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Review Article

Taste receptors in the upper airway

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Abstract Taste receptors were named for their originally-identified expression on the tongue and role in the sensation of taste (gustation). They are now known to be involved in many chemosensory processes outside the tongue. Expression of the receptors for bitter, sweet, and umami was recently identified in many organs, including the brain, airway, gastrointestinal tract, and reproductive systems. We do not yet know the full roles of these receptors in all of these tissues, nor do we know all of the endogenous ligands that activate them. However, taste receptors are emerging as potentially important therapeutic targets. Moreover, they may mediate some off target effects of drugs, as many medications in common clinical use are known to be bitter. The focus of this review is on recent basic and clinical data describing the expression of bitter (T2R) and sweet (T1R) receptors in the airway and their activation by secreted bacterial compounds. These receptors play important roles in innate immune nitric oxide production and antimicrobial peptide secretion, and may be useful targets for stimulating immune responses in the upper respiratory tract via topical therapies. Moreover, genetic variation in these receptors may play a role in the differential susceptibility of patients to certain types of respiratory infections as well as to differential outcomes in patients with chronic rhinosinusitis (CRS). CRS is a syndrome of chronic upper respiratory infection and inflammation and has a significant detrimental impact on patient quality of life. CRS treatment accounts for approximately 20% of adult antibiotic prescriptions and is thus a large driver of the public health crisis of antibiotic resistance. Taste receptors represent a novel class of therapeutic target to potentially stimulate endogenous immune responses and treat CRS patients without conventional antibiotics.

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Introduction

Taste receptors were first described as sensory receptors located on the tongue, where they are expressed in taste cells of taste buds. However, bitter and sweet G protein-coupled taste receptors have recently been identified in other tissues ranging from the lungs and gut to the brain.[1–3] The purpose of these seemingly misplaced, so-called "extra-oral" taste receptors was at first baffling, but it now known that taste is only part of the responsibility of these receptors. Bitter and sweet receptors serve more general chemosensory roles in many tissues, making them potential therapeutic targets or possibly important mediators of off-target drug effects,[4] particularly as many medications in clinical use taste bitter.[5–7] G protein-coupled receptor (GPCR) taste receptors have been found in a large variety of extra-oral tissues, including but not limited to the airway, brain, lungs, testes, and colon.[1,8] These extra-oral taste receptors do not mediate "taste" *per se* as they are not linked to neuronal perceptive pathways, but they still serve as local chemoreceptors in the body. The known distribution of bitter and sweet taste receptors varies between organs, with some thought to express only bitter or only sweet receptors, while others express both (Fig. 1). The upper airway (nose and sinuses) has both bitter and sweet receptors in several different cell types that have multiple local effects on innate immunity.

We are only beginning to understand the diverse roles of these receptors. For example, sweet taste receptors in the pancreas and intestine may regulate insulin secretion,[9–12] and glucose transporter expression,[13–15] respectively, in response to glucose levels. Bitter taste receptors in the male reproductive system are important for fertility,[16–18] though the mechanism behind this is unknown. In the airway, both bitter and sweet receptors play a role in the front line of innate defense, alerting cells to harmful pathogens and activating immune responses to remedy the situation, described in more detail below. Because taste receptors have a wide range of genetic polymorphisms that alter receptor functionality and contribute to the complex individual variations in taste preferences,[19] their role in immunity suggests that taste receptor genetics may play a role in susceptibility to respiratory or other infections. This hypothesis has been supported by recent clinical data also described below.

Brief overview of taste receptors

Taste receptors on the tongue alert the brain to the presence of different nutrients, toxins, and other chemicals that contribute to the overall flavor of ingested materials. Flavor is a complex sensation of taste, smell (olfaction), mouth feel (texture), and sometimes pain, as in the case of spicy foods containing capsaicin or allylisothiocyantes that activate pain-sensitive neurons. However, the human tongue can only detect five canonical basic tastes: sweet, bitter, salty, sour, and umami, which is the taste of savory amino acids like L-glutamate.[20] Other tastes may also be detected by the tongue, such as metallic taste[21] or the taste of fat,[22–26] though these have been controversial and hard to study, as high metal salt concentrations can cross-

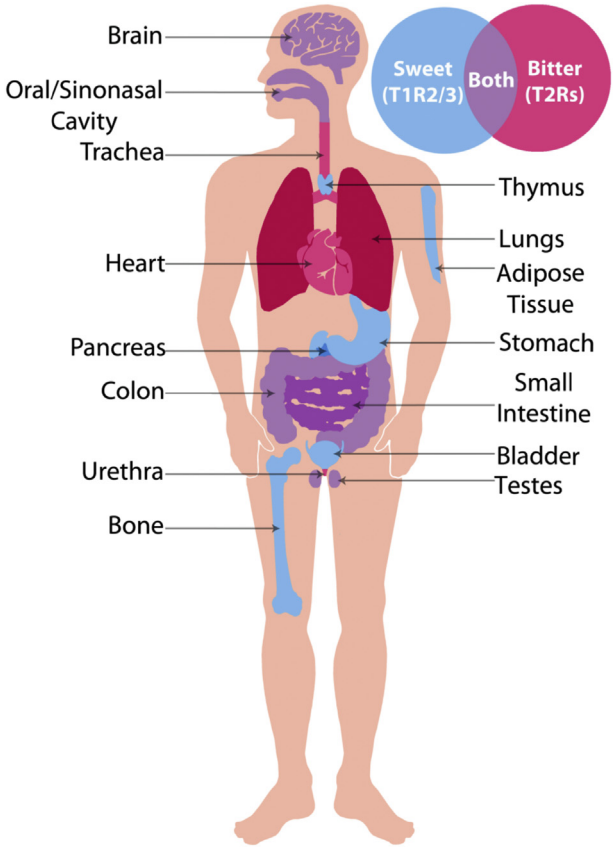

Fig. 1 "Extra-oral" expression of G protein-coupled receptors (GPCRs) involved in bitter, sweet, and umami taste. While named for their originally-identified role on the tongue, taste receptors are have been found in multiple organs and tissues outside of the oral cavity, where they play largely unknown roles in response to largely unknown ligands.[2,3] Red and blue colors indicate organs/tissues where bitter and sweet taste receptors, respectively, have been identified. Purple color indicates organs where both types of receptors have been identified. Bitter taste receptors are generally believed to be primarily composed of homo- or hetero-oligomers of isoforms of the taste receptor 2 (T2R) family. Umami and sweet receptors are made up of oligomers of the taste receptor 1 (T1R) family. T1R1 and T1R3 oligomers form umami receptors, while T1R2 and T1R3 oligomers form sweet receptors.

react with bitter receptors[27] and fat is an important contributor to the mouth feel component of flavor. Receptors that may contribute to fat taste have recently been identified, including GPR40 (also known as FFA1) and GPR120, which can be activated by omega-3 fatty acids.[23,28] If other tastes do exist beyond the classic five tastes above, the purported receptors involved may also serve important extraoral chemosensory roles in other organs.

There are two main classes of taste receptors for the 5 basic tastes in vertebrates: ion channels and G protein-coupled receptors (GPCRs). Ion channels are responsible for salty and sour tastes, mediated by the epithelial sodium channel (ENaC) and acid-sensing ion channel (ASIC) proteins that detect Na^+ and H^+ ions, respectively.[8,29] GPCRs mediate sensation of bitter, sweet, and umami tastes.[30] GPCRs are transmembrane proteins that change conformation when activated by an extracellular ligand, setting off an intracellular signal cascade.[1,3,8,31,32] There are two families of GPCR taste receptors, taste family type 1 (T1R) and taste family type 2 (T2R) receptors.[1,3,8,31,32] The T1R family contains three isoforms, T1R1, T1R2, and T1R3. Sweet is detected by activation of a receptor comprising a heterodimer of T1R2 and T1R3 (T1R2/3), while umami is detected by activation of a receptor composed of T1R1 and T1R3. Some type II taste cells have been reported to express only T1R3 without T1R1 or T1R2[33,34], and T1R3 homodimers may also act as glucose[10,35,36] or calcium/magnesium receptors.[21]

Bitter taste is mediated by T2R receptors (T2Rs).[1,3,8] Humans have 25 different functional T2R isoforms, which may heterodimerize to form even more variants. Bitter taste is thus unique in that many different receptors contributing to bitter recognition, which fits with the hypothesized role of bitter taste being protective against a wide variety of harmful plant poisons,[37] including toxic alkaloids like strychnine.[38,39] On the tongue, bitter (T2R), sweet (T1R2/3), and umami (T1R1/3) receptors are expressed in distinct cells of the taste bud, called type 2 cells. Each taste cell can detect one type of taste, and coupling of that cell to different afferent gustatory neurons dictates how the response is perceived by the brain.[40] By contrast, bitter and sweet receptors are co-expressed together in many extraoral chemosensory cell types, including intestinal tuft cells that regulate anti-parasite immunity[41,42] and solitary chemosensory cells in the mouse and human airway.[3,43–46]

These taste receptors vary in number and functionality between species, shaped by evolutionary pressures.[37,38,47] For example, cats, which are obligate carnivores, do not naturally eat significant amounts of sweet sugars and, over the course of evolution, have lost their functional *TAS1R2* gene for T1R2 and thus the ability to taste sweet.[47] By contrast, herbivores typically have expanded numbers of T2R isoforms to protect against ingestion of toxic plants.[37] Gene deletions, pseudogenizations, and duplications underlie these species-to-species differences. However, even within the same species, taste receptor function varies from individual to individual due to genetic polymorphisms. While only a few of these polymorphisms have well-documented phenotypic effects, hundreds of T2R polymorphisms and several T1R polymorphisms have been noted in humans.[19,48] The most well-known and well-characterized example is the bitter receptor isoform T2R38.

The *TAS2R38* gene encoding T2R38 has two common polymorphisms, one encoding a functional receptor and one encoding a nonfunctional receptor.[49] The differences in the resulting proteins are at amino acid positions 49, 262, and 296. The functional T2R38 receptor contains proline (P), alanine (A), and valine (V) residues while the nonfunctional T2R38 contains alanine (A), valine (V), and isoleucine (I) at these positions, respectively.[49] Loss of the valine at the third position in the AVI variant prevents receptor activation.[50–52] These polymorphisms are distributed in a nearly Mendelian ratio in Caucasian populations. Homozygous AVI/AVI individuals (~30% frequency in Caucasian populations) are "non-tasters" for the T2R38-specific agonists phenylthiocarbamide (PTC; also known as phenylthiourea or PTU) and 6-propyl-2-thiouracil (PROP).[49] PAV/PAV individuals (~20% frequency in Caucasian populations[49]) are termed "super tasters" for these agonists because they perceive them as intensely bitter, while AVI/PAV heterozygotes have varying intermediate levels of taste.[49,53] There are also several rarer haplotypes in other populations, such as the non-functional AAI polymorphism more common in those of African descent.[54] Because T2R38 contributes to detection of isothiocyanate compounds in leafy green vegetables like Brussels sprouts, these polymorphisms can impact individual taste preferences.

As we describe below, these *TAS2R38* polymorphisms also have clinical implications due to the extraoral expression of T2R38. T1R sweet receptor polymorphisms also exist, including a polymorphism resulting in either an isoleucine or valine at position 191. Individuals homozygous for valine 191 may have higher risk of dental caries, higher carbohydrate intake, or hypertriglyceridemia.[55,56] While the effects of some *TAS1R* polymorphisms may be due to dietary changes in sugar ingestion, they may also have some phenotypic effects due to extra-oral roles of T1Rs. Further study of these polymorphisms has become increasingly important in light of the roles of these receptors in innate immunity,[2,3] beta cell function and insulin production,[9,10,12,35,57,58] and even neuronal function[59–62] related to learning and memory.[63]

Bitter taste receptors in airway ciliated cells

In the airway, T2R bitter receptors were first discovered on the ciliated cells lining the bronchial[64] and sinonasal epithelium.[65–67] Ciliated cells are integral to airway defense (Fig. 2). A thin layer of mucus secreted by airway secretory goblet cells and submucosal glands traps inhaled pathogens and particulates. The coordinated and rapid (~8–12 Hz) beating of motile cilia then drives transport of this mucus and trapped pathogens out of the airway to the oropharynx, where it is cleared by expectoration or swallowing.[68–71] It was previously thought that motile cilia (9 + 2 microtubule structure) have only mechanical functions, as in moving airway mucus and in setting left–right asymmetry in the developing embryo,[72] unlike primary cilia (9 + 0 microtubule structure, e.g. in the kidney or in neurons), which function in signal transduction.[73] The expression of

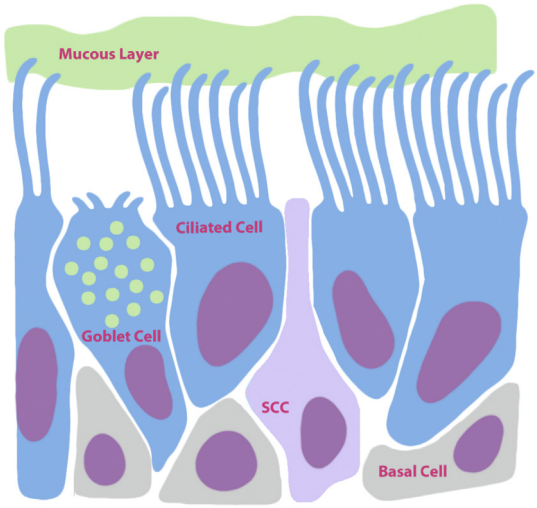

Fig. 2 The upper airway epithelium and innate immunity. Inhaled viruses, bacteria, and fungi are trapped by sticky mucus created by mucin macromolecules secreted by secretory goblet cells and submucosal exocrine glands (not shown). Trapped pathogens are removed from the airway by mucociliary transport, which is driven by ciliary beating.[144] Mucociliary transport also requires proper regulation of ion and fluid transport by epithelial cells regulates the mucus viscosity. In addition to mucociliary transport, direct pathogen killing or inactivation can occur via the secretion of antimicrobial peptides as well as the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). During longer-term exposure to pathogens, epithelial cells can also secrete cytokines to recruit dedicated immune cells and activate inflammatory pathways. Airway epithelial basal cells serve as a local stem cell-like population to regenerate ciliated or basal cells during normal turnover or after epithelial damage. Ciliated cells express bitter taste receptors, while a specialized cells known as solitary chemosensory cells (SCCs) express both bitter and sweet taste receptors, all of which regulate sinonasal immunity, as described in the text.

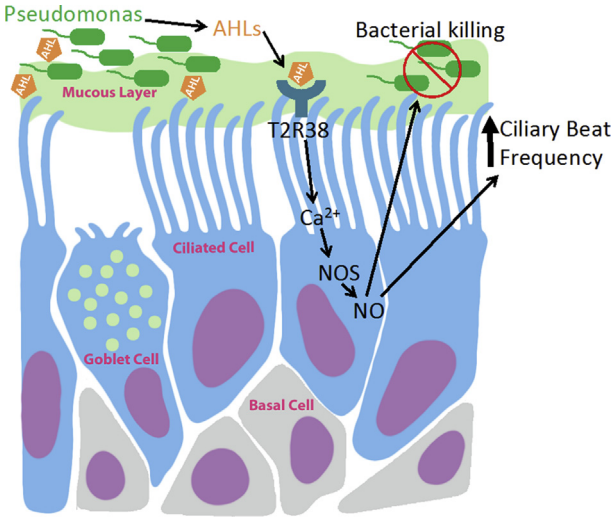

Fig. 3 T2R38 bitter taste receptor regulation of airway epithelial innate immunity. Acyl-homoserine lactone (AHL) molecules secreted by gram-negative bacteria like *Pseudomonas aeruginosa* activate the T2R38 bitter taste receptor expressed in human sinonasal cilia,[67] which causes initiation of a calcium (Ca^{2+}) signal that stimulates nitric oxide synthase (NOS)-dependent nitric oxide (NO) production. The NO has two distinct effects. First, NO activation of guanylylcyclase produces cyclic-GMP to activate protein kinase G (PKG), which phosphorylates ciliary proteins[72,145] to increase ciliary beating and thus mucociliary transport.[65,67] NO also diffuses directly into the airway surface liquid, where it can directly kill bacteria as well as possibly damage viral or fungal pathogens.[67].

chemosensory "taste" receptors in motile cilia showed that, like primary cilia, motile cilia can also play a role in cell chemosensation.

We found several T2R isoforms, T2R4, T2R16, T2R14, and T2R38, in sinonasal ciliated cells.[67,74,75] Stimulation of these receptors by known bitter compounds activates calcium-dependent nitric oxide (NO) production that increases phosphorylation of ciliary proteins through protein kinase G (PKG). This increases ciliary beat frequency to facilitate the movement mucus out of the airway by increasing mucociliary transport rates. The generated NO also diffuses into the airway surface liquid (ASL) and acts as an antibacterial defense mechanism. NO damages bacterial cell walls and DNA and may also damage fungal pathogens and inactivate viral proteins.[67,75–80]

We found that the T2R38 isoform in airway cilia is activated by acyl-homoserine lactone quorum-sensing molecules (Fig. 3),[67] which are secreted by nearly every species of gram-negative bacteria.[81] Activation of T2R38 by bacterial AHLs in primary sinonasal epithelial cells *in vitro* causes NO production that can directly kill the opportunistic respiratory pathogen *Pseudomonas aeruginosa*.[67] This suggests that cilia T2Rs contribute to immune detection of bacterial invaders similarly to classic immune pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), that are also expressed in the airways. PRRs detect conserved bacterial, viral, and/or fungal products known as pathogen-associated molecular patterns (PAMPs),[82] such as viral nucleic acids or bacterial surface glycoproteins. Activation of TLRs up-regulates mRNA for proteins involved in sustained antimicrobial responses, like the defensin family of antimicrobial peptides. These TLR responses typically occur over the course of hours.[70,83] However, the NO responses activated by T2Rs are much faster, occurring within seconds. Thus, we hypothesize that T2Rs represent a fast arm of innate immunity, while other PRRs activate complementary longer-term responses.

Clinical data suggest these rapid T2R responses may be important in chronic rhinosinusitis (CRS), a syndrome of chronic upper respiratory inflammation and/or infection.[84] CRS leads to substantial decreases in patient quality of life, creates >$8 billion in direct healthcare costs in the US alone, and can seed lower respiratory infections and exacerbate lung diseases.[31,70,84] CRS also impacts public health, as it accounts for ~20% of antibiotic prescriptions in adults in the US,[84–89] making it a significant driver for the emergence of antibiotic resistant organisms.[90–96] While multiple etiologies contribute to CRS pathogenesis, a common CRS hallmark is defective mucociliary clearance,[70,84] possibly through alterations of basal[97,98] or

stimulated[99] ciliary beat frequency. We found that sinonasal ciliated cells from patients homozygous for the AVI polymorphism in the *TAS2R38* gene resulting in a nonfunctional T2R38 receptor (described above) have decreased NO and ciliary beat frequency responses to bacterial AHLs *in vitro*. Clinical studies subsequently revealed that *TAS2R38* AVI/AVI homozygous patients are more susceptible to gram-negative bacterial infection,[67] have a higher prevalence of biofilm-forming sinonasal bacteria,[100] and are at greater risk for CRS requiring functional endoscopic sinus surgery (FESS).[101,102] AVI/AVI patients may have worse outcomes after FESS for CRS without nasal polyps compared with patients homozygous for the functional (PAV) allele of *TAS2R38*.[103]

The full picture of T2R38's role in sinonasal immunity in different patient populations is still being elucidated. While one subsequent study found no correlation of *TAS2R38* genotype with CRS in Italian patients,[104] this population had different clinical characteristics (e.g. more recalcitrant disease and stronger Th2 inflammatory phenotype) than other studies. A more recent study supported a correlation between *TAS2R38* AVI or PAV status and CRS severity in Poland.[105] An Australian study concluded that AVI/AVI *TAS2R38* genotype is predictive of the presence of culture-positive bacteria in CRS patients.[106] Moreover, others have reported that T2R10 and T2R14 also respond to some bacterial AHLs when expressed in HEK293 cells,[38] and yet other studies have suggested that T2R38 is important for immune cell detection of AHLs.[107,108] A genome-wide association study demonstrated that polymorphisms in at least two *TAS2R* genes, *TAS2R38* and *TAS2R13*, correlate with CRS.[109]

Multiple T2Rs likely serve an immune sentinel role in the upper airway and beyond, and it is likely that certain T2Rs can detect other bacterial products beyond AHLs. Future work on determining the full range of T2Rs endogenously expressed by airway cells may reveal useful therapeutic compounds to target these receptors to stimulate endogenous innate immune responses in the absence of antibiotics. Larger scale clinical studies will likewise reveal the contribution of the genetics of these receptors to outcomes and disease risk in different CRS patient populations. Another intriguing implication of these data are that oral taste tests targeting certain T2R receptors may be useful for predicting susceptibility to certain infections, an idea already supported by preliminary studies.[110]

Bitter and sweet taste receptors in sinonasal solitary chemosensory cells

Solitary chemosensory cells (SCCs) are individual specialized cells in the sinonasal epithelium with an elongated morphology that express chemosensory signal transduction components, including T1R sweet and T2R bitter receptors.[2,3,44–46,111] In mice, SCCs make up approximately 1% of the nasal surface epithelial cells, and activation of T2Rs in nasal SCCs with bitter compounds can activate trigeminal afferent nerves resulting in reflexive breath holding[44] and neurogenic inflammation.[112] SCCs exist in the human sinonasal cavity in the inferior and middle turbinates, septum, and uncinate process.[43,113] In contrast to mice, activation of T2Rs in human SCCs results in immediate secretion of β-defensin 1 and 2 from surrounding epithelial cells (Fig. 4) in an *in vitro* culture model.[45,46] Defensins are antimicrobial peptides effective against both gram-positive and gram-negative bacteria, and thus SCC T2R activation is likely a defensive immune response. As the T2Rs expressed in SCCs (T2R10, 46, and 47) are different from those expressed in ciliated cells (T2R4, 14, 16, and 38), it remains to be determined what pathogen products might activate SCC T2Rs.

Intriguingly, T1R2/3 sweet taste receptors are co-expressed with T2Rs in the same SCCs, and can be activated by artificial sweeteners or by physiological concentrations of glucose found in ASL from tonic epithelial glucose leak from serosal fluid. ASL glucose is ~0.5 mmol/L in healthy patients, or approximately 10-fold below resting serum values. Activation of SCC T1R2/3 by 0.5–1.0 mmol/L glucose attenuates signaling of the T2Rs within the same SCC, reducing antimicrobial peptide release.[45,46]

This may be a method of preventing "false alarms" of bacterial infection. In a true instance of infection, a decrease in sugar concentrations on the airway surface due to bacterial glucose metabolism is expected.[114–117] T1Rs in the airway are tuned to sugar concentrations physiologically relevant to healthy levels in the airway surface liquid. The presence of bacterial SCC T2R ligands in the ASL

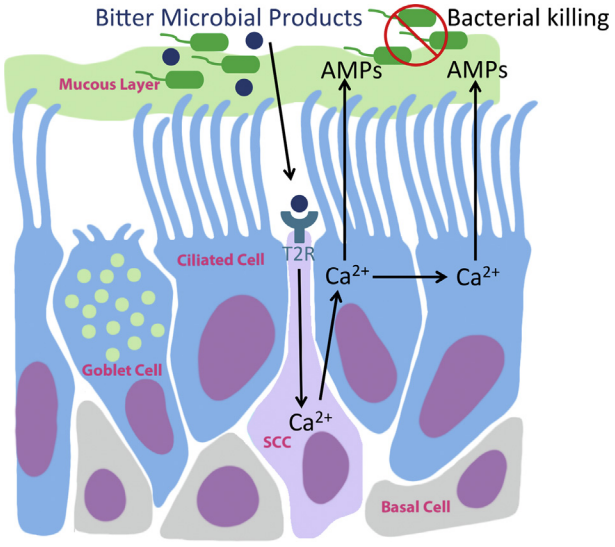

Fig. 4 Nasal solitary chemosensory cells (SCCs) in airway innate immunity. Bitter chemicals secreted by microbes during infection may activate T2R bitter receptors expressed in solitary chemosensory cells (SCCs), producing a calcium (Ca^{2+}) response that propagates to surrounding epithelial cells via gap junctions.[46] This causes the surrounding cells to rapidly (within ~5 min) secrete antimicrobial peptides (AMPs), including β-defensins, which directly kills both gram-positive and gram-negative bacteria. Distinct sets of taste receptors in ciliated cells (T2Rs 4, 14, 16, 38) and SCCs (T2Rs 10, 46, 47) respond to different bitter agonists and likely allow differential activation of these two distinct responses depending on the nature of the infecting organisms and which bitter metabolites are produced.

without a concomitant decrease in glucose may prevent rampant killing of commensal bacteria under normal conditions until a drop in airway glucose levels signals too much bacteria growth.

However, this mechanism may adversely contribute to airway disease in both CRS and diabetes. Higher concentrations of ASL glucose than normal (≥3—4 fold) are observed in patients with elevated serum glucose levels due to diabetes[114—117] as well as in CRS patients, who have decreased epithelial barrier function due to inflammation.[46,118] We hypothesize that the topical use of a T1R2/3 antagonist, such the compound lactisole purified from coffee beans,[119] could dampen the T1R response to elevated glucose and restore proper T2R immune responses in some patients.

It was also recently observed that T1R2/3 in human sinonasal SCCs can also be activated by certain bacterial D-amino acids. Some D stereo-isomer forms of amino acids (e.g. D-Phe, D-Trp, D-Leu) are known to taste sweet through activation of T1R2/3 on the tongue.[120] Others have shown that bacteria secrete various D-amino acids that may be important for cell-to-cell communication.[121] We found that both *Staphylococcus aureus* and coagulase-negative *Staphylococcus* (likely *Staphylococcus epidermidis*) cultures isolated from sinonasal cavities of CRS patients produced D-Phe and D-Leu. D-Phe and D-Leu were produced at levels sufficient to activate T1R2/3 and repress T2R-mediated SCC responses and airway epithelial defense in an *in vitro* culture model.[45] It remains to be determined whether this interkingdom T1R2/3 signaling exists to allow infecting *Staphylococcus* to evade immune detection or if this is a mechanism for epithelial cells to recognize and not eradicate commensal *Staphylococcus*.

Conclusions

Host-pathogen interactions and the determination of pathogenic vs commensal bacteria are paramount to maintaining host immunity. Taste receptors may be involved in this process through detection of various bitter and sweet bacterial metabolites. However some patients are thought to be born with a hampered line of innate defense. Many studies have suggested a genetic component to human infection[122,123] and infectious diseases, including CRS.[124—126] As mentioned earlier, taste receptors have many common polymorphisms that can render specific receptors unable or less able to detect cognate agonists, which may include secreted pathogen metabolites, as in the case of AHL activation of T2R38. Thus, the genetics of taste receptors may play an important but previously unrecognized role in susceptibility to infection.

It also possible that medicine has unknowingly taken advantage of extra-oral bitter taste receptors for centuries. A common Chinese proverb roughly states "a good medicine tastes bitter." Many herbal remedies and modern medicinal compounds activate T2R receptors and taste bitter.[6,7,75,127] Perhaps some of these medicines work in part by stimulating host immunity or other responses though extraoral T2Rs. Beyond the role in immunity described above, bitter and sweet taste receptors regulate cellular metabolism,[128,129] absorption of nutrients in the GI tract,[13,15,130—138] fertility,[17] muscle relaxation,[139—142] hormone secretion,[9,10,12,14,35,143] and likely many other physiological processes. More research is necessary to uncover the roles that taste receptors play in the human body and discover how their genetic polymorphisms may affect these functions and contribute to disease.

Acknowledgments

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