Team finds molecule that could improve cancer vaccines and therapy for other diseases

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Investigators at St. Jude Children's Research Hospital have discovered a new signaling molecule that prevents immune responses from running amok and damaging the body. The finding could lead to the development of new treatments for cancer, using vaccines; for autoimmune diseases, such as Type 1 diabetes; and for inflammatory diseases, such as inflammatory bowel disease (IBD) and asthma.

The St. Jude team discovered that specialized immune lymphocytes called regulatory T cells release a protein complex composed of two proteins called Ebi3 and Il12a. This protein complex acts like a brake on the activity of the aggressive immune cells called effector T lymphocytes. A report on this discovery appears in the journal *Nature* Nov. 22, 2007.

The newly recognized protein complex is one of a large group of signaling molecules called cytokines that cells use to communicate with each other. Since the immune system cytokines are called interleukins, the St. Jude team named this protein interleukin-35 (IL-35). Most cytokines stimulate immune system cells by driving the immune attack or causing inflammation. However, IL-35 is one of the few signaling molecules known to inhibit immune system activity.

“The discovery of IL-35 is important because the manipulation of regulatory T cells is a key goal of immunotherapy,” said Dario Vignali,

Ph.D., associate member in the St. Jude Department of Immunology, and the paper's senior author. Immunotherapy is the treatment of infections, cancer or other diseases by manipulating the immune system to enhance or restrict its activity. Despite the fact that regulatory T cell-mediated immunotherapy holds promise for patients, the molecules responsible for the cells' ability to suppress immune system activity are largely unknown, a problem that has slowed progress in this field.

The St. Jude team showed that the genes that produce IL-35 (Ebi3 and Il12a) are active in regulatory T cells but not in effector T cells and are critical to regulatory T cell function. In fact, regulatory T cells that lack the Ebi3 and Il12a genes lose much of their ability to suppress effector T cells. In addition, these regulatory T cells are unable to cure mouse models of an inflammatory disease that closely resembles human IBD.

When the researchers added regulatory T cells to a culture dish with effector T cells, the regulatory T cells dramatically increased their production of the decoded forms (messenger RNA) of the Ebi3 and Il12a genes. This suggests that effector T cells had released signals that stimulated the regulatory T cells to decode these genes and make IL-35, the researchers reported.

"The identification of IL-35 as a key cytokine released by regulatory T cells adds significantly to our understanding of how these cells prevent immune responses from running out of control and causing damage," Vignali said. "Regulatory T cells are seen as a major impediment to the development of effective anti-cancer vaccines and may prevent sterilizing immunity in certain chronic infections, such as hepatitis C and tuberculosis. As the maximal suppressive function of regulatory T cell is dependent on IL-35, blocking its activity may reduce regulatory T cell function and reduce their ability to block anti-tumor immune responses. Thus, treatments that block IL-35 activity may make anti-cancer vaccines more effective." Vaccines work by stimulating the immune

system to recognize and attack specific targets, such as germs or cancer cells.

“Autoimmune diseases and inflammatory diseases are caused by a breakdown of the normal regulatory processes that control our immune system,” Vignali said. “Novel treatments that add IL-35 or boost IL-35 activity may also provide new therapeutic opportunities for these diseases.”

“The identification of IL-35 is especially exciting because, to date, it is the only known cytokine that is made specifically by regulatory T lymphocytes and can suppress the activity of effector T cells directly,” said Lauren Collison, Ph.D., a postdoctoral fellow in Vignali’s laboratory who contributed significantly to the project. “This suggests that controlling levels of IL-35 in patients might one day allow clinicians to dial the immune response up or down depending on the needs of the patient.” Collison is the paper’s first author.

Source: St. Jude Children's Research Hospital