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Novel aspects of corneal angiogenic and lymphangiogenic privilege

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ABSTRACT

In this article, we provide the results of experimental studies demonstrating that corneal avascularity is an active process involving the production of anti-angiogenic factors, which counterbalance the pro-angiogenic/lymphangiogenic factors that are upregulated during wound healing. We also summarize pertinent published reports regarding corneal neovascularization (NV), corneal lymphangiogenesis and corneal angiogenic/lymphangiogenic privilege. We outline the clinical causes of corneal NV, and discuss the angiogenic proteins (VEGF and bFGF) and angiogenesis regulatory proteins. We also describe the role of matrix metalloproteinases MMP-2, -7, and MT1-MMP, anti-angiogenic factors, and lymphangiogenic regulatory proteins during corneal wound healing. Established and potential new therapies for the treatment of corneal neovascularization are also discussed.

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1. Introduction

Angiogenesis is the process by which new blood vessels derive from pre-existing ones. First termed in 1787 (Folkman, 2008), angiogenesis remains an incompletely understood process that involves the interaction of multiple cell types, including endothelial cells, pericytes, and circulating cells, as well as parenchymal cells and stromal cells (Penn et al., 2008). It was not until three decades ago that major *in vivo* angiogenesis models were developed for testing potential therapeutic drugs. Derived from the word “cornu”, the cornea was first characterized as a hard structure etymologically related to an animal horn. The transparent and seemingly delicate anterior surface of the eye has contributed to major discoveries in the field of angiogenesis and, more recently, lymphangiogenesis (Alitalo et al., 2005; Lohela et al., 2009, 2003) (Table 1).

Judah Folkman proposed the hypothesis that the growth of cancerous tumors depends on angiogenesis (Folkman, 1971). His proposal of anti-angiogenesis cancer therapies in 1971 led to major discoveries of angiogenesis inhibitors. His group described the first experimental corneal angiogenesis model demonstrating that tumors implanted into the stromal layers at various distances from the limbus of the rabbit cornea can induce neovascularization, as opposed to merely inducing vessel dilation (Gimbrone et al., 1974). These experiments were followed by the micropocket pellet assays used to influence specific molecules/proteins involved in angiogenesis (Langer and Folkman, 1976) and corneal chemical and suture induced injury, which more closely mimic the complex nature of human diseases (Montezuma et al., 2009; Norrby, 2006; Rogers et al., 2007).

The maintenance of corneal avascularity has recently been termed ‘angiogenic privilege’ (Azar, 2006). This terminology mirrors the special protection the cornea enjoys against the immune rejection of grafted tissues, called ‘immune privilege.’ Just as most parts of the body do not have special protection against immune rejection of foreign antigens, the ‘angiogenic privilege’ designation implies that the absence of blood vessels in the

Table 1
Milestones in corneal angiogenesis/lymphangiogenesis research.

1627	First description of lymphatic vasculature	(Asellius, 1627)
1787	First use of the term angiogenesis	(Hunter, 1787)
1939	Laboratory studies of angiogenesis	(Ide et al., 1939)
1971	Hypothesis of angiogenesis and anti-angiogenesis	(Folkman, 1971)
1974	First experimental model of corneal angiogenesis	(Gimbrone et al., 1974)
1976	First use of micropocket pellet assay of corneal angiogenesis	(Langer and Folkman, 1976)
1989	Vascular endothelial growth factor sequenced	(Leung et al., 1989)
1994	Angiostatin	(O'Reilly et al., 1994)
1995	First lymphatic endothelial cell marker (FLT4/VEGFR-3)	(Kaipainen et al., 1995)
1997	Endostatin	(O'Reilly et al., 1997)
1999	Discover lymphatic vessel hyaluronan (HA) receptor-1 (LYVE-1) marker	(Banerji et al., 1999)
2002	Corneal lymphangiogenesis model to dissociate from angiogenesis	(Chang et al., 2002)
2006	Corneal angiogenic privilege	(Azar, 2006)
2006	VEGF trap hypothesis for corneal avascularity	(Ambati et al., 2006; Cursiefen et al., 2006a)