New discovery brings hope to treatment of lymphatic diseases

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Researchers in the laboratory of Dr. Jayakrishna Ambati at the University of Kentucky have discovered the first naturally occurring molecule that selectively blocks lymphatic vessel growth. In an article in the Aug. 9, 2009 online edition of *Nature Medicine*, they report the identification of a new molecule known as soluble VEGFR-2 that blocks lymphangiogenesis - the growth of lymphatics - but not blood vessel growth.

The twin circulatory systems of mammals - blood and lymphatic - are intricately intertwined, both anatomically and functionally. Until now it has been difficult to selectively target one without affecting the other. The lymphatic vessel network is essential for transporting fluids, molecules, and immune cells. It is crucial for wound healing and immune defense. Disturbances in the lymphatics are involved in diseases as varied as lymphedema, transplant rejection, and tumor metastasis, which collectively affect hundreds of millions of people worldwide.

This article, whose lead author is Dr. Romulo Albuquerque, currently a medical student in the UK College of Medicine, showed that soluble VEGFR-2 specifically blocks lymphatic vessel growth both during development and following injury by blocking VEGF-C, a powerful lymphatic growth factor. It also reports that loss of soluble VEGFR-2 during development led to the spontaneous invasion of lymphatic vessels, but not blood vessels, into the cornea, solving the long-standing mystery of why the cornea is normally devoid of lymphatics. Soluble VEGFR-2 was also required for normal development of lymphatics in the skin.

Importantly, administration of soluble VEGFR-2 to mice following corneal transplantation nearly eliminated graft rejection. This finding might also be applicable in kidney transplant rejection because it is known that lymphatic vessels are the culprit in the rejection of that organ as well. In addition, it challenges the prevailing dogma that abnormal blood vessels are responsible for transplant rejection.

The Ambati group also studied a childhood tumor known as lymphangioma, which is estimated to affect 1 in 50 babies and for which there is no satisfactory medical treatment. Administration of soluble VEGFR-2 blocked the growth of lymphangioma cells isolated from children with this tumor. Because this molecule spares blood vessels, it might offer a safer and more targeted treatment for this pediatric tumor. The potential benefit of modulating soluble VEGFR-2 in other diseases such lymphedema due to filariasis and or following surgery for breast cancer, as well as in tumor metastasis, are also under study.

"This paper by Dr. Ambati and his coworkers represents another in a line of highly novel and important findings from their laboratory," said Patricia A. D'Amore, Professor of Ophthalmology and Pathology, Harvard Medical School and Senior Scientist at the Schepens Eye Research Institute.

"The report of the first endogenous inhibitor of lymphangiogenesis is an exciting development and holds great therapeutic promise for a number of pathologies in which lymphatic growth is a serious complication."

Source: University of Kentucky

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