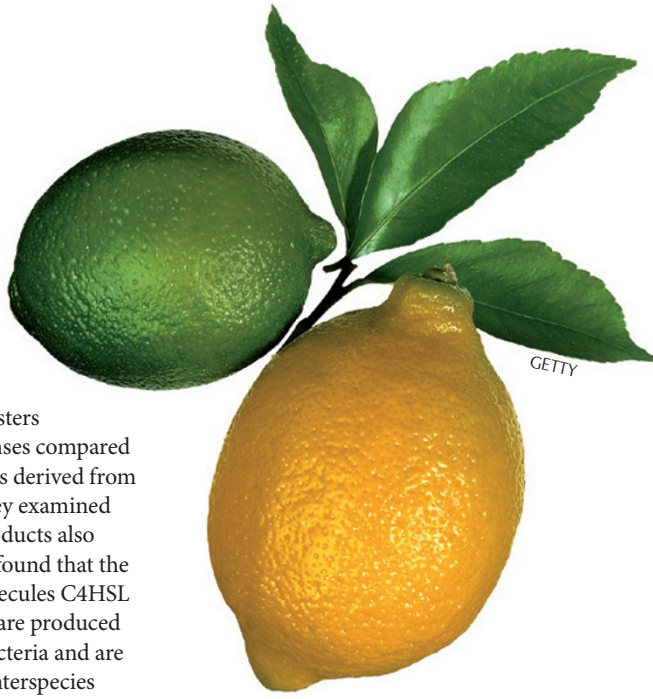
INNATE IMMUNITY

Bitter enemies



GETTY

> the immune system may have a taste for trouble

It seems that the immune system may have a taste for trouble. Lee *et al.* report that airway epithelial cells can use the bitter taste receptor T2R38 to sense the presence of and promote innate immunity to Gram-negative bacteria. Importantly, the authors show that humans with loss-of-function mutations in *TAS2R38*, which encodes T2R38, are more susceptible to sinonasal infections with Gram-negative bacterial species, such as *Pseudomonas aeruginosa*.

As well as being expressed on the tongue, the bitter taste receptors (T2Rs) are expressed by epithelial cells in the upper and lower airways. Previous work had shown that the activation of T2Rs can increase ciliary beat frequency, which promotes microbial clearance by expelling mucus from the respiratory tract. The authors therefore hypothesized that microbial products might activate T2Rs. Interestingly, common polymorphisms that occur in *TAS2R38* affect whether or not an individual can taste bitter compounds, such as phenylthiocarbamide (PTC). Thus, the authors further reasoned that 'tasters' (that is, those with a functional T2R38) and 'non-tasters' may respond differently to any microbial-derived ligands for T2R38.

Preliminary screens indicated that T2R38 is expressed at the apical membrane and by cilia in human sinonasal respiratory epithelial cells (HSECs). When cultures of primary HSECs were treated with PTC, the cells showed a sustained increase in intracellular Ca^{2+} levels. Moreover, the magnitude of the PTC-induced calcium flux correlated with the *TAS2R38* genotype of HSECs, with cells isolated and cultures derived from tasters having greater responses compared with cells and cultures derived from non-tasters. Next, they examined whether bacterial products also trigger T2R38. They found that the quorum-sensing molecules C4HSL and C12HSL (which are produced by Gram-negative bacteria and are thought to mediate interspecies communication) could induce Ca^{2+} fluxes in taster HSECs, but not in non-taster HSECs. In addition, knockdown of *TAS2R38* expression in taster HSECs blocked their response to C4HSL and C12HSL. So bacterial quorum-sensing molecules can activate T2R38 — but what is the functional outcome of this?

Lee *et al.* showed that T2R38 activation does not promote the secretion of cytokines or antimicrobial peptides by HSECs. Instead, stimulation of T2R38 led to nitric oxide (NO) production by cultured taster HSECs. Treatment of HSECs with media from cultures conditioned by *P. aeruginosa* also induced NO production. However, HSECs did not generate NO in response to medium conditioned by a *Pseudomonas* strain that does not produce C4HSL or C12HSL. The authors found that T2R38-induced production of NO promoted the killing of Gram-negative bacteria *in vitro*. In addition, further experiments using *in vitro* systems showed that activation of T2R38 can increase ciliary beat frequency and mucociliary transport velocity. Importantly, all of these innate-type immune responses promote the clearance of bacteria from the upper airways.

To determine the relevance of their findings *in vivo*, the authors assessed the *TAS2R38* genotypes of patients who had undergone sinonasal surgery. They used laboratory results from sinonasal swabs to divide the patients into different groups on the basis of whether or not they tested positive for Gram-negative bacteria. Interestingly, none of the sinonasal swabs from individuals who were homozygous for the functional *TAS2R38* gene tested positive for Gram-negative bacteria. By contrast, almost half of the swabs from patients who possessed one or two non-functional *TAS2R38* alleles tested positive for Gram-negative bacteria.

The authors suggest that the clinical implications of these data are twofold. First, bitter taste responses to PTC could be used to predict whether a more aggressive treatment regimen should be used in patients with rhinosinusitis. Second, the topical application of T2R38 agonists could be used therapeutically in patients with upper airway infections.

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