Multiple allergic reactions traced to single protein

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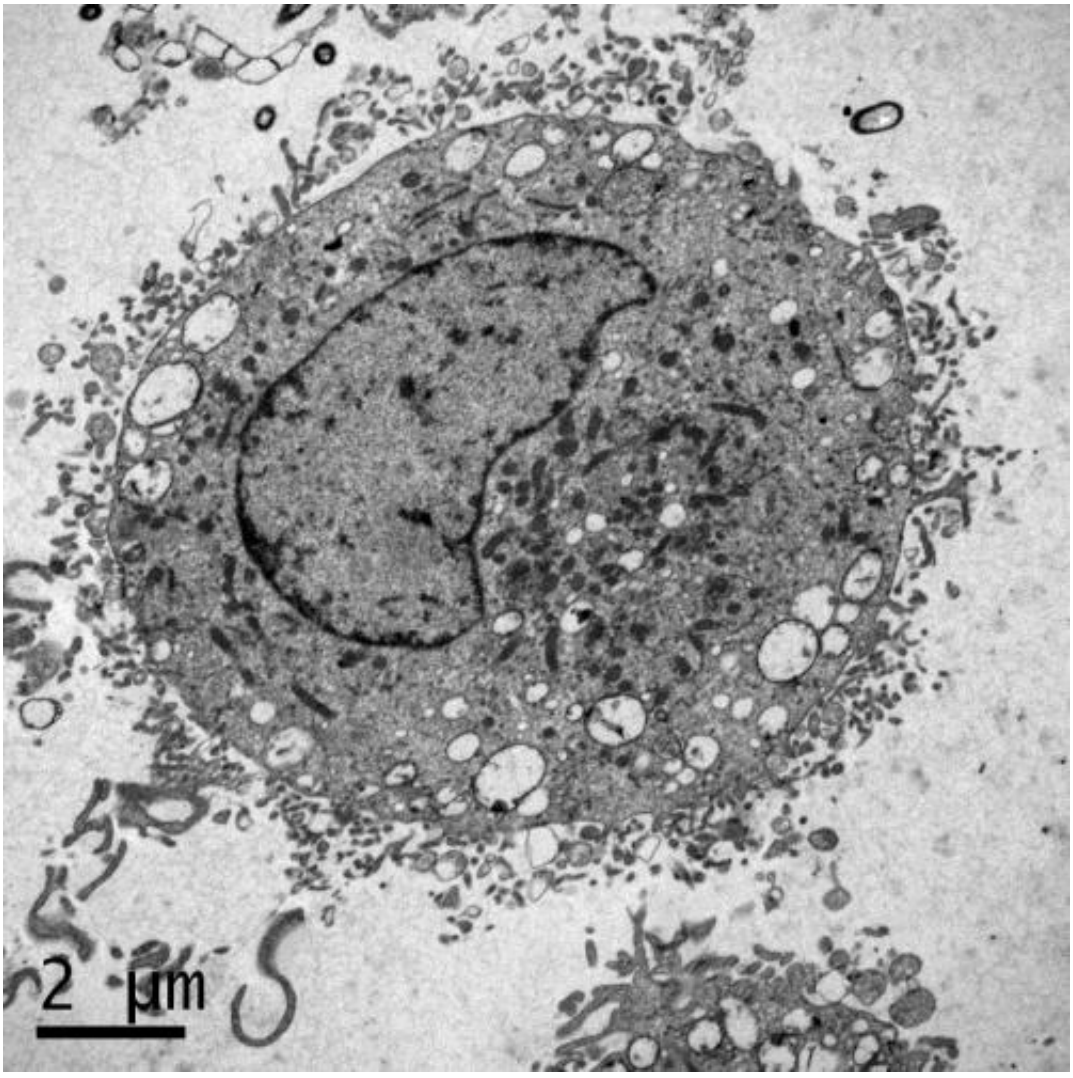

A mast cell. Credit: Priyanka Pundir/University of Alberta

Johns Hopkins and University of Alberta researchers have identified a single protein as the root of painful and dangerous allergic reactions to a range of medications and other substances. If a new drug can be found that targets the problematic protein, they say, it could help smooth treatment for patients with conditions ranging from prostate cancer to diabetes to HIV. Their results appear in the journal *Nature* on December 17.

Previous studies traced reactions such as pain, itching and rashes at the injection sites of many drugs to part of the immune system known as mast cells. When specialized receptors on the outside of mast cells detect warning signals known as antibodies, they spring into action, releasing histamine and other substances that spark inflammation and draw other immune cells into the area. Those antibodies are produced by other immune cells in response to bacteria, viruses or other perceived threats. However, "although many of these injection site reactions look like an allergic response, the strange thing about them is that no antibodies are produced," says Xinzhong Dong, Ph.D. , an associate professor of neuroscience in the Institute for Basic Biomedical Sciences at the Johns Hopkins University School of Medicine.

To zero in on the cause of the reactions, Benjamin McNeil, Ph.D., a postdoctoral fellow in Dong's laboratory, first set out to find which mast cell receptor—or receptors—responded to the drugs in mice. Previous studies had identified a human receptor likely to be at fault in the allergic reactions; McNeil found a receptor in mice that, like the human receptor, is found only in mast cells. He then tested that receptor by putting it into lab-grown cells and found that they did react to medications that provoke mast cell response. He found similar results for the human receptor that previous studies had indicated was a likely culprit.

"It's fortunate that all of the drugs turn out to trigger a single receptor—it

makes that receptor an attractive drug target," McNeil says.

To find out whether eliminating the receptor really would eliminate the allergic reactions, the research team also disabled the gene for the suspect receptor in mice. These "knockout" mice did not have any of the drug allergy symptoms that their genetically normal counterparts displayed.

The researchers are now working to find compounds that could safely block the culprit receptor in humans, known as MRGPRX2. Such a drug would not prevent true allergic reactions, which produce antibodies, but only the pseudoallergic reactions triggered by MRGPRX2. Still, it could improve the lives of many patients, says McNeil, by lessening the drug side effects they currently endure. Medications that trigger MRGPRX2 include cancer drugs cetrorelix, leuprolide and octreotide; HIV drug sermorelin; fluoroquinolone antibiotics; and neuromuscular blocking drugs used to paralyze muscles during surgeries.

Dong's research group is also looking into the possibility that MRGPRX2 could be behind immune conditions such as rosacea and psoriasis that don't stem from medication use.

More information: Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions, *Nature*, DOI: 10.1038/nature14022" target="_blank">nature.com/articles/DOI: 10.1038/nature14022

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