Asthma and other allergies tied to absence of specialized cells

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When it comes to allergies, both the problem and the solution are found within us. Our immune systems respond to foreign substances with an arsenal of cells. Some are programmed to "remember" invaders they've encountered in the past. Normally, anything previously identified as harmless is allowed to pass. Sometimes, however, the immune response goes awry, triggering an allergic reaction.

Now, researchers at NYU School of Medicine have zeroed in on a class of custom-made immune cells that block allergic reactions. These regulatory T cells are manufactured according to instructions from a gene called Foxp3 whenever we eat or inhale a potential allergen for the first time, ensuring that the next time we encounter that substance, we will not mount an allergic response.

"We don't become allergic to lots of things—we eat all kinds of things, we breathe all kinds of things, and what prevents us from developing allergies is that we make regulatory T cells, which specifically recognize this allergen," says Maria A. Curotto de Lafaille, Ph.D., Associate Research Scientist at NYU Langone Medical Center. "Every time we don't react to something or don't become allergic, it's not because nothing is happening," Dr. de Lafaille explains. "It's because something very important is happening: We're making these cells,"

Mucosal tissue, which lines both the respiratory and digestive tracts, has long been known as an effective barrier against allergens, which are always protein molecules. The NYU research shows that Foxp3-directed

regulatory T cells (Treg) are produced in the mucosal tissue and remain there to prevent allergic reactions. New ones are tailor-made every time an unknown protein is inhaled or ingested. The inability to make Treg cells results in high susceptibility to becoming allergic.

The NYU researchers induced allergic reactions in mice with a Foxp3 mutation that prevented formation of Treg cells. Exposure to the same allergen—in this case egg protein—did not elicit an allergic response in mice that were able to make Treg cells. The findings are reported in the July 18, 2008, issue of the journal Immunity.

The formation of Foxp3-positive Treg cells occurs in response to any potential allergen, so the findings are applicable to a broad range of allergic reactions and autoimmune diseases, says Dr. de Lafaille. When people suffer from allergies, including life-threatening ones such as asthma, something goes wrong in the process by which Foxp3 signals Treg cell formation. The problem is not necessarily a mutation in the Foxp3 gene, which is known to cause severe autoimmune disease. Rather, something occurs, or fails to occur, in the lungs or the gut that interferes with the production or activity of allergen-specific Treg cells.

The NYU researchers also determined that Treg cells control damage from long-term inflammation. They found high concentrations of Treg cells in inflamed lung tissue of mice without the Foxp3 defect. "The question arose about what these cells are doing in the tissue—are they beneficial or not?" Dr. de Lafaille says. It turns out that even though the Treg cells did not prevent inflammation in an ongoing allergic reaction, they kept it under control, ensuring it did not worsen or spread to other areas of the body. "We think that over time these regulatory T cells become more important than the inflammatory cells and end up completely shutting off the inflammation. But it's not overnight and it's not black and white," Dr. de Lafaille emphasizes.

This finding provides a key to one of the most serious consequences of asthma. In addition to breathing problems during an acute attack, people with asthma have chronic inflammation, which can permanently damage their airways. If a means could be found to increase the number of Treg cells in inflamed tissue, this might be prevented. Allergic asthma, the most common and best-understood type, affects more than 10 million people in the US, many of them children. Acute asthma attacks are responsible for nearly 4000 deaths in the United States each year.

Dr. Yi Ding, Dr. de Lafaille, and other members of Dr. Juan Lafaille's laboratory have been investigating ways to grow allergen-specific Treg cells in the lab and inject them into people who cannot make their own. The group published a paper in Nature Medicine in February 2008 describing a method of making the cells. "The big challenge is how to isolate the cells that will recognize the right allergens that the person is allergic to," Dr. de Lafaille says. Another approach is to stimulate the body to manufacture the cells itself, an area of ongoing research.

This work represents an important step in understanding the genetic and cellular mechanisms underlying the allergic response, which may lead to more effective therapies. Current treatment is aimed at suppressing symptoms and reducing inflammation after an allergic reaction has already occurred. Having identified the cell type that must be present to prevent allergies, Dr. de Lafaille and her colleagues are now looking for the glitch that blocks formation of those cells.

Source: NYU Langone Medical Center