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Major review

Matrix metalloproteinase 14 modulates signal transduction and angiogenesis in the cornea

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ABSTRACT

The cornea is transparent and avascular, and retention of these characteristics is critical to maintaining vision clarity. Under normal conditions, wound healing in response to corneal injury occurs without the formation of new blood vessels; however, neovascularization may be induced during corneal wound healing when the balance between proangiogenic and anti-angiogenic mediators is disrupted to favor angiogenesis. Matrix metalloproteinases (MMPs), which are key factors in extracellular matrix remodeling and angiogenesis, contribute to the maintenance of this balance, and in pathologic instances, can contribute to its disruption. Here, we elaborate on the facilitative role of MMPs, specifically MMP-14, in corneal neovascularization. MMP-14 is a transmembrane MMP that is critically involved in extracellular matrix proteolysis, exosome transport, and cellular migration and invasion, processes that are critical for angiogenesis. To aid in developing efficacious therapies that promote healing without neovascularization, it is important to understand and further investigate the complex pathways related to MMP-14 signaling, which can also involve vascular endothelial growth factor, basic fibroblast growth factor, Wnt/β-catenin, transforming growth factor, platelet-derived growth factor, hepatocyte growth factor or chemokines, epidermal growth factor, prostaglandin E2, thrombin, integrins, Notch, Toll-like receptors, PI3k/Akt, Src, RhoA/RhoA kinase, and extracellular signal-related kinase. The involvement and potential contribution of these signaling molecules or proteins in neovascularization are the focus of the present review.

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1. Introduction

Neovascularization (NV) is the term used to describe the local formation of new vascular structures at previously avascular sites. Several models of neovascular processes have been proposed[10,14,18,24,25,43,81,104,117] including 1) vasculogenesis, which is the formation of new blood vessels from bone marrow-derived angioblasts, predominantly during

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embryogenesis; 2) local recruitment of endothelial progenitor cells; and 3) angiogenesis, which is the formation of new vessels from preexisting vascular structures.[31,170] Angiogenesis is a common feature of corneal and retinal disorders as well as cancer metastasis and is usually stimulated by changes in the endothelial cell microenvironment (e.g., trauma, hypoxia, oxidative stress, mechanical strain, and genetic changes).[46] Physical changes that occur during NV include extracellular matrix (ECM) degradation, ECM remodeling, cellular migration, and cellular invasion. The pathologies associated with NV in the normally avascular cornea include herpetic stromal keratitis, diverse inflammatory disorders, systemic or autoimmune diseases, corneal graft rejection, infectious keratitis (and other corneal infection/inflammation), contact lens–related hypoxia, alkali burns, stromal ulceration, corneal epithelium weakness, recurrent erosion syndrome, diabetes mellitus–related epithelial weakening, and limbal stem cell deficiency.[171] Corneal NV is also seen in some congenital disorders such as aniridia, which involves complete or partial absence of the iris. In such conditions, the balance between proangiogenic and antiangiogenic factors favors NV, with both upregulation of proangiogenic factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), and downregulation of antiangiogenic factors, such as endostatin and thrombospondin-1.[43,47,176]

The cornea is avascular under normal conditions and, even when damaged, typically heals without NV.[24] This persistent avascularity of the cornea, which is necessary for vision clarity, may be facilitated by: 1) the tightly organized packing of collagen fibrils, 2) the angiostatic nature of corneal epithelial cells, 3) the immune privilege of the cornea, mediated by factors such as transforming growth factor-β (TGF-β) in tears, 4) the comparatively hypothermic nature of the cornea, 5) extensive neuronal innervation, 6) the movement of the aqueous humor on the endothelium, 7) low levels of proangiogenic matrix metalloproteinases (MMPs), 8) active production of antiangiogenic factors after corneal injury, and 9) the barrier function of the limbus.[14,43]

To maintain corneal clarity, proper corneal wound healing is critical. Corneal stromal wound healing occurs in 4 phases. In the first phase the keratocytes adjacent to the area of the epithelial defect undergo apoptosis, leaving a central zone devoid of cells. This cell death has been suggested to initiate the healing response.[111] In the second phase the keratocytes immediately adjacent to the area of cell death proliferate to repopulate the wound area. For example, in rat corneas, proliferation occurs 24 to 48 hours postwound.[34] Within this phase the keratocytes transform into fibroblasts that migrate into the wound area, a process which may take up to 1 week.[34] This transformation is evident at the molecular level, with reorganization of the actin cytoskeleton in the development of stress fibers and focal adhesion structures and activation of new genes encoding ECM components, such as fibronectin, cell adhesion molecule, α5 integrin, ECM-degrading MMPs, and cytokines.[14–16] The same transition can be seen *in vitro*. When keratocytes are isolated from the corneal stroma and subcultured in serum-containing medium, they acquire the fibroblast phenotype.[104] The migratory repair fibroblasts contain filamentous-actin and are elongated, spindle shaped, and highly reflective. These fibroblasts induce the synthesis of the α5 integrin chain, which results in the formation of the α5β1 integrin heterodimer, the classic fibronectin receptor. This occurs concomitant with a reduction in fibronectin content in the wound area. In addition to forming the ECM, these repair fibroblasts synthesize several MMPs, including MMP-1, -2, -3, -9, and -14.[104]

In the third phase of stromal wound healing, transformation of fibroblasts into myofibroblasts may occur and can be observed *via* α-smooth muscle actin staining. Myofibroblasts appear as stellate cells and are highly reflective, but are limited to within the wound area. The extent of fibroblast transformation into myofibroblasts seems to be dependent on the type of wound and the integrity of the Bowman membrane. In general, gaping wounds and wounds in which the Bowman membrane is removed result in greater myofibroblast generation than wounds that do not penetrate the Bowman membrane. This process, which may take up to 1 month to become histologically apparent, can lead to a decrease in corneal clarity and vision deterioration.

The fourth and final phase of stromal wound healing involves stromal remodeling and is largely dependent on the characteristics of the original wound. Within this setting, intricate, but incompletely understood, relationships among keratocytes, fibroblasts, and myofibroblasts play key roles.[45] It is theorized that TGF-β and fibroblast-like synoviocytes are key intermediaries in the process of remodeling.[34] Wounds that have completely healed contain few, if any, myofibroblasts, presumably because these cells revert to the fibroblast phenotype or undergo apoptosis during wound healing.[69] The entire process of corneal healing after an injury may take more than 1 year.[34]

In the setting of certain inflammatory, infectious, degenerative, and traumatic states, corneal NV may be induced during wound healing.[24,183] When NV does occur, blood vessel invasion into the cornea is associated with significant visual impairment, which can ultimately progress to blindness. Three distinct morphologies of corneal NV are most commonly diagnosed: 1) deep NV overlying Descemet membrane (Fig. 1A), 2) stromal NV observed in interstitial keratitis (Fig. 1B), and 3) superficial vascular pannus (Fig. 1C).

NV occurs when there is a disturbance in the balance between proangiogenic and antiangiogenic factors. Proangiogenic factors include VEGF, bFGF (also referred to as FGF-2), and platelet-derived growth factor (PDGF). Antiangiogenic factors include angiostatin, endostatin, pigment epithelium-derived factor (PEDF), thrombospondin-1, and soluble VEGF receptor 1 (VEGFR1). A striking indication of this delicate balancing act is that many of the antiangiogenic factors are proteolytic degradation products derived from ECM fragments formed during the initial invasion of cells into the ECM during angiogenesis.[7,14] MMPs have been implicated as both proangiogenic and antiangiogenic molecules that are, in part, responsible for orchestrating the delicate balance between corneal angiogenesis and avascularity.[14,63] In this review, we present evidence for the facilitative role of MMPs, specifically MMP-14, in corneal NV.