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## New Itch Receptors Identified

From the brain's point of view, not every itch is the same. And while researchers have learned enough about certain kinds of itch to intervene with drugs, such as antihistamines, other kinds of itch have remained a ticklish subject. Now, Howard Hughes Medical Institute researchers and their colleagues have found receptors on sensory nerves in the skin that transmit itch sensations and operate separately from the best-known itch receptor, the histamine receptor.

The research, published in the December 25, 2009, issue of the journal *Cell*, expands the scientific understanding of itch sensation and points to better treatments for conditions that can't be remedied with anti-histamines. One of these conditions is "chloroquine itch," a side-effect of the anti-malarial drug chloroquine that causes many people to stop taking the drug.

The itch receptors identified by Howard Hughes Medical Institute (HHMI) scientists belong to a family of proteins known as Mrg receptors. "We think that chloroquine causes itching primarily by binding to an Mrg receptor on nerve fibers in skin," said Xinzhong Dong, the senior author on the study and an HHMI Early Career Scientist at Johns Hopkins University.

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**- Xinzhong Dong**

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For Dong, the new findings conclude a nearly decade-long quest to understand the main functions of these receptors, which he first identified in 2001 while he was a postdoctoral researcher in the laboratory of HHMI investigator David Anderson at the California Institute of Technology. Mice have several dozen *Mrg* genes, and Dong found that most were active almost exclusively in a set of neurons that run from the skin to the dorsal root

ganglia of the spine. These neurons were thought to be the primary sensors of pain signals. Later studies determined that *Mrg* genes in humans also were expressed only in dorsal root ganglia neurons.

The possibility that these Mrg receptors might mark a pain-related pathway made them attractive targets for medical research, and Merck & Co., soon licensed Caltech's patents on the Mrg receptors. To determine their function, Dong, Anderson, and their colleagues developed a line of mice that lacked a cluster of about half of the *Mrg* genes. Dong expected these mice to be less sensitive to pain, but after running a battery of tests, he found that they were at least as pain-sensitive as normal mice. "We were quite disappointed," Dong remembers.

At the time, few researchers were looking for itch pathways in sensory nerves. "There weren't even scientific meetings then whose primary focus was itch," remembers Anderson, who is a coauthor of the current study. But in 2007, after Dong had set up his own lab at Johns Hopkins, a group led by his former Caltech labmate, Zhou-Feng Chen, discovered a receptor that enabled neurons in the spine to communicate itch sensations to the brain.

"That really drew my attention to itch research," Dong said. Indeed, he began to wonder whether the mysterious Mrg receptors were not pain receptors at all, but rather, itch receptors.

To find out, he asked his postdoctoral researcher Qin Liu to inject two sets of mice with a series of itch-inducing compounds. One set of mice had the *Mrg* gene cluster, the second set did not. "The first one we tried was chloroquine, simply because it was the cheapest drug on the list," said Dong. "And when Qin injected the two groups of mice with it, we immediately saw an itch behavior deficit in the *Mrg*-cluster knockout mice."

The mice with the *Mrg* receptors scratched at their itches, but those without the *Mrg* cluster didn't scratch nearly as much. When they did scratch, it was only after a pronounced delay, and further experiments indicated that this was probably in response to a chloroquine-provoked release of histamine in the skin. *Mrg*-knockout mice, they knew, could respond normally to itch-inducing histamine.

Twelve *Mrg* genes lay within the deleted stretch of DNA in the *Mrg*-knockout mice. After evaluating each gene in that region, the researchers confirmed that a single gene, *MrgA3*, accounted for the sensitivity to chloroquine. Sifting through human *Mrg* genes, they again found only one, *MrgX1*, that conferred chloroquine-sensitivity.

Dong and his colleagues found that MrgA3 was expressed in only about four percent of neurons in the dorsal root ganglion, in mice and humans respectively. All or nearly all neurons within this small subset also produced gastrin-releasing peptide (GRP), which, as Chen and his colleagues had

reported in 2007, transmits itch signals on the next leg of their journey from the spine to the brain.

The nerve fibers that express chloroquine-sensitive receptors express other receptors too. Dong and his colleagues found that the chloroquine-sensitive DRG neurons in mice also respond to a separate itch-causing substance known as BAM8-22, apparently via an Mrg receptor known as MrgC11. The same neurons respond as well to histamine, via histamine receptors.

“There’s been a long debate in the sensory biology field about whether itch and pain sensations are mediated by their own separate neuronal pathways, or by the same neuronal pathway,” Dong said.

“The data in the *Cell* paper raise the possibility that there is a small and specific family of neurons that are only involved in responding to this family of itch-inducing compounds,” Anderson said, “but that has yet to be formally demonstrated.” Dong suspects that this subpopulation of itch-sensitive dorsal root ganglion neurons evolved to mediate itch sensations exclusively, and he plans experiments to resolve the issue.

Dong also hopes that his group’s work eventually will clear up another mystery, concerning the interactions between pain and itch in the nervous system. “Itch and pain sensations antagonize each other, so that when you feel an itch and you scratch it, the scratch induces pain and suppresses the itch,” he said. “At what level this pain-versus-itch antagonism occurs is not yet fully understood.”