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Fibroblast biology in pterygia

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ABSTRACT

Activation of fibroblasts is a vital process during wound healing. However, if prolonged and exaggerated, profibrotic pathways lead to tissue fibrosis or scarring and further organ malfunction. Although the pathogenesis of pterygium is known to be multi-factorial, additional studies are needed to better understand the pathways initiated by fibroblast activation for the purpose of therapeutic translation. Regarding pterygium as a possible systemic disorder, we discuss the different cell types that pterygium fibroblasts originate from. These may include bone marrow-derived progenitor cells, cells undergoing epithelial–mesenchymal transition (EMT), and local resident stromal cells. We also describe how pterygium fibroblasts can be activated and perpetuate profibrotic signaling elicited by various proliferative drivers, immune-inflammation, and novel factors such as stromal cell-derived factor-1 (SDF-1) as well as a known key fibrotic factor, transforming growth factor-beta (TGF-β). Finally, epigenetic modification is discussed to explain inherited susceptibility to pterygium.

1. Introduction

Pterygium is a common ocular surface disease characterized by triangular-shaped growth consisting of fibrotic subconjunctival connective tissue and hypertrophy of overlying conjunctival epithelium. Although pterygium has a worldwide distribution, it occurs mostly within the peri-equatorial latitudes, that is between 37° north and south, where the ultraviolet (UV) radiation intensity is strongest (Saw and Tan, 1999). This supports that the exposure to chronic UV light has been known to be a predominant factor for the development of pterygium and such an importance of the environmental factor in the pathogenesis is a unique characteristic of pterygium. UV radiation may damage the corneal limbus, and thus lead to a limbal deficiency featuring a growth of conjunctival epithelium into the corneal zone with vascularization in pterygia.

Pterygium has been classically described as an 'elastotic degeneration' by UV radiation, that is a degenerative process characterized by deposition of subepithelial collagen fibers. However, the degenerative process does not provide a good explanation for the rapid growth feature and aggressive invasion of the cornea of pterygia. Based on the pterygium's propensity for growth, there have been investigations suggesting that pterygium may be a proliferative disorder rather than a degenerative process (Hill and Maske, 1989; Kwok and Coroneo, 1994). Moreover, abnormal expression of the p53 tumor suppressor gene was shown in pterygium epithelial cells (Tan et al., 1997a) and stromal fibroblasts in fibrovascular component in pterygia revealed better growing phenotype compared to normal conjunctival fibroblasts (Chen et al., 1994).

Severe fibrovascular ingrowth encroaches the extensive normal-functioning conjunctiva and further leads to adhesion to the eyelid called symblepharon. Scarring emanating from the caruncle and adhering to the sclera, especially remarkable in severe cases, highlights the importance of the pterygium as a cicatricial fibrotic disorder. Scarring on the ocular surface is not a simple cosmetic problem but can lead to vision loss or motility restriction-associated diplopia that can affect the quality of life and psychosocial function (Wu-Chen et al., 2011). Conversely, if a recurrence-free period persists after pterygium removal, corneal astigmatism and surface irregularity are often reversed and patients experience visual improvement (Fong et al., 1998).

Myofibroblasts, which are activated fibroblasts, are the key mediators of tissue fibrosis in diverse human fibrotic diseases. During wound healing, abundant myofibroblasts are physiologically activated and extracellular matrix (ECM) accumulates for wound closure and stabilization during the initial 3–6 weeks of the proliferative phase. However, myofibroblasts remain resistant to programmed cell death during the tissue fibrosis and may perpetuate synthesis of the ECM for fibrotic tissue remodeling (Hinz et al., 2007; Wynn and Ramalingam, 2012). α-SMA-

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expressing myofibroblasts have also been reported to exist in fibrovascular tissue specimens (Touhami et al., 2005) or pools of cultured pterygium body fibroblasts (Kim et al., 2013a, 2013b).

Despite many studies which address the biology of pterygium fibroblasts, research on the diverse mechanisms of fibrosis associated with recruitment and activation of fibroblasts in pterygia is still needed to further understand the pterygium pathogenesis and to develop new treatment methods. In this review, we describe and focus on identifying the biologic features in the development of pterygia and important activation mechanisms of pterygium fibroblasts. Furthermore, we discuss anti-fibrotic developments and highlight ways in which the pterygium can be targeted for future therapeutic strategies.

2. Where do pterygium fibroblasts come from?

The issue, 'what are the precursor cells of myofibroblasts?' is important because the information may provide a new perspective on the pathogenic view of fibrotic diseases (i.e., are they locally confined or systemic). In general, the myofibroblast lineage in tissue fibrosis consists of three progenitor cell populations. First, tissue-resident fibroblasts are activated and transform into myofibroblasts to restore and regenerate homeostasis of the organ after injury. However, on some occasions, circulating $CD34^+$ progenitor cells derived from the bone marrow (BM) have also been shown to be recruited to the site of fibrosis to increase the population of myofibroblasts. In addition, in a variety of tissues, profibrotic myofibroblasts can also arise from epithelial or endothelial cells via epithelial-(EMT) or endothelial–mesenchymal transition (EndMT) (Wynn and Ramalingam, 2012).

Although it is clear that stromal (myo)fibroblasts play a pivotal role also in pterygium progression, the origin of pterygium fibroblasts has been a matter of debate. Interestingly, in a previous study that first advocated the presence of myofibroblasts in pterygia, myofibroblasts were found in normal periorbital fibroadipose tissues near the nasal conjunctiva rather than in the pterygium body (Touhami et al., 2005). Furthermore, recently, mesenchymal progenitor cells have been isolated from human orbital adipose tissue (Chen et al., 2014).

Previously, we proposed that BM-derived mesenchymal (STRO-1 positive) and hematopoietic (CD34, AC133, or c-kit positive) progenitor cells might contribute to fibrovascular stroma in pterygia via differentiation into fibroblasts and vascular endothelial cells (Ye et al., 2004; Song et al., 2005). In this study, surgically-removed pterygium tissues showed strong immunoreactivities against progenitor cell markers including CD34, c-kit, VEGF receptor (VEGFR)-1, and -2. In addition, with viewing pterygium as a product of exaggerated repair after injury on the ocular surface, we have speculated (Fig. 1) that circulating chemokine receptor 4 (CXCR4)-positive cells are recruited into pterygium stroma in response to the ligand of CXCR4, stromal cell-derived factor 1 (SDF-1) which is a known mediator for wound healing (Kim et al., 2013b). These cells probably represent the intermediate stage of differentiation for monocyte precursors into myofibroblasts at tissues (Bellini and Mattoli, 2007). To confirm this theory would require identification of CXCR4-positive fibroblasts and assessment of their expression of specific markers for BM-derived fibrocytes.

Tissue-specific epithelial cells have also been attractive candidates for the cellular origin of fibroblasts. Homeostasis of the corneal epithelium is maintained by limbal epithelial stem cells (SCs) (Kinoshita et al., 2001; Lavker et al., 2004). Limbal SCs are usually mitotically quiescent in their specialized niches when in an uninjured state; however they proliferate on corneal epithelia during wounding while maintaining corneal limbal status. In the same context, bidirectional interactions between the epithelium and mesenchyme are considered to be important for the maintenance of homeostasis in adults (Kao et al., 2013). However, limbal epithelial SCs may undergo EMT on occasion to generate fibrosis in the limbal stroma and possibly trigger epithelial intrastromal invasion manifesting limbal SC deficiency via the Wnt/β-catenin pathway (Kawakita et al., 2005). In a similar vein, the intranuclear accumulation of β-catenin and down-regulation of E-cadherin with expression of α-SMA and vimentin were identified in $K14^+$ epithelial cells at the leading edge of epithelial invaginations of pterygia (Kato et al., 2007). Moreover, a recent publication demonstrated that the microRNA (miRNA)-200 family, which is known to regulate EMT, is different in terms of expression profiling in pterygium compared to normal conjunctiva (Engelsvold et al., 2013).

The multiple origins of pterygium fibroblasts (summarized in

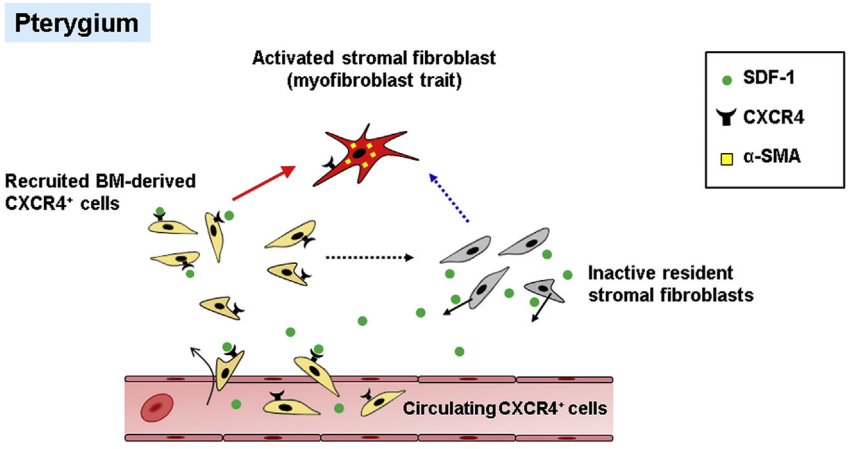

Fig. 1. Proposed schematic illustration describing the involvement of SDF-1 and its cognate receptor CXCR4 in the pathogenesis of the pterygium. SDF-1, possibly produced from resident fibroblasts, may recruit circulating cells expressing CXCR4 to the ocular surface where the pterygium is being generated. Recruited CXCR4-positive cells may be activated and transform into myofibroblasts through SDF-1/CXCR4 signaling (red arrow), depending on the local level of SDF-1 which can interact with CXCR4. On the other hand, unoccupied CXCR4-positive cells may lose their phenotype over time and change into inactive resident stromal fibroblasts that are CXCR4-negative (black dotted arrow). Then, some of these cells may eventually transform into myofibroblasts through a non-SDF-1 dependent pathway (blue dotted arrow). Dotted arrows, not proven but hypothesized (Kim et al., 2013b). SDF-1 = stromal cell-derived factor-1. CXCR4 = circulating chemokine receptor 4.