MOLECULAR BLOCKADE OF LYMPHANGIogenesis IN PROMOTING HIGH-RISK CORNEAL TRANSPLANT SURVIVAL

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Public Abstract

Though corneal transplantation enjoys a low rejection rate of 10% in uninfamed recipient corneas or "low-risk" setting, the rejection rate of corneal grafts on the inflamed and lymphatic-rich recipient corneas or "high-risk" setting can be as high as 90%, which is even worse than that of kidney or heart transplantation. Unfortunately, many patients who are blind from corneal diseases due to traumatic, infectious, inflammatory, chemical, and toxic insults fall into this category. To date, there is no effective treatment for high-risk transplant rejection. Interestingly, it has been shown that surgical severing of the lymphatic pathway or "lymphadenectomy" leads to universal corneal graft survival. However, surgical lymphadenectomy for promoting transplant survival is not practical. We are therefore interested in regulation of the lymphatic pathway through molecular modulation of lymphatic factors, which are key players in the development of new lymphatic vessels, or "lymphangiogenesis."

Lymphatic research represents an explosive field of new discovery owing to the recent identification of several lymphatic specific factors (Nature 2005; 436:456-458), such as: VEGFR-3 (vascular endothelial growth factor receptor-3), LYVE-1 (lymphatic vessel endothelial hyaluronan receptor-1), and VLA-1 (Very late antigen-1). The cornea provides an ideal site for lymphatic studies due to its accessible location, transparency, and lymphatic-free and -inducible character. The fruitfulness of using the cornea as a model for lymphangiogenesis studies can also be predicted from the fact that during the past few decades, nearly half of our basic knowledge on angiogenesis is derived from studies with the cornea, for the similar reason of its blood vessel-free and -inducible character. I am fortunate to have already established collaborations with several pioneering groups so that I am able to share resources with them, such as: the VEGFR-3 neutralizing antibody (ImClone Systems, Incorporated, New York), and VLA-1 neutralizing antibody and knockout mice (Biogen Idec, Cambridge, MA), which will be used for this study. It is also worth mentioning that I have successfully developed a system to isolate and culture both mouse and human lymphatic endothelial cells. Only a few laboratories in the world are able to perform this line of work. A dditionally, I anticipate that my established collaboration with Dr. M. Judah Folkman, a leading authority in vasculogenesis research, will be valuable in conducting significant research.

This project aims to investigate the effect of molecular blockade of lymphangiogenesis for promoting high-risk corneal transplant survival, a necessary prerequisite to the development of new therapeutic strategies. Our hypothesis is that corneal lymphangiogenesis and high-risk transplant survival can be manipulated by molecular modulation of specific lymphatic factors, and the combined blockade of several lymphatic factors optimizes transplant survival. This hypothesis is based on our preliminary data on the roles of VEGFR-3 (Nature Medicine 2004; 10:813-815), LYVE-1 (IOVS, 2005; 46:4536-4540), and VLA-1 (manuscript submitted) in corneal inflammation and transplantation immunity. The first aim will determine the effect of VEGFR-3 blockade (via neutralizing antibody administration) on prevention and regression of corneal inflammatory lymphangiogenesis, modification of high-risk recipient beds, and transplant survival. The second aim will define the effect of VLA-1 blockade (via neutralizing antibody administration) on human lymphatic endothelial functions in culture and inflammatory lymphangiogenesis and high-risk graft survival in mice. Lastly, the third aim will study the interaction between respective lymphatic factors and the concurrent blockade of VLA-1 and VEGFR-3 in high-risk graft survival.

These studies are important because: (i) corneal inflammation accompanies many diseases after inflammatory, infectious, traumatic, or toxic insults. The clinical burden of graft rejection in the high-risk transplantation is tremendous, since as high as 50% to 90% of the grafts are rejected irrespective of the treatment delivered; (ii) the current mainstay regimen with corticosteroids is fraught with serious side-effects such as glaucoma, cataracts, and opportunistic infections; and (iii) the current studies will offer insights into important lymphatic factor-mediated mechanisms of corneal transplant immunity and provide possible novel molecular strategies to combat transplant rejection. The combination of animal work and human primary cell culture should provide highly translatable information to the patient conditions.

Research on corneal lymphangiogenesis has broader clinical implications, because the lymphatic network penetrates most tissues in the body and is crucial for cancer metastasis, wound healing, and tissue fluid regulation. Indeed,
lymphangiogenesis is becoming an emerging focus of cancer research. It is estimated that lymphedema alone (primary or secondary to surgeries or radiation therapy) affects over 6 million individuals in the U.S. and more than 170 million people worldwide. It is hoped that beyond its contributions to eye diseases, this study will also shed some light on the development of new therapeutic strategies for other lymphatic disorders, including cancer metastasis, arthritis, delayed wound healing, diabetics, AIDS, and lymphedema, among many others.