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pHirst sour channels pHound?

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Abstract

Newly discovered acid channels may finally resolve sour taste mystery

Do you enjoy the tartness of apples or grapes? A touch of sour can be delicious. But, highly sour foods are repulsive. This reaction warns against consuming foods spoiled by bacterial growth, such as rancid milk. So, it is no surprise that many animals have a sense of sour taste. In humans, it is one of five basic tastes, which includes sweet, bitter, salty, and umami (the savory taste induced by L-glutamate). Many receptors and ion channels in taste buds that are critical for detecting these chemicals in foods are now known (1). However, a mammalian sour taste receptor has been elusive. On page XXX of this issue, Tu *et al.* (2) reveal a previously unrecognized H⁺-selective channel that functions in mouse taste receptor cells (TRCs, which occur in taste buds of the tongue) that are essential for sour taste. The protein, Otopetrin-1 (Otop1), was originally identified due to its requirement in the vestibular system to maintain balance and to perceive gravity and limb orientation (3). The work by Tu *et al.* not only provides a strong candidate for the mammalian sour taste receptor, but raises questions concerning the broader roles of Otop channels.

High Na⁺ and H⁺ are perceived as salty and sour, respectively, and are sensed by type III TRCs in our taste buds through mechanisms different from sugars, bitter compounds and L-glutamate, which are sensed by type II TRCs. These latter substances bind to and activate G-protein coupled receptors, which initiate signaling cascades culminating with the TRPM5 (Transient Receptor Potential cation channel subfamily M member 5) channel (1). By contrast, Na⁺ and H⁺ are detected by cation channels. In mammals, the low salt sensor is an epithelial Na⁺ channel (ENaC) (4). However, the H⁺ channel has been enigmatic. In the mouse, the H⁺-sensing TRCs express a distant cousin of TRPM5, called PKD2L1 (Polycystic Kidney Disease 2-like 1 protein) (see the figure) (5). Type III TRCs respond to acids by activating a H⁺ channel that is blocked by Zn²⁺, an inhibition common to the only other known eukaryotic H⁺ channel, hydrogen voltage-gated channel 1 (Hv1) (6, 7).

Multiple sour taste receptors have been proposed, including PKD2L1, Acid-Sensing Ion Channels (ASICs), and Hyperpolarization-activated, Cyclic Nucleotide-gated HCN channels (1). One by one, the candidates have not stood up to experimental scrutiny. To solve the mystery of the sour-sensing channel, Tu *et al.* cataloged several dozen genes predicted to encode proteins with multiple transmembrane domains (indicative of a channel) that are expressed in PKD2L1-positive TRCs, but not in TRCs expressing TRPM5. They introduced the candidate proteins in *in vitro* cell-expression systems, looking for a H⁺ influx current induced by extracellular acidity, and inhibited by Zn²⁺. Otop1—with 12 predicted

transmembrane domains— had >200,000 fold selectivity for H⁺ over Na⁺ and, in contrast to Hv1, showed only minor voltage-dependence (2). However, it is unresolved if Otop1 is simply regulated (gated) by acid, or whether there is greater regulatory complexity.

Is Otop1 is the long-sought after sour taste receptor? Strongly favoring this conclusion, the acid-activated H⁺ conductance specific to *Pkd2l1* TRCs, is virtually eliminated in TRCs from *tilted* mice, which have a missense mutation in *Otop1* that impairs vestibular. While, the preponderance of evidence supports that Otop1 is the sour taste receptor, behavioral analysis is needed to be certain. Complicating the behavioral analyses is that high acid not only stimulates TRCs, but also activates nociceptor (pain) afferents (8). Thus, in the absence of a repulsion to the taste of high sour, such as in the *tilted* mice, the H⁺ would still cause aversive behavior since it would activate nociceptive neurons through an Otop1-independent mechanism.

Because low levels of sour are appealing, and high levels are aversive, do separate TRCs and H⁺ channels respond to slightly and strongly acidic foods? This would be reminiscent of Na⁺-responsive TRCs whereby one type senses low Na⁺ through the ENaC channel and stimulates feeding; another class senses high Na⁺ and other salts through an unknown channel and induces repulsion (4, 9). Alternatively, there may exist only one class of H⁺-activated TRC. Slight tanginess would stimulate the TRCs slightly and promote feeding, whereas high acidity would induce a greater response of the same TRCs, and cause repulsion. Type III TRCs are also required for sensing water, carbonation, and contribute to detecting high salt (9–11). Are these the same, overlapping or distinct PKD2L1-positive type III TRCs that express Otop1? Does loss of Otop1 affect any of these other tastes? Interestingly, acidification suppresses the water taste response (10).

The finding that Otop1 is a H⁺ channel raises questions about its role in the vestibular system. In the inner ear, the functions of the sacculus and utricle, which aid in the perception of linear accelerations and gravity, depend on otoconia. These extracellular calcium carbonate-containing crystals overlay the gelatinous otolithic membrane surrounding the stereocilia of hair cells. When the head tilts, movement of the otolithic membrane weighed down by otoconia deflects the stereocilia, depolarizing hair cells. Mutations that impair the H⁺ conductance through Otop1, which is expressed in support cells adjacent to the otolithic membrane, prevent formation of otoconia. Otop1 is proposed to regulate intracellular Ca²⁺ levels (12), and might be required to attain high Ca²⁺ levels in globular substance vesicles in support cells, which are required for otoconia formation. However, the relationship of Otop1 and these vesicles to otoconia formation is unclear. Ca²⁺ channel activity can be inhibited by intracellular acidification. Therefore, Otop1 might contribute to a homeostatic mechanism to maintain pH. Opposite to functioning in H⁺ influx as in TRCs, it might promote H⁺ efflux from support cells, to prevent intracellular acidification.

Otops are a conserved protein family and Tu *et al.* found that mouse Otop1 and Otop2, human Otop1 and a fly Otop each conduct H⁺ upon lowering extracellular pH. Otop family members are expressed in many cell types in humans and mice. Although intracellular acidification is typically cytotoxic, there are cells other than type III TRCs that may be

endowed with H⁺ influx channels. For example, osteoclasts, which are exposed to low extracellular pH (<5.5) in resorption pits in bones, have a H⁺ influx pathway (13). However, it is only slightly inhibited by Zn²⁺ (13), differing from Otop-dependent conductances.

A decrease in extracellular pH can accompany tissue injury or inflammation, and enhance pain by increasing the activities of channels in nociceptors, such as TRPV1 (Transient Receptor Potential cation channel subfamily V member 1), in peripheral sensory neurons. Because positive allosteric modulation of TRPV1 by mild acidification only occurs in response to extracellular acidification, Otop-dependent H⁺ influx might attenuate nociception. Indeed, Otop1 expression is increased in dorsal root ganglion (DRG) neurons exposed to neuropathic conditions (14). However, H⁺ influx would have to be moderate to prevent cytotoxic acidosis.

Given their wide expression patterns, loss of Otops might result in many pathologies. The intracellular pH of most cells is ~7.2 and the extracellular pH is usually ~7.4. However, cancer cells often have an elevated intracellular pH (~7.4), while the extracellular pH is reduced (6.8–7.0) (15). This pH dysregulation can contribute to cancer by attenuating apoptosis, and promoting cell proliferation and directed cell migration (15). Might loss of Otops contribute to certain cancers by limiting H⁺ influx, which would otherwise reduce intracellular pH?

Mouse Otop2 and Otop3 have somewhat distinct biophysical properties from Otop1 (2). How does this relate to their biological roles? Do different Otops interact with distinct downstream effector proteins, which expand their functions? Clearly, the work of Tu *et al.* is only the pHirst taste of this pHamily of H⁺ channels.

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Sour taste reception

Mice and humans have five basic tastes: sweet, bitter, salty, umami and sour. Many receptors and ion channels in taste buds are critical for detecting these chemicals in foods, but the sour taste receptor has been elusive. The H^+ -selective channel, Otopetrin 1, is expressed in and functions in mouse acid sensing taste receptor cells (TRCs), which occur in taste buds of the tongue, and may be essential for sour taste.

Figure. Otop1 channel is expressed in PKD2L1-positive TRCs in the taste bud, and is selective for H^+ .