

Calming a Misguided Immune System

New findings link custom-made cells to allergic reactions.

WHEN IT COMES TO ALLERGIES, the problem and the solution both lie within us. Our immune systems respond to foreign proteins with an arsenal of cells, some of them programmed to recognize and attack harmful invaders they have encountered in the past. Normally, any protein previously identified as harmless is allowed to pass, but sometimes the immune response goes awry and attacks in the absence of a real threat, triggering an allergic reaction.

Now, in hopes of finding a way to prevent these misguided responses, researchers at the School of Medicine have zeroed in on another class of immune cells that block allergic reactions. These regulatory T (Treg) cells are custom-made every time we eat or inhale an unknown protein for the first time—ensuring that the next time we encounter the substance, the body won't mount an allergic response. Defects in the ability to make these cells, which are manufactured according to instructions from a gene called *Foxp3*, leave a person highly susceptible to becoming allergic.

"Every time we don't have an allergic reaction to something, it's not because

nothing is happening," says Maria A. Curotto de Lafaille, Ph.D., research assistant professor of pathology, who led the research. "In fact, something very important is happening: We're making regulatory T-cells that recognize a specific allergen we've eaten or inhaled."

While most T-cells originate in the thymus, the researchers have found that *Foxp3*-directed Treg cells arise in mucosal tissue, which lines the respiratory and digestive tracts and serves as a barrier against allergens. Dr. de Lafaille and her colleagues in the Program of Molecular Pathogenesis at the Helen L. and Martin S.

Kimmel Center for Biology and Medicine at the Skirball Institute for Biomolecular Medicine described their investigations in a recent issue of the journal *Immunity*.

One of their findings may hold the key to understanding a serious consequence of asthma: permanent lung damage due to chronic inflammation. When the researchers induced allergic asthma in mice with and without *Foxp3* defects, they found high concentrations of protective Treg cells in the inflamed lung tissue of those without the defect. Although the cells didn't prevent inflammation, they kept it under control and stopped it from spreading to other areas of the body.

"We think that, over time, these regulatory T-cells end up completely shutting off the inflammation," Dr. de Lafaille explains. If a way could be found to increase the number of Treg cells in the lungs, long-term inflammation might be prevented.

Dr. de Lafaille and her colleagues in Dr. Juan J. Lafaille's laboratory are currently investigating ways to grow allergen-specific Treg cells in the lab. "The big challenge," she says, "is how to isolate the cells that recognize the specific allergens an individual is allergic to." If they succeed in doing this, it may be possible someday to inject Treg cells into people who can't make their own. The group published a paper in *Nature Medicine* last February, with Yi Ding as the lead investigator, describing one method of making the Treg cells. Another promising area of research involves stimulating the body itself to manufacture the cells.

Their work represents an important step in understanding the genetic and cellular mechanisms underlying allergies. This may lead to more-effective therapies that prevent allergic responses from occurring, rather than just suppressing symptoms and reducing inflammation after an allergic reaction has already occurred, as current treatments do. And since Treg cells are produced in response to all potential allergens, the findings are applicable to a broad range of allergic reactions and autoimmune diseases. The study published in *Immunity* identifying the role of *Foxp3*-positive Treg cells in blocking allergies and controlling inflammation was supported by grants from the National Institutes of Health, the National Multiple Sclerosis Society, and the Sandler Foundation. Co-authors of the study were Maria A. Curotto de Lafaille; two former postdoctoral students in pathology, Nino Kutchukhidze and Shiqian Shen; Yi Ding, a recent Ph.D. in pathology; Herman Yee, M.D., Ph.D., associate professor of pathology; and Juan J. Lafaille, Ph.D., senior investigator and associate professor of pathology and medicine. Co-authors of the paper published in *Nature Medicine* were Yi Ding; Shiqian Shen; Andreia C. Lino, a graduate student; Maria A. Curotto de Lafaille; and Juan J. Lafaille. ●

