Immunology researchers uncover pathways that direct immune system to turn 'on' or 'off'

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(Medical Xpress)—A key discovery explaining how components of the immune system determine whether to activate or to suppress the immune system, made by Kelvin Lee, MD, Professor of Oncology and Co-Leader of the Tumor Immunology and Immunotherapy Program at Roswell Park Cancer Institute (RPCI), and colleagues led to published findings being selected as the "Paper of the Week" by the *Journal of Biological Chemistry* (JBC). The honor places his work among the top 2 percent—in terms of significance and overall importance—of the year's manuscripts reviewed by the journal.

This research focused on the immune system's dendritic cells (DCs), crucial cells that initiate and regulate immune responses. For example, the dendritic cells activate T lymphocytes to fight an infection or cancer. Curiously, they are also known to suppress the immune response. Determining when DCs turn the immune response "on" or "off" is a major question in immunology.

For this project, Dr. Lee's team explored two receptors (called CD80 and CD86) expressed on the surface of dendritic cells that trigger the cells to make either immune-stimulating factors (interleukin-6) or immune-suppressive factors (indolemine 2, 3 dioxygenase, IDO). They defined the intracellular pathways by which the receptors triggered each response and also uncovered a previously unrecognized interaction with another receptor called Notch-1.

Understanding how these pathways are put together opens the door to targeting components of the pathway so physicians can manipulate the dendritic cells to either activate or suppress the immune system in a way that's therapeutically beneficial.

"Activating the immune response would enhance a patient's response to a vaccine designed to prevent a cancer from growing or recurring," explains Dr. Lee. "Suppressing or blocking an unwanted immune response would be helpful in organ-transplant cases, to prevent rejection, or in autoimmune diseases like lupus and rheumatoid arthritis."

With regard to cancer, Dr. Lee explains how manipulating the CD80/CD86 pathway could impact treatment for multiple myeloma, a cancer of a type of white blood cell in the bone marrow.

"Myeloma cells use this pathway to survive and grow by inducing the DC to make IL-6—which promotes the cancer cells' survival—and IDO, which blocks anti-cancer responses," he says. "Targeting this pathway would be a novel treatment strategy for multiple myeloma."

The paper was published March 14, 2014, in *JBC* and is available online at jbc.org.

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