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ASTHMA

Breathing new life into research

Asthma was once thought to be a uniform disease triggered by one type of immune cell. Researchers are now revealing the complexity of the condition and hope to hasten new drugs for forms unresponsive to steroids.

BY AMY MAXMEN

According to textbooks, type 2 helper T cells (Th2 cells) preside over asthma. T cells are a subset of the white blood cells known as lymphocytes, and the conventional view is that an asthma attack occurs when Th2 cells secrete a certain set of immune-signalling proteins called cytokines that inflame the lungs, irritate the chest and cause asthma's characteristic wheezing. However, another cytokine, interleukin-17 (IL-17), which does not belong to Th2's signature set, has been caught lurking in lung tissue, sputum and the blood of asthmatic patients (see 'New partner in crime?'.) "We thought we understood asthma, but now we know it's much more complex," reflects immunologist Manfred Kopf at the Swiss Federal Institute of Technology in Zurich.

Recent research is reframing our picture of asthma. Numerous molecular, immune-system pathways are now being implicated in different manifestations of a disease once considered uniform. By mapping these networks, scientists plan to identify new treatment targets for each form of asthma. The discovery of IL-17 in the lungs of some asthmatics has drawn attention to IL-17-producing cells previously thought unrelated to asthma. What's more, if researchers discover what spurs the anomalous and harmful surge in IL-17 in the first place, they might gain an insight into why the prevalence of asthma and other IL-17-driven diseases — such as inflammatory bowel disease and multiple sclerosis — has increased in the industrialized world.

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ROUNDING UP THE SUSPECTS

Implicating IL-17 in asthma and proposing new disease subtypes has solved several puzzles. For example, in many asthmatic patients, other types of white blood cell called eosinophils accumulate in the lungs, but individuals with the most severe form of asthma harbour neutrophils, yet another type of immune cell. Normally, these neutrophils surround the site of an acute infection or injury, lured there by IL-17, to protect the body. It appears that in asthma, IL-17 is drawing neutrophils into the lung — but they are not there to protect. Instead, they make asthma attacks worse.

Furthermore, compared to people with mild asthma, individuals with severe asthma not only have more IL-17, they tend to have more of the cells known to secrete IL-17, namely Th17 cells. Research has also shown that mice with more Th17 cells get little breathing relief from steroids, a common treatment for asthma but one to which severe asthma patients rarely respond. "Patients who come into the hospital needing help are usually those with severe asthma who are resistant to steroids," explains Bart Lambrecht, at Ghent University in Belgium. "For a long time we knew these patients had neutrophils in their sputum, but the link to Th17 cells wasn't made until recently."

By secreting IL-17 and other cytokines, Th17 cells constrict the lungs' airways. What triggers Th17 cells to churn out these lung-damaging molecules, however, is less well understood. Viruses, allergens, cigarette smoke and airborne pollutants have all been fingered as potential culprits, but how they initiate Th17 cells in asthma remains elusive. For example, cigarette smoke triggers the proliferation of Th17 cells, and smoking is a risk factor for asthma, but the steps between these two observations are obscure.

"Perhaps you first have a predisposition to drive a Th2 response, and IL-17 comes on board later," says Marsha Wills-Karp, an immunologist at the Cincinnati Children's Hospital Research Foundation in Ohio. "It may have something to do with the exposures you have early in life, such as infections, cigarette smoke or air pollutants."

In 2010, Wills-Karp and her colleagues discovered a way for allergens to provoke Th17 cells, and thereby exacerbate asthma. Their discovery concerned the complement systempart of the immune system that connects innate and adaptive T cells, and Th17 in particular. After an extract consisting of the allergy-inducing portion of house dust mites activated the C3 system, a molecular cascade caused the number of Th17 cells to rise. And IL-17A, a cytokine produced by Th17 cells, reactivated the C3 system and perpetuated the response.

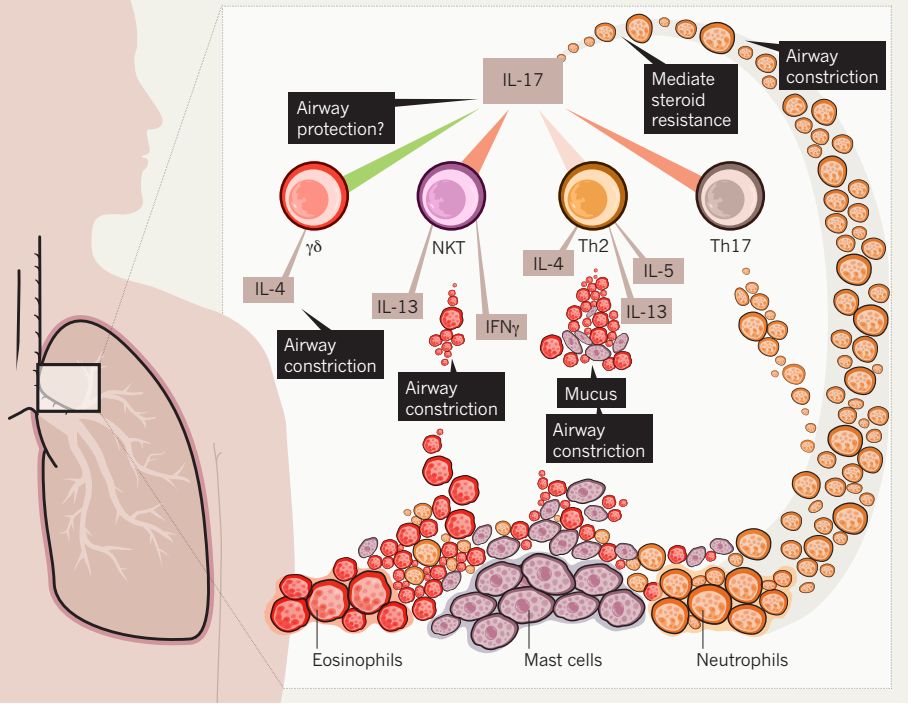
Wills-Karp says that abnormally bad, and

sometimes lethal, infections of the common respiratory syncytial virus (RSV) might cause asthma through the C3 complement system as well. "Almost 100% of kids have been infected by RSV by the time they are two years old, and besides a cold, they're just fine," she explains, "but a subset get hospitalized, and if they survive they almost always go on to have severe asthma." Wills-Karp had previously led a study that found postmortem signs of complement activation in children who died during an RSV vaccine trial in the 1960s — these children had experienced breathing problems. This study was conducted before we knew about Th17 cells, she says, but she now speculates that, when the RSV activated the complement system, a Th17 cascade was set in motion leading to severe asthma. "If we went back and looked at those children's lungs, we'd probably find Th17 cells", she says.

Another possible factor in the role of Th17 in asthma is vitamin D. This vitamin seems to slow production of cytokines by Th17 cells, so a vitamin D deficiency might lead to the overproduction of cytokines by Th17 cells, which could be a problem if the triggering agents were benign. In a study of asthmatic children in Costa Rica, those with lower levels of vitamin D circulating in their blood were more likely to be hospitalized for severe asthma than those with higher levels of vitamin D.

NEW PARTNER IN CRIME?

Allergens, infections, or pollution might trigger T cells involved in asthma to produce IL-17. This cytokine seems to make asthma worse (although sometimes it may bring relief).



A THICKENING PLOT

The story does not end there: Th17 cells might not be the sole producers of IL-17 in people with asthma. In a murine model of asthma, Dale Umetsu, a paediatrician at Harvard Medical School and Children's Hospital in Boston, Massachusetts, reported that natural killer T (NKT) cells produce IL-17 and cause asthma-like symptoms.

Umetsu's mice had difficulty breathing after inhaling ozone at concentrations equivalent to ozone-polluted air. Although the mice produced more IL-17, Th2 and Th17 cells were not to blame. "You can take mice that don't have helper T cells, expose them to ozone, and they still have trouble breathing because they have plenty of NKT cells," explains Umetsu. "This was at odds with the prevailing wisdom," he says, "but there is a growing feeling that Th2 cells are not the only way to get asthma."

Another unusual suspect is a T helper cell going against the grain. In a study reported in 2010, Th2 cells from asthmatic patients were found to produce IL-17. Although surprising, this wasn't the first report of T helper cells secreting uncharacteristic proteins. Immunologists are unsure of how this plasticity arises in a small percentage of T cells. It is also uncertain whether a T cell producing a new cytokine or combination of cytokines should be assigned to a new T-cell subset. "People are slowly acknowledging that there are more T-cell subsets than we had imagined," says immunologist Carsten Schmidt-Weber, at the Technical University and Helmholtz Center Munich, Germany. "But if we want to design new treatments for asthma, what matters is their function, not their name."

PERSONALIZING ASTHMA TREATMENT

Figuring out what cells produce IL-17 in response to certain stimuli should help the design of new medicines to treat asthma in patients unresponsive to current steroid treatments. In order to test any new drug, patients must be clearly categorized to define the underlying pathology. Otherwise, a drug tailored for one form of asthma could be ineffective in treating a different form of the disease.

"There is a lot to learn before we start to use highly specific therapies," says Schmidt-Weber. Phenotyping asthmatic patients is one aim of the German Center for Lung Research, a virtual centre that links asthma research from across five cities in Germany. Meanwhile, in the United States, the multicentre Severe Asthma Research Program (SARP) has thus far assessed about 1,600 patients and outlined three main types of severe asthma. SARP investigators are analysing sputum and blood samples from patients in each of these groups to determine the immune response associated with symptoms.

Blood and sputum, however, might not reflect what occurs in the lungs. And there are limits to what tests you can do in people in the name of research. Clare Lloyd at Imperial College London cuts tiny tissue samples from the airways of consenting asthmatic patients in order to analyze the protein expression of immune cells. Yet even this invasive method permits only a snapshot of the lungs. "We hope the sample represents what's going on in the lungs, but really it is only a small slice," she says. "In an ideal world, we could see which cytokines are being secreted in real time within a patient's lungs — but we are far from having the technology to do that in a way that's safe and ethical."

Such issues help account for asthma researchers' heavy reliance on mice. Dependence on a single murine model of asthma originally misled researchers into believing Th2 was the primary immune cell at fault, some immunologists argue that new models are needed to help scientists understand other immune pathways. "People have said that the old mouse model of asthma didn't explain how a viral infection or ozone exposure caused asthma," Umetsu says. "The key is to develop new models to explore different types of asthma."

Recent findings on IL-17 and NKT cells have raised more questions than answers, but Imperial's Lloyd finds the challenge invigorating. "People are starting to work towards a greater understanding of all kinds of asthma," says Lloyd. "If we can identify the cytokines involved in each case, we can develop better, more personalized treatments." ■

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