Digging Deeper Beyond Itch

Scientists identify an immune cell receptor that may be at the root of some drug allergies.

XINZHONG DONG HAS been scratching an itch for the past 14 years. Like a case of hives that won't go away, the Mrg family of proteins has been nagging at Dong ever since he discovered the receptors on sensory neurons in 2001. He's been consumed with trying to figure out what the proteins do. And it's no easy task – there are 31 different versions of the receptor in mice and 8 in humans. So far, the HHMI early career scientist has learned that some of the receptors sense itch and others sense pain. His lab team's most recent discovery is somewhat of an anomaly: they've found an Mrg receptor on immune cells that plays a role in drug allergies.

Allergic reactions occur when immunoglobulin E (IgE) antibodies perceive a threat to the body – often an otherwise harmless substance like cat dander or pollen. The IgE antibodies bind to these substances and dock onto specific receptors on mast cells. These immune cells are packed with granules of histamine and other proinflammatory molecules that lead to the hives, irritation, or pain associated with allergies. When triggered by IgE antibodies, mast cells release their payload, producing an allergic reaction.

Though mast cells are typically activated by an allergy-specific IgE antibody, they can also be activated by a wide range of other unrelated things, explains Benjamin McNeil, a postdoc in Dong's lab at Johns Hopkins University. "People who display severe allergic reactions to environmental chemicals, FDA-approved drugs, and parasites, for example, often don't have any IgE antibodies against these things," he says. "Their reactions are mast cell-mediated, but via a different pathway." The majority of compounds that trigger such antibody-independent reactions are collectively known as "basic secretagogues," because of their positive, or basic, charge and their ability to cause mast cells to secrete their granules.

When McNeil joined the lab, in 2011, he picked what he thought was a fairly simple project: figure out the function of a human Mrg receptor called MRGX2. "It was supposed to be a straightforward project," McNeil says. "I was a neuroscientist and wanted to study sensory biology. We thought that MRGX2 was on neurons, too, so this was a way for me to learn the techniques in the lab while characterizing the receptor." But, as is often the case in scientific research, it wasn't that simple. The very first thing McNeil discovered was that MRGX2 is not expressed in neurons.

In 2006, a group of Japanese scientists published a paper suggesting that MRGX2 might be involved in non-IgE mast cell responses. Following up on this lead, McNeil discovered that ample amounts of the protein were expressed in human and mouse mast cells. In fact, he says, "It's the most mast cell-specific gene in the entire genome. The only way to really define a mast cell is by this." In other words, if a cell expresses the *MRGX2* gene, it's definitely a mast cell.

The next step was confirming the receptor's function. After McNeil discovered that a similar Mrg protein – Mrgb2 – exists on mouse mast cells, he created mice that didn't express the gene to test the protein's affinity for different compounds. Chemicals that triggered the receptor would cause an allergic reaction in normal mice but not in the knockout mice. McNeil went on to test every basic secretagogue he could get his hands on. Strikingly, everything he tried seemed to activate the receptor. "After that, I realized, 'Okay, this is a really bizarre receptor,' and started expanding the list of candidates," he recalls.

Graham Roumieu

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—BENJAMIN MCNEIL

In the end, the list of compounds that activated the Mrg mouse analog receptor was huge. It included insect venoms, cancer and HIV medications, neuromuscular-blocking drugs commonly used for anesthesia during surgery, and several molecules in a class of antibiotics called fluoroquinolones. All of the compounds had two characteristics in common – they were small and positively charged. "They are otherwise completely unrelated, structurally speaking," McNeil says. "They can differ by a factor of ten in their size and have totally different compositions. It's really remarkable that there's just one single receptor for all of these substances."

The study, published in *Nature* on March 12, 2015, has opened the floodgates for dozens of new experiments and collaborations in the Dong laboratory. McNeil is screening other suspected allergy-causing compounds for binding to MRGX2. Dong has started working with scientists at GlaxoSmithKline to find small molecules that can block MRGX2 but still allow IgE-mediated activity in mast cells. He's also developing a drug-binding assay for MRGX2 that will allow pharmaceutical companies to test whether their new compounds elicit allergic reactions.

And there's also more work to be done on other Mrg family members. "We still have many other genes to study," says Dong. "We don't know exactly where they are located, where they're expressed in tissues, and what their functions are." Clearly, it's an itch he's not ready to stop scratching any time soon. *–Nicole Kresge*