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New Genetic Mechanism of Immune Deficiency Discovered

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DENVER — Researchers at National Jewish Health have discovered a novel genetic mechanism of immune deficiency. Magdalena M. Gorska, MD, PhD, and Rafeul Alam, MD, PhD, identified a mutation in Unc119 that causes immunodeficiency known as idiopathic CD4 lymphopenia. Unc119 is a signaling protein that activates and induces T cell proliferation. The mutation impairs Unc119 ability to activate T cells. Dr. Gorska, will present her findings April 20 at Translational Science 2012, an NIH-funded conference in Washington D.C.

“A better understanding of the molecular mechanisms associated with this mutation will improve diagnosis and pave the way for development of new therapies,” said Dr. Gorska.

Drs. Gorska and Alam previously published their findings in the journal *Blood*, and Dr. Gorska delivered a Presidential Plenary on the topic at the annual meeting of the American Academy of Allergy Asthma & Immunology.

Nearly a decade ago Drs. Alam and Gorska identified Unc119 as a novel activator of SRC-type tyrosine kinases, important regulators of cellular function. Since then, they have published numerous papers where they characterized the function of this protein in various aspects of the immune system.

Idiopathic CD4 lymphopenia is a rare and heterogeneous syndrome defined by low levels of CD4 T cells in the absence of HIV infection, which predisposes patients to infections and malignancies. Recent research by others had linked the syndrome to reduced activation of the SRC-type kinase known as Lck. The latter kinase is involved in T cell development, activation and proliferation.

So, Drs. Alam and Gorska thought Unc119, an activator of Lck, might be involved. They kept an eye out for patients with CD4 lymphopenia coming to National Jewish Health, which specializes in immune-related disorders as well as respiratory and cardiac diseases. They identified three patients with CD4 lymphopenia, then sequenced their Unc119 gene as well as the Unc119 gene in several patients who suffered low CD4 T cell counts as a result of other conditions.

One of the three patients, a 32-year-old woman with a history of recurrent infections, had a missense mutation in her Unc119 gene. The same mutation was not present in other lymphopenia patients nor in any genetic database.

The researchers then performed several studies with the woman’s blood cells, to understand the mutation’s effect. They introduced the mutated gene into normal T cells and examined the outcome.

The mutation prevents Lck activation and its downstream signaling. It also reduces the amount of Lck found near the plasma membrane, where it plays a major role in propagating signals from the T-cell receptor. Proliferation of T cells, which normally occurs on stimulation of T-cell receptors, was profoundly reduced in cells from the patient.

“Since we originally published our findings earlier this year, we have received inquiries from many physicians with lymphopenia subjects,” said Dr. Alam. “Working with them, we expect to find several more patients with this novel mutation, which should help us better understand its effect, improve diagnosis and possibly find therapies.”

At this point there is no treatment for CD4 lymphopenia caused by this mutation other than close monitoring of the patient and treatment of resulting infections and malignancies.

National Jewish Health is the leading respiratory hospital in the nation. Founded 124 years ago as a nonprofit hospital, National Jewish Health today is the only facility in the world dedicated exclusively to groundbreaking medical research and treatment of patients with respiratory, cardiac, immune and related disorders. Patients and families come to National Jewish Health from around the world to receive cutting-edge, comprehensive, coordinated care. To learn more, visit the

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Media Contacts

Our team is available to arrange interviews, discuss events and story ideas.

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