, 1997). By 6–8 months of myopia development there is a highly significant reduction in collagen fibril diameter across the whole scleral thickness, with the greatest reduction in diameter, around 35%, apparent in the outer layers of the sclera (McBrien et al., 2001). The shift in fibril diameter in myopic eyes results in a reduction in the gradient in fibril diameter across the scleral thickness and it is interesting to note that this gradient is virtually absent in eyes with longstanding high myopia (Fig. 3B) (McBrien et al., 2001). Findings indicate that the gradual change in fibril diameter, with many more small diameter fibrils is related to the ratio of fibrillar collagen types I, III & V (Birk et al., 1990; Birk, 2001) and the preferential loss of collagen type I compared to types III and V in the sclera of myopic eyes (Gentle et al., 2003).

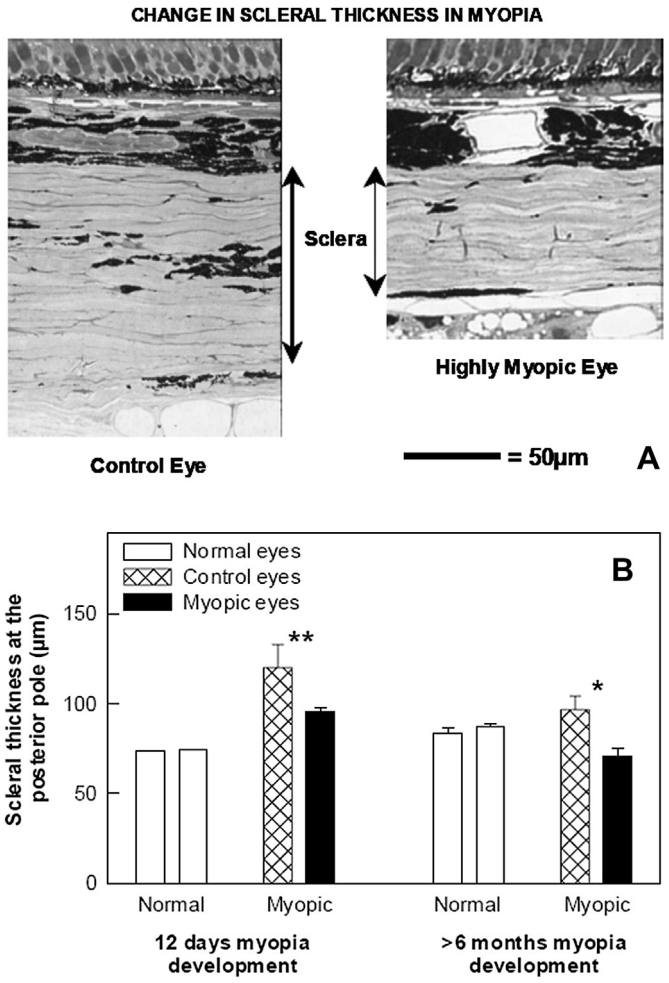

Fig. 1. Thinning of the posterior sclera in mammalian eyes with progressive high myopia. **A**. Light micrographs of toluidine blue-stained transverse-sections of the posterior sclera of a highly myopic and fellow control eye of a tree shrew, following 8 months of myopia progression. **B**. Mean posterior scleral thickness in the myopic, fellow control and age-matched normal eyes of tree shrews following 12 days ($n = 2$ normal and $n = 5$ myopic) or 6–20 months ($n = 4$ each group) of myopia progression. Error bars are 1 SEM. $^{**}p < 0.01$, $^{*}p < 0.05$ by paired t-test. (Reproduced with permission from McBrien et al., 2001 © Association for Research in Vision and Ophthalmology.)