A New Target for Simultaneous Inhibition of Hem- and Lymphangiogenesis

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Toyono et al.1 established a new mediator of corneal hem- and lymphangiogenesis: angiopoietin-like protein 2 (Angptl2). Angptl2 was expressed by the corneal epithelium and stroma after corneal suture injury, and increased infiltrating macrophages and expression of interleukin 1-β. RNAi-mediated knockdown of Angptl2 inhibited hem- and lymphangiogenesis. Studies in conditional knock-in and knock-out mice corroborated these observations. Because Angptl2 does not bind Tie1 or Tie2 but rather operates through α5β1 integrin, this paper opens up a new target for antiangiogenic therapy. Anti-angptl2 inhibitors (small molecules, antibodies, siRNAs, aptamers) could be envisioned. An α5β1 small-molecule antagonist (developed by Jerini Ophthalmic, Inc. prior to that company’s demise) and volociximab, a monoclonal antibody against α5β1 that has shown promise in renal and ovarian cancer, has been in-licensed (Ophthotech Corp., Princeton, NJ) for therapy of macular degeneration. However, α5β1 functions through multiple pathways in many cell types, and it may be reasonable to target the adverse factors that are responsible for its activation in the context of angiogenesis rather than inactivate all the receptor transductive activities of α5β1. In that perspective, the finding of Angptl2 activity in inducing pathologic angiogenesis (both in the blood and lymphatic vessels) through α5β1 gains additional relevance, by potentially offering a more specific target for therapy that may avoid side effects of global α5β1 inhibition. The ramifications of such discoveries are unknown—but fruitful and exciting—with broad implications. This work highlights Angptl2’s significance in blood vessel and lymphatic growth and as a therapeutic target for treatment of many maladies such as cornea transplant rejection, macular degeneration, or proliferative diabetic retinopathy.

Reference