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RESEARCH NEWS

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Researchers Identify Cells and Receptor for Sour Taste

In the last seven years, Howard Hughes Medical Institute researcher Charles S. Zuker and Nicholas J.P. Ryba at the National Institutes of Health have worked together to identify the cells, receptors and signaling mechanisms for three of the five tastes humans can sense — sweet, bitter, and umami (the taste of monosodium glutamate). Now, Zuker, Ryba, and their team of researchers have identified the cells and the receptor responsible for sour taste, the primary gateway in all mammals for the detection of spoiled and unripe food sources.

The receptor is found in a subpopulation of taste receptor cells of the tongue that do not function in sweet, bitter, or umami taste, the researchers report in the August 24, 2006, issue of the journal *Nature*.

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— Charles S. Zuker

This finding is very satisfying, said Zuker, because it seals the case that we had built before with sweet, bitter, and umami, showing that each taste is mediated by fully dedicated sensors. A contrasting view held that individual tongue cells detect more than one taste modality, with the quality of the taste being encoded in a complicated pattern of nerve signals sent to the brain.

The hunt for the sour receptor began with a search of DNA and protein sequence databases. Angela Huang, a graduate student in Zuker's lab at the University of California, San Diego, and the lead author of the paper, screened the mouse genome for all of the genes encoding proteins that have transmembrane domains — sections of the protein that allow the protein to be located in cell membranes.

That screen narrowed the list significantly, from 30,000 to about 10,000, Huang said. She then used what Zuker calls a stroke of ingenuity to reduce the list further. Proteins that could detect sour compounds are likely to be found only in small numbers of tissues, including taste cells in the tongue. Huang therefore eliminated from the list all those proteins that are expressed in many different tissues. That got it down to about 900 candidates, she said.

Huang then used a technique called reverse transcriptase polymerase chain reaction (RT-PCR) to find which of the candidates were expressed specifically in taste receptor cells. Of the approximately 30 proteins identified through RT-PCR, Huang searched for genes that were expressed in a small population of taste receptor cells — the pattern that Zuker's and Ryba's team had previously discovered with taste receptors for sweet, bitter, and umami.

The researchers' attention was drawn immediately to a receptor molecule known as PKD2L1, which is related to a large family of proteins that shuttle ions into and out of cells. As predicted for a candidate sour receptor, PKD2L1 was not found in the cells that express the receptors for sweet, bitter, and umami, but instead was found in a novel population of taste cells. Our fundamental premise was that salt and sour were going to be mediated by dedicated cells, said Zuker, and those candidate receptors should not be present in sweet-, bitter-, or umami-sensing cells.

To link the receptors with the taste of sour, Zuker and his colleagues turned to another clever experimental strategy. Using a special mouse strain, they created genetically engineered mice that produced a diphtheria toxin in cells that expressed PKD2L1, thus killing the cells. They then recorded the nerve signals and tongue function coming from taste cells in the genetically-engineered mice. Remarkably, no matter what sour compounds they fed the mice, nerve signals from the taste cells remained absent; the animals were completely insensitive to all kinds of acids. But these sourless mice continued to be able to taste sweet, bitter, umami, and salt. Killing these cells and showing that the mice now are totally unable to detect sour proved that these cells are the sensors for sour taste, and that indeed no other taste cells detect sour, said Zuker.

In an interesting extension of this work on taste, the investigators then examined whether cells expressing the sour receptor might be found anywhere else in the body, perhaps where sensing acidity might be important. They looked for the receptor in a large number of other tissues and discovered that it is expressed in a particular set of neurons surrounding the central canal of the spinal cord. Suspecting that these cells might be responsible for monitoring the level of acidity in the cerebrospinal fluid (CSF), the researchers recorded nerve signals from the cells in a slice of spinal cord tissue. When the surrounding solution turned acid, the cells became activated selectively, and immediately began firing nerve signals much more rapidly than when the solution was neutral or basic.

Discovery of the sour (acid) receptor in the central nervous system could help explain how the body monitors the quality of critical body fluids, Zuker said. For example, the body controls respiration in part by monitoring the acidity of the blood, since an increase in carbon dioxide dissolved in the blood increases acidity. Defects in these blood-, CSF-, and brain-fluid-sensing systems may underlie a wide range of disorders, said Zuker.

Several intriguing questions can be pursued now that the sour-taste cells and candidate receptor have been found. One is how the PKD2L1 receptor is activated by acid stimuli. Another concerns the role of the neurons that innervate the central canal. And as Zuker pointed out, This work also proved that salt-sensing cells, just like those mediating sweet, bitter, umami and sour, must function as independent sensors because the sourless mice have perfectly normal salt perception, he said. So this opens an exciting experimental platform to molecularly dissect the last of the five basic taste qualities: salt taste.