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Evolution of the vertebrate corneal stroma

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ABSTRACT

Although the cornea is the major refractive element of the eye, the mechanisms controlling corneal shape and hence visual acuity remain unknown. To begin to address this question we have used multiphoton, non-linear optical microscopy to image second harmonic generated signals (SHG) from collagen to characterize the evolutionary and structural changes that occur in the collagen architecture of the corneal stroma. Our studies show that there is a progression in complexity of the stromal collagen organization from lower (fish and amphibians) to higher (birds and mammals) vertebrates, leading to increasing tissue stiffness that may control shape. In bony and cartilaginous fish, the cornea is composed of orthogonally arranged, rotating collagen sheets that extend from limbus to limbus with little or no interaction between adjacent sheets, a structural paradigm analogous to 'plywood'. In amphibians and reptiles, these sheets are broken down into broader lamellae that begin to show branching and anastomosing with adjacent lamellae, albeit maintaining their orthogonal, rotational organization. This paradigm is most complex in birds, which show the highest degree of lamellar branching and anastomosing, forming a 'chicken wire' like pattern most prominent in the midstroma. Mammals, on the other hand, diverged from the orthogonal, rotational organization and developed a random lamellar pattern with branching and anastomosing appearing highest in the anterior stroma, associated with higher mechanical stiffness compared to the posterior stroma.

1. Introduction

Vision is arguably the most important sense to perceive our environment. While all the major phyla have structures that detect light information, their anatomy, origin and degree of sophistication differ immensely according to their environmental and functional constraints (Jonasova and Kozmik, 2008; Land and Nilsson, 2012). The evolution of visual perception has occurred in four stages: 1) simple photoreception; 2) photoreception with some degree of directionality; 3) low-resolution spatial vision and 4) high-resolution multipurpose vision (Land and Nilsson, 2012; Nilsson, 2009). Comparative anatomical studies have identified a range of animal eyes, including pinhole eyes, reflecting mirror eyes and camera-type eyes with a single lens (Arendt and Wittbrodt, 2001; Lacalli, 2004; Land, 2012; Land and Nilsson, 2012).

In the vertebrate, camera-type eye, visual acuity is dependent, in part, on the crystalline lens and the transparent cornea, the eye's refractive components, which form an optical system that refracts and transmits light to the retina (Benedek, 1971; Clark, 2004; Delaye and

Tardieu, 1983; Land and Nilsson, 2012; Piatigorsky, 2001; Ruberti and Klyce, 2002). The cornea is the tissue covering the front of the eye and it specifically fulfils two important roles. As the outermost layer of the eye, it helps to shield the internal parts of the eye and has a protective function dependent on the mechanical strength of the outer ocular tunic of which the cornea is a continuous part. The biomechanical strength of the cornea must therefore be great enough to prevent tissue rupture following blunt force trauma. These properties of the cornea are thought to be derived from the compositional makeup of the tissue, which is predominantly comprised of collagen fibrils and proteoglycans.

Aside from its protective role, the cornea also focuses light onto the retina and accounts for over 2/3 of the refractive power in the human eye. Corneal shape and curvature are vitally important to determining the refractive power and aberrations in corneal curvature can cause refractive errors including, myopia, hyperopia and astigmatism (Garner and Smith, 1997; Llorente et al., 2004; Mouroullis, 1999; Thibos, 2000). Overall, refractive errors are the most common vision-related disorder, affecting over 200 million Americans (Wittenborn and Rein, 2013).

Abbreviations: 3D, Three dimensional; FFT, Fast Fourier Transform; HRMac, High Resolution Macroscopy; NLO, Non-linear optical; SHG, Second Harmonic generation

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The refractive properties of the cornea are governed by Snell's law, also known as the law of refraction, which dictates that when light travels between two isotropic media, such as water, glass or air, the angle of refraction is proportional to the difference in refractive indices between the two media. Since the evolution of the vertebrate eye initially occurred in water, the cornea with a refractive index (1.376) almost identical to that of water (1.333) played little role in the refraction of light to the retina regardless of corneal shape, serving primarily as a transparent protective cover, while the crystalline lens with a higher refractive index (1.4–1.5) performed the refractive function (Collin and Collin, 2000; Leonard and Meek, 1997; Patel, 1987; Patel et al., 1995; Sivak et al., 1989). The vertebrate cornea has a greater potential refractive power in air given the difference in the refractive index between air (1.000) and the cornea. Because of the large difference in these refractive indices, vertebrate eyes functioning in both environments would have to be hyperopic in water and myopic in air. To overcome this problem with excessive focusing power, adaptations in the corneal structure and curvature, as well as the accommodative ability of the lens, have emerged during evolution (Graham and Rosenblatt, 1970; Howland and Sivak, 1984; Knowles et al., 1967; Murphy et al., 1990; Sivak et al., 1989). A fine example of adaptations to an air/water visual existence is found among *Anableps anableps*, the “four-eyed” fish, where structural modifications in corneal shape and lens placement allow *Anableps* to simultaneously accommodate in both air and water (Schwab et al., 2001; Sivak, 1976; Swamyathan et al., 2003). Similar to *Anableps anableps*, aquatic mammals like the seal also have a paracentral corneal region that is flat allowing them to have similar visual acuity in both air and in water (Land and Nilsson, 2012).

While the shape of the cornea determines its refractive power, the cellular, molecular and biomechanical mechanisms regulating shape have long served as one of the most intriguing questions in corneal biology that has remained largely unknown. The biomechanical properties of the cornea have been extensively examined by numerous investigators using distinct methodologies (Dupps et al., 2007; Hjortdal, 1995, 1996; Hoeltzel et al., 1992; Hollman et al., 2002; Jue and Maurice, 1986; Last et al., 2012; Lepert et al., 2016; Liu and Roberts, 2005; Mikula et al., 2016; Nyquist, 1968; Petsche et al., 2012; Scarcelli et al., 2015; Tanter et al., 2009; Woo et al., 1972; Zeng et al., 2001). Nevertheless, defining even the Young's elastic modulus for the cornea has proven to be challenging and the results reported in the literature vary from a few kilopascals to gigapascals, depending on the type of measurement and the experimental environment. This variation in corneal material properties has been attributed to the anisotropy in stromal architecture, particularly regarding collagen fibril organization that is thought to define the mechanical behaviour of the tissue (Martin and Boardman, 1993; Martin and Ishida, 1989).

In this review, we focus on the structural and architectural differences in the collagen fiber/lamellar organization of the vertebrate cornea from different extant species that provide a range of corneal shapes and refractive adaptations that have been acquired during vertebrate eye evolution. To perform these structural analyses, we have used second harmonic generation (SHG) imaging to three-dimensionally reconstruct the collagen organization and establish a 'structural blue-print' of the corneal stroma from these diverse corneal shapes. These studies have identified a common structural theme of increasing fiber/lamellar complexity involving branching and anastomosing of collagen bundles that appears to control regional corneal stiffness and, hence, corneal shape and biomechanics.

2. Imaging corneal stromal structure

The corneal stroma represents 90% of the corneal thickness and is composed predominantly of fibrillar collagen representing 70% of the dry weight of the cornea (Abahussin et al., 2009). The basic structure of the stroma has been described using a wide range of different techniques (Abahussin et al., 2009; Aghamohammadzadeh et al., 2004; Daxer

et al., 1998; Han et al., 2005; Komai and Ushiki, 1991; Meek et al., 1987; Morishige et al., 2006), and has been shown to be comprised of uniformly thin (~32 nm diameter) collagen fibrils, which are bundled together to form collagen fibers or lamellae in a wide range of vertebrate corneas. The combination of electron microscopic studies, which provide insights on the corneal nanostructure by resolving individual collagen fibrils (Hamada et al., 1972; Komai and Ushiki, 1991; Muller et al., 2001; Radner et al., 1998), and x-ray scattering studies which visualize the bulk collagen alignment across the entire cornea while measuring fibril diameter and spacing (Aghamohammadzadeh et al., 2004; Meek and Boote, 2009), have provided the baseline of our current understanding of corneal structure. The sum results of these studies indicate that collagen fibrils exist in bundles which coalesce to form approximately 200 lamellae organized parallel to the corneal surface with a bulk preferential alignment in the organization of the lamellae along the horizontal or vertical meridians of the cornea. In non-mammalian vertebrate corneas, each lamella is rotated about 90° relative to its adjacent lamella, acquiring an overall orthogonal arrangement (Aghamohammadzadeh et al., 2004; Newton and Meek, 1998; Svoboda, 1991; Svoboda and Hay, 1987; Svoboda et al., 1988; Trelstad and Coulombre, 1971). To the contrary, in mammals, collagen lamellae are randomly arranged in a single plane with large amounts of fiber branching and anastomosis, especially in the anterior corneal stroma (Morishige et al., 2006, 2007; Winkler et al., 2011; Muller et al., 2001). Regarding collagen organization at the peripheral cornea, fibrils may exhibit a more circumferential orientation perhaps creating a boundary between corneal and scleral curvature (Aghamohammadzadeh et al., 2004; Kokott, 1938).

While the cellular and molecular mechanisms involved in collagen fibrillogenesis are well established (Zhang et al., 2005), as well as the mechanisms underlying corneal transparency, considerably less is known concerning the mechanisms controlling corneal structure and biomechanics. Although the mechanical properties of the cornea have been comprehensively studied (Dupps et al., 2007; Hjortdal, 1995, 1996; Hoeltzel et al., 1992; Hollman et al., 2002; Jue and Maurice, 1986; Last et al., 2012; Lepert et al., 2016; Liu and Roberts, 2005; Mikula et al., 2016; Nyquist, 1968; Petsche et al., 2012; Scarcelli et al., 2015; Tanter et al., 2009; Woo et al., 1972; Zeng et al., 2001), the cellular and molecular mechanisms controlling these properties are not well understood. This challenge is mainly due to the difficulty in interpreting the anisotropy of the structural elements comprising the cornea in terms of their mechanical effects on determining tissue form and function. Amongst the various structural components, collagen certainly plays the fundamental role in defining the cornea's structural and biomechanical properties (Martin and Boardman, 1993; Martin and Ishida, 1989; Aghamohammadzadeh et al., 2004; Han et al., 2005; Ruberti and Zieske, 2008). While fibrous collagen exhibits distinct longitudinal tensile strength, it is comparatively weak along the other axes. Therefore, it is important to appreciate at this point, that the unique spatial orientation and supramolecular architecture of collagen fiber most likely will have a major impact on the mechanical properties of tissues, as well as exert distinct effects on the cornea's response to mechanical strains that will define the shape and refractive power of the cornea. This understanding was first articulated by Kokott in 1938 when he attempted to map the supramolecular organization of collagen in the cornea and sclera in order to develop a structural 'blue-print' of the eye to identify the mechanical mechanisms controlling ocular shape (Kokott, 1938). While his pioneering studies were the first to address this question, improvements in optical and digital imaging now enable the spatial mapping of collagen over large regions of the eye to begin to build-up a true collagen 'blue-print' on which mechanical models can be developed that can lead to a better understanding of how corneal shape is controlled.

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