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Novel anti(lymph)angiogenic treatment strategies for corneal and ocular surface diseases

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ABSTRACT

The cornea is one of the few tissues which actively maintain an avascular state, i.e. the absence of blood and lymphatic vessels (corneal [lymph]angiogenic privilege). Nonetheless do several diseases interfere with this privilege and cause pathologic corneal hem- and lymphangiogenesis. The ingrowths of pathologic blood and lymphatic vessels into the cornea not only reduce transparency and thereby visual acuity up to blindness, but also significantly increases the rate of graft rejections after subsequent corneal transplantation. Therefore great interest exists in new strategies to target pathologic corneal (lymph) angiogenesis to promote graft survival. This review gives an overview on the vascular anatomy of the normal ocular surface, on the molecular mechanisms contributing to the corneal (lymph)angiogenic privilege and on the cellular and molecular mechanisms occurring during pathological neovascularization of the cornea. In addition we summarize the current preclinical and clinical evidence for three novel treatment strategies against ocular surface diseases based on targeting pathologic (lymph) angiogenesis: (a) modulation of the immune responses after (corneal) transplantation by targeting pathologic (lymph)angiogenesis prior to and after transplantation, (b) novel concepts against metastasis and recurrence of ocular surface tumors such as malignant melanoma of the conjunctiva by anti(lymph) angiogenic therapy and (c) new ideas on how to target ocular surface inflammatory diseases such as dry eye by targeting conjunctival and corneal lymphatic vessels. Based on compelling preclinical evidence and early data from clinical trials the novel therapeutic concepts of promoting graft survival, inhibiting tumor metastasis and dampening ocular surface inflammation and dry eye disease by targeting (lymph) angiogenesis are on their way to translation into the clinic.

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1. Introduction

The blood and lymphatic vascular systems are essential to supply organs and tissues with oxygen and nutrients, to drain redundant fluid and to facilitate the immune system to observe and defend the body against foreign organisms (Potente et al., 2011; Rovenska and Rovensky, 2011). But there are some organs and tissues which naturally are partly or completely devoid of blood and/or lymphatic vessels to maintain their unique structure and function. The cornea is one of these rare tissues which actively maintain an avascular state (corneal [lymph]angiogenic privilege). Nonetheless do several diseases interfere with this privilege and cause pathologic corneal hem- and lymphangiogenesis. The ingrowths of pathologic blood and lymphatic vessels into the cornea causes not only reduced transparency and thereby reduced visual acuity (Bachmann et al., 2013) up to blindness but also significantly increases the rate of graft rejections after subsequent transplantation. With the advent of novel anti(lymph)angiogenic drugs it became possible to test novel treatment concepts for neovascular diseases of the cornea and the ocular surface initially in animal models. Several of these novel concepts are already in the phase of translation within clinical trials or off-label use. In addition it was recognized that the cornea is, due to its normal vessel-free status and its easy accessibility, an ideal tissue to search for novel (endogenous) modulators of (lymph) angiogenesis and to study the interaction of immune cells and lymphatic vessels in (corneal) transplant immunology.

This review first gives an overview on normal ocular surface vascular anatomy and the molecular mechanisms contributing to the corneal (lymph)angiogenic privilege. This article also gives insights into the cellular and molecular mechanisms occurring during pathological neovascularization of the cornea and which efforts are done, clinically and preclinically in terms of translation, to avoid or reduce corneal hem- and lymphangiogenesis. Finally novel treatment concepts for neovascular diseases of the cornea and the ocular surface, where our group is primarily involved, are discussed. Preclinical conceptual evidence is provided alongside with current translational efforts. Here the authors focus on:

1.) Modulation of immune responses after corneal transplantation by anti(lymph)angiogenic therapy as well as novel concepts for antiangiogenic therapy against mature and budding corneal neovascularization.
2.) Novel concepts against metastasis and recurrence of ocular surface tumors by anti(lymph)angiogenic therapy.
3.) New ideas on how to target ocular surface inflammatory diseases such as dry eye by targeting conjunctival and corneal lymphatic vessels as well as their imaging.

2. Anatomy of blood and lymphatic vessels of the cornea, limbus and conjunctiva

2.1. Corneal angiogenic and lymphangiogenic privilege: basic mechanisms

Normal corneal avascularity is evolutionary highly conserved, so that in all vertebrates which depend on good vision the cornea is free of blood and lymphatic vessels (Cursiefen, 2007; Cursiefen et al., 2003a, 2006c, 2002b, 2003c). The fact that the normal cornea is free of blood and lymphatic vessels and its ability to actively inhibit the ingrowths of vessels is also called the “angiogenic privilege of the cornea” (Cursiefen, 2007) in analogy to corneal

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