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Myofibroblast transdifferentiation: The dark force in ocular wound healing and fibrosis

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ABSTRACT

Wound healing is one of the most complex biological processes to occur in life. Repair of tissue following injury involves dynamic interactions between multiple cell types, growth factors, inflammatory mediators and components of the extracellular matrix (ECM). Aberrant and uncontrolled wound healing leads to a non-functional mass of fibrotic tissue. In the eye, fibrotic disease disrupts the normally transparent ocular tissues resulting in irreversible loss of vision. A common feature in fibrotic eye disease is the transdifferentiation of cells into myofibroblasts that can occur through a process known as epithelial-mesenchymal transition (EMT). Myofibroblasts rapidly produce excessive amounts of ECM and exert tractional forces across the ECM, resulting in the distortion of tissue architecture. Transforming growth factor-beta (TGFβ) plays a major role in myofibroblast transdifferentiation and has been implicated in numerous fibrotic eye diseases including corneal opacification, pterygium, anterior subcapsular cataract, posterior capsular opacification, proliferative vitreoretinopathy, fibrovascular membrane formation associated with proliferative diabetic retinopathy, submacular fibrosis, glaucoma and orbital fibrosis. This review serves to introduce the pathological functions of the myofibroblast in fibrotic eye disease. We also highlight recent developments in elucidating the multiple signaling pathways involved in fibrogenesis that may be exploited in the development of novel anti-fibrotic therapies to reduce ocular morbidity due to scarring.

Contents

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1. Introduction

Wound healing is a fundamental biological process that enables the systematic replacement of injured cells; however, prolonged and exaggerated wound healing may result in the pathological condition of fibrosis (Leask and Abraham, 2004). Fibrosis can be defined as the disruption of normal structural components of tissue, with the accumulation of excessive, many times aberrant, forms of extracellular matrix (ECM) proteins, resulting in a distorted and non-functional aggregation of scar tissue (Diegelmann, 1997). This process typically occurs over many months to years in humans and can result in complete organ dysfunction (Leask and Abraham, 2004). To date, there is no effective treatment for fibrotic disease and often, organ transplantation is the only viable option for patients (Leask and Abraham, 2004). In the context of the eye, fibrotic diseases such as corneal opacification and submacular fibrosis render millions of people worldwide visually impaired and blind, and remains one of the major areas of unmet need in clinical ophthalmology (Yu-Wai-Man and Khaw, 2015).

Myofibroblast transdifferentiation is a key feature of pathological tissue repair (Klingberg et al., 2013). Myofibroblasts rapidly synthesize and accumulate excessive amounts of ECM during wound healing and exert synchronized tractional forces across the ECM, resulting in the distortion of tissue architecture and subsequent scarring (Wynn and Ramalingam, 2012). Since their first discovery in healing skin wounds over forty years ago (Gabbiani et al., 1971), our knowledge of the structure and activity of the myofibroblast has progressed profoundly. In addition to skin wound healing, myofibroblasts have been identified in multiple tissues and pathologies including liver cirrhosis, renal fibrosis (Gabbiani, 2003), pulmonary fibrosis (Zhang et al., 1994), epithelial tumours (Radisky et al., 2007) and fibrotic eye diseases (Saika et al., 2008; Yamanaka et al., 2010).

The purpose of this review is to summarize key biological features of the myofibroblast and to discuss the role of the myofibroblast in various fibrotic eye diseases of the cornea, conjunctiva, lens, retina, optic nerve and orbit (Table 1). We highlight recent developments in elucidating the growth factor signaling pathways, including TGFβ signaling that govern the activation of myofibroblast transdifferentiation in ocular fibrosis; together with the antagonists of this signaling pathway that may hold promise as novel therapeutic agents in the treatment of fibrotic eye disease.

1.1. The myofibroblast

Myofibroblasts, sometimes referred to as being 'activated' fibroblastic cells, possess similar ultrastructural and physiological characteristics to smooth muscle cells (Darby et al., 2014). The prominent microfilament bundles of myofibroblasts form stress fibers that permit contraction of the cell and hence, remodeling of the adjacent ECM (Darby et al., 2014). One key feature of the myofibroblast is neo-expression of alpha-smooth muscle actin (α-SMA), the actin isoform typically seen in vascular smooth muscle cells (Darby et al., 1990). Incorporation of α-SMA into the cellular stress fibers significantly augments the contractile activity of myofibroblasts and represents a key marker of the myofibroblastic phenotype (Hinz et al., 2001). The actin bundles that comprise the stress fibers terminate at the surface of the myofibroblast and form specialized cell-matrix junctions known as a "fibronexus junctions" *in vivo* (Dugina et al., 2001), and "large mature focal adhesions" *in vitro* (Hinz et al., 2003). This creates a mechano-transduction system that enables the force generated by stress fibers to be transmitted to the surrounding ECM. Moreover, this mechano-transduction system also enables extracellular mechanical signals to be transduced into intracellular signaling (Geiger and Bershadsky, 2001).

The expression of α-SMA is precisely regulated by the combined activity of growth factors/cytokines such as TGFβ, specialized ECM proteins such as fibronectin, and the surrounding mechanical microenvironment (Darby et al., 2014). Under normal physiological conditions, the maintenance and turnover of ECM molecules is tightly regulated to maintain a dynamic balance between ECM

Table 1
List of ocular cell types that transdifferentiate to myofibroblasts leading to fibrotic eye disease.

Ocular Cell Type	Fibrotic Eye Disease	Reference
Keratocytes	Corneal opacification	Tandon et al., 2010
Corneal endothelial cells	Fuchs endothelial corneal dystrophy	Okumura et al., 2013
Conjunctival epithelial cells	Pterygium	Kato and Shimmura, 2008
	Subconjunctival fibrosis post-glaucoma filtration surgery	Cordeiro et al., 1999
Trabecular meshwork cells	Glaucoma	Takahashi et al., 2014
Lens epithelial cells	Anterior subcapsular cataract	de Iongh et al., 2005
	Posterior capsular opacification	Eldred et al., 2011
Retinal pigment epithelial cells	Proliferative vitreoretinopathy	Tamiya and Kaplan, 2016
	Proliferative diabetic retinopathy	Abu El-Asrar et al., 2015
	Subretinal fibrosis	Lopez et al., 1996
Astrocytes	Glaucoma	Gottanka et al., 2005
Laminar cribrosa cells	Glaucoma	Kirwan et al., 2005a
Orbital fibroblasts	Graves Ophthalmopathy	Koumas et al., 2003

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