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# Subtle Mutations in Immune Gene May Increase Risk for Asthma

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A gene that encodes a protein responsible for determining whether certain immune cells live or die shows subtle differences in some people with asthma, a team led by Johns Hopkins researchers reports in the June European Journal of Human Genetics.

The protein, known as Siglec-8, has been studied for more than a decade by a team led by Bruce S. Bochner, M.D., director of the Division of Allergy and Clinical Immunology at the Johns Hopkins University School of Medicine. Siglec-8, whose name is an acronym for sialic acid-binding, immunoglobulin-like lectin number 8, is present on the surfaces of a few types of immune cells, including eosinophils, basophils and mast cells. These different cell types have diverse but cooperative roles in normal immune function and allergic diseases. When functioning correctly, they play a valuable role in keeping the body healthy and infection-free. However, in conditions such as allergic reactions and asthma attacks, the cells unleash an overwhelming response that can harm the body more than it helps.

The researchers found in previous studies that when they bound antibodies or specially engineered sugar-coated polymers to the Siglec-8 protein on eosinophils, the cells promptly died, an effect that might be useful in stemming an allergy or asthma attack. Indeed, the Bochner lab is interested in pursuing the possibility of developing new therapies based on treatments that activate Siglec-8.

Natural sugar-based molecules in the body fulfill a similar role in

keeping eosinophils in check in healthy people, explains Bochner. However, he and his colleagues hypothesized, if Siglec-8 were compromised — perhaps through a mutation in the gene that produces this protein — people who carried such a mutation might be more susceptible to getting asthma or other immunological diseases because they might end up with extra eosinophils.

To test this idea, Bochner and his colleagues used data from Genomic Research on Asthma in the African Diaspora (GRAAD), a group of National Institutes of Health-funded studies of asthma in pediatric and adult African-American populations and one study of healthy African-Americans. The team examined DNA taken from 464 asthma patients and 471 healthy individuals who participated in these studies. They looked for single-letter differences in the genetic code, mutations called single nucleotide polymorphisms (SNPs, pronounced “snips”), that might be associated with a higher risk of asthma. Their results turned up a single SNP, called rs36498, which was associated with a significantly higher susceptibility to asthma.

To confirm these results, the researchers performed a similar investigation on two racially different populations: 822 individuals among 356 nuclear families, each with at least one child with asthma, recruited from the Conde District of Bahia, Brazil, and 468 volunteers with asthma and 457 without asthma recruited from a pulmonary clinic at Hokkaido University Hospital in Hokkaido, Japan.

The researchers found that the same SNP, rs36498, was found in significantly more Brazilian individuals with a history of wheezing in the last 12 months or had a lifetime history of asthma than those without these characteristics. A different SNP, rs10409962, was found in higher numbers in the Japanese asthmatic volunteers compared to the healthy ones.

To see if either of these SNPs might be involved in other conditions that affect eosinophils, the researchers examined 166 Caucasians who each had a condition called eosinophilic esophagitis, an inflammatory condition that affects the walls of the esophagus, and 132 healthy Caucasian volunteers. Neither SNP appeared prominently in these populations. The results suggest that these SNPs affect asthma susceptibility, but not susceptibility to eosinophilic esophagitis.

“Our results suggest these mutations in the Siglec-8 gene may play a role in asthma. It’s reasonable to assume that efforts to target Siglec-8 might be able to influence this disease and others associated with eosinophils,” says Bochner. “If we’re able to understand these mutations better, we might be able to use them to develop a diagnostic test or new treatment.”

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