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## Breathing New Life into Allergy Research

Over the past several years, physicians have seen a dramatic rise in the incidence of asthma and atopy, allergic conditions that affect about 40 percent of the population. Environmental factors are partially responsible for the increase, but there is mounting evidence that some individuals inherit susceptibility to these conditions.

In the December 11 issue of *The New England Journal of Medicine*, researchers at Washington University in St. Louis - including Talal Chatila and Howard Hughes Medical Institute investigator Matthew Thomas - present strong evidence that a mutant protein is associated with atopy, a condition that causes hypersensitivity to common allergens such as cat dander or dust mite feces.

Chatila and Thomas found that the mutation occurs in the interleukin-4 receptor (IL-4R), a protein found on the surface of B cells of the immune system. When the receptor latches onto IL-4, a chemical secreted by T cells, it transmits a signal to the nucleus of the B cell to stimulate production of immunoglobulin E, IgE. Atopic individuals overproduce IgE, resulting in an allergic reaction. "Much of atopy is essentially a failure to regulate IL-4 signaling," said Thomas.

Searching for the cause of the IgE overproduction, the St. Louis researchers examined the gene that codes for the alpha subunit of IL-4R. They compared the DNA sequences of the alpha subunit gene from control individuals to that from atopic patients, and found an alteration in the amino acid sequenceroughly where the tail of the subunit protrudes into the interior of the cell. Thirteen of 20 atopic individuals tested had the amino acid arginine at this position (instead of the usual glutamine), whereas only 5 of 30 control individuals had the same arginine mutation.

Thomas and his colleagues examined the effect of the amino acid substitution on IL-4R function, and found that the arginine mutation caused a 50% increase in production of IgE. Thomas' and Chatila's groups also showed that the altered tail of the IL-4R subunit was not as effective as the normal subunit at binding SHP-1, a protein which Thomas calls "one of the key negative regulators of receptors on all sorts of leukocytes."

These findings suggest that people with the arginine variant of IL-4R are less able to bind SHP-1, which is likely to "put the brakes" on the IL-4 signaling pathway. "This could lead to the failure to regulate IL-4 signaling in an appropriate manner, which, in turn, results in the overproduction of IgE," said Thomas.

Thomas noted that despite the excitement of these results, much remains to be done. The data need to be confirmed and extended in larger groups of individuals from different populations, he said. Thomas and Chatila are gearing up to verify the functional effects of the amino acid variants in physiologically relevant models.