

Immune system pathway identified to fight allergens, asthma

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For the first time, researchers from the University of Pittsburgh School of Medicine have identified genetic components of dendritic cells that are key to asthma and allergy-related immune response malfunction. Targeting these elements could result in more effective drugs to treat allergic disorders and asthma, according to a study reported in the May edition of the journal *Nature Medicine*.

Dendritic cells are vital to immune response in that they recognize, capture and introduce threatening organisms to T lymphocytes other immune cells that secrete potent proteins called cytokines that surround and destroy the invaders. However, the Pittsburgh team's study goes further to illuminate a pathway that allergens use to act directly on dendritic cells to propel differentiation into the T lymphocytes that fight back.

“We now have identified a molecule, c-Kit, that is central to the process of allergic response,” said Anuradha Ray, Ph.D., co-corresponding author and professor of medicine and immunology in the Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh School of Medicine. “We show that genes encoding for c-Kit and the cytokine interleukin 6 (IL-6) are significantly activated when allergens are present, but c-Kit is the very first molecule that gets triggered.”

Interactions between viruses and bacteria and molecular steps that initiate the immune defense have remained largely unknown. Using cells cultured from c-Kit mutant mice, Dr. Ray, her husband and co-

corresponding author Prabir Ray, Ph.D., and their colleagues studied molecular reactions to assaults by cholera toxin and a standard allergen, house dust mites. In addition to c-Kit and IL-6, they found effects on stem cell factor and Jagged-2 immune system molecules that are parts of the activation process.

“We have known the T-cell side of the story for many years, and we know that dendritic cells are important, but what we did not know was how the dendritic cell does what it does,” said Dr. Prabir Ray. “Therapy directed against c-Kit specifically on dendritic cells using compounds coupled to c-Kit inhibitors such as Gleevec, a drug that is already FDA-approved and used in cancer treatment, may alleviate allergic diseases and, potentially, inflammatory bowel disease.”

The Pittsburgh team incubated dendritic cells with cholera toxin and house dust mite allergens, finding that both substances induced significant secretion of c-Kit and IL-6, initial steps in a cascade resulting in the activation of T helper cells.

“Dual upregulation of c-Kit and stem cell factor has been noted in some cancers, such as small cell lung cancer. IL-6 has been associated with cancers such as multiple myeloma,” said Dr. Anuradha Ray.

“Collectively, similar approaches to inhibit c-Kit, in addition to Gleevec or other inhibiting compounds could alleviate multiple cancers.”

Source: University of Pittsburgh

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