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BASIC AND APPLIED SCIENCE (I LEWKOWICH, SECTION EDITOR)

# Bitter Taste Receptors: an Answer to Comprehensive Asthma Control?

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## Abstract

**Purpose of Review** Asthma is marked by peculiar pathological features involving airway contraction, an impinging inflammation in the lungs, and an inexorably progressive remodeling of pulmonary architecture. Current medications for management of asthma exacerbations fail to optimally mitigate these pathologies, which is partly due to the intrinsic heterogeneity in the development and progression of asthma within different populations. In recent years, the discovery of the ectopic expression of TAS2Rs in extraoral tissues and different cell types, combined with significant strides in gaining mechanistic understanding into receptor signaling and function, has revealed the potential to target TAS2Rs for asthma relief.

**Recent Findings** TAS2R activation leads to relaxation of airway smooth muscle cells and bronchodilation. In addition, findings from preclinical studies in murine model of asthma suggest that TAS2R agonists inhibit allergen-induced airway inflammation, remodeling, and hyperresponsiveness.

**Summary** In this review, we expand on the opportunity presented by TAS2Rs in the development of a comprehensive asthma treatment that overcomes the limitations set forth by current asthma therapeutics.

**Keywords** Asthma · TAS2R · Bitter tastant · Airway smooth muscle · SCC

## Introduction

In higher vertebrates, chemoperception of distinct edible molecules is an evolutionarily preserved mechanism to provide dietary advantage for sensing potentially harmful or corrupted food. The primary site for avoidance of toxic foods is in the oral cavity and is achieved by the recognition of harmful compounds that are presumably often bitter tasting in nature. This function is imparted by the bitter taste receptors (belonging to type II taste receptors, TAS2R), which are a family of the seven transmembrane G protein–coupled receptors (GPCRs) expressed on the taste buds on the tongue [1]. Chemoperception of bitter taste is initiated by interaction of a specific taste stimulus with the highly specialized TAS2R on cells on the tongue and subsequent transmission of purinergic signals to the brain through various cranial nerves [2, 3]. A physical consequence of activation of this arc is the rejection of the contaminated food. Similarly, the gastrointestinal (GI) system, through an elaborate system (reviewed in detail elsewhere [4–6]) can detect toxic chemicals or various infectious agents present in contaminated food and stimulate an autonomous defense reaction or emesis reflex to reject contaminated/harmful foods [7]. It is now understood that the specialized chemosensory cells in the gastric system ectopically express TAS2Rs that could contribute to this innate host defense mechanism [7, 8••]. Several lines of evidence suggest that TAS2Rs are expressed on a variety of cell types (Table 1) outside of the gustatory organs and play an important role in the regulation of physiological functions such as immune response, contraction/relaxation of smooth muscle, and mucus production. In this report, we will review the essentiality of TAS2Rs to airway biology in the context of obstructive lung diseases such as asthma and highlight the growing evidence for their development for asthma therapy.

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## Pathogenesis of Asthma

Asthma is a disease that afflicts more than 300 million individuals worldwide [9]. The disease pathology is marked with

**Table 1** TAS2Rs expressed on a variety of cell types

| Cell type | Expressed Tas2R receptor subtypes |
|---|---|
| Tuft cells | *Tas2R108*, *Tas2R110*, *Tas2R117*, *Tas2R122*, *Tas2R130*, *Tas2R136*, *Tas2R143* |
| Ciliated epithelial cells | *Tas2R4*, *Tas2R43*, *Tas2R38*, *Tas2R46* |
| Solitary chemosensory cells | *Tas2R8*, *Tas2R19* |
| Tracheal brush cells | *Tas2R105*, *Tas2R108* |
| Neutrophils, monocytes, eosinophils | *Tas2R38* |
| Mast cells | *Tas2R4*, *Tas2R46*, *Tas2R14* |
| Lymphocytes | *Tas2R4*, *Tas2R10*, *Tas2R14*, *Tas2R38* |

excessive airway hyperresponsiveness, inflammation, and a seemingly irreversible and progressive remodeling of the airway compartments (Fig. 1). These individual pathologies work in an integrated manner and form an interacting network that drives asthma disease. A major challenge in therapeutic management of asthma is the considerable heterogeneity in the development and progression of the associated pathologies [10–12]. Further, while the current gold standards of asthma care including long-acting beta-agonists (LABAs; agonists of the $\beta_2$ adrenergic receptor ($\beta_2$AR)) and corticosteroids can mitigate airway hyperresponsiveness and inflammation in many asthmatics, ~ 50% of asthmatics are estimated to receive suboptimal care for their symptoms and exacerbations [13–15]. This is in part because of lack of effect of these drugs on multiple features of asthma. Finally, concerns remain regarding the long-term efficacy and safety of LABAs [16]. Thus, identification of novel and clinically efficacious targets is necessary to address this unmet clinical need. More recently, using a combination of *in vitro*, *ex vivo*, and *in vivo* approaches, agonists of TAS2Rs have been shown to (a) stimulate ASM relaxation [17••], (b) inhibit ASM proliferation [18, 19], and (c) mitigate multiple features of allergen-induced asthma in preclinical models [20••] (Fig. 1). Herein, we will detail how targeting TAS2Rs in the lung may provide multimodal control of various asthma-associated pathologies.

## AHR, AR, and Inflammation—Breaking the Axis

As discussed earlier, airway hyperresponsiveness (AHR), airway remodeling (AR), and airway inflammation work in concert to progressively drive asthma pathology. Airway inflammation is accompanied by infiltration of activated immune cells into the peribronchial regions of the lungs and within the airways. These immune cells may release Th2 and other inflammatory cytokines (IL-13, TNF-α), chemokines, and mitogens that act on epithelial cells and ASM cells [21–24]. Another feature of asthma is the excessive mucus accumulation in the airways, which can influence optimal airflow. Epithelial cells may be stimulated by noxious agents (including allergens) and immune cells to secrete excessive mucus that may physically block the airway lumen. This feature is more common in fatal asthma cases but has been observed in individuals within the mild-moderate asthma spectrum [25, 26]. Further, epithelial cells may release growth factors that

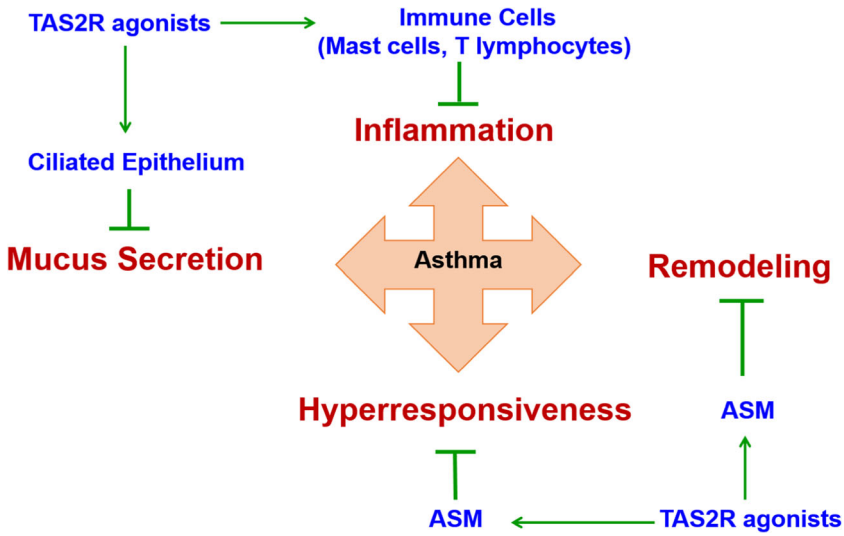


**Fig. 1** Multimodal action of TAS2Rs for controlling asthma symptoms. Asthma is marked by distinct yet interlinked pathologies such as airway inflammation, hyperresponsiveness, remodeling and excessive mucus secretion. Owing to their expression and their ability to regulate physiological outcomes in various cell types important to asthma pathology, TAS2Rs have emerged as a promising candidate for the development of comprehensive anti-asthma therapy

may stimulate proliferation of ASM thus driving AR [21]. Extensive investigations have demonstrated that the mesenchymal cells including ASM cells secrete inflammatory mediators and function as immunomodulatory cells in asthma [27, 28]. Chemokines such as RANTES, IL-8, and others provide impetus for immune cell migration, proliferation, and maturation in the lungs. Of note, in asthmatics, mast cells have been shown to localize to the airway smooth muscle regions of the lung and contribute to airway dysfunction [29]. These cross talks among immune and mesenchymal cells provide a perpetual trigger for asthma pathology to persist. Secretory products from immune cells and resident airway cells not only include cytokines and chemokines but also contain a number of molecules (e.g., histamine, leukotrienes) that are agonists of GPCRs and activate a variety of signaling in airway cells. The inflammatory milieu in airways may also render the ASM tissue increasingly sensitive to cholinergic stimulation and consequently drive an enhanced contractile response. This process may be further exacerbated by the infiltrating immune cells and their mediators acting directly on ASM cells. Collectively, this multicellular process progressively worsens the airway function in asthmatics and clinically manifests as bronchoconstriction and difficulty in breathing.

**a) Airway hyperresponsiveness (AHR):** AHR is defined as the enhanced contractile sensitivity of the ASM, the central effector cell type in the maintenance of airway tone [30–32]. A major outcome of this increased sensitivity to contractile stimulus results in rapid narrowing of the airway lumen following exacerbation, which is a hallmark feature of asthma pathology. The immediate goal of asthma therapy is to reverse this airway constriction either by bronchodilation or by antagonizing bronchoconstriction. GPCRs are promising targets in achieving this goal by virtue of their predominant role in regulating ASM contraction and airway tone [33–35].

Almost a decade ago, our group published the seminal paper describing the ectopic distribution of TAS2Rs in ASM cells and established the essentiality of targeting these receptors to stimulate ASM relaxation and bronchodilation [17••]. Most interestingly, the studies demonstrated that TAS2Rs mediate ASM relaxation through a mechanism distinct from the typical GPCRs involving the heterotrimeric Gs protein subunit. Specifically, stimulation of TAS2Rs stimulates increase in intracellular $Ca^{2+}$, similar to that observed in taste cells, which is the canonical site for expression of TAS2Rs. In contrast to taste cells where this $Ca^{2+}$ elevation culminates in bitter taste perception [36, 37], in ASM cells, stimulation of TAS2Rs results in relaxation. The role and precise mechanism (discussed in sections below) by which calcium elevation upon stimulation of ASM cells with TAS2R agonists contributes to airway relaxation is an active area of investigation and is dictated by whether the ASM cells are stimulated with bitter tastants alone or in combination with other contractile agonists. Spatiotemporal aspects of calcium signaling by TAS2Rs and cross talk between TAS2R and contractile Gq-coupled GPCR signaling are complex and need additional investigation. However, since these initial studies, the ability of TAS2Rs to relax ASM has been unequivocally established in distinct species [17••, 38–40]. Consequently, bitter tastants have emerged as novel bronchodilators. TAS2R-mediated relaxation of ASM is additive to beta agonist–induced relaxation suggesting that bitter tastants could be used as adjunct therapy to standard beta agonist treatment. Aerosol exposure of airways to TAS2R agonists results in bronchodilation in normal and allergen-sensitized and challenged mice. A study by Robinett et al., using asthmatic ASM cells and human lung slices, demonstrated that TAS2R expression and signaling, and ASM relaxation and bronchodilatory effects are not altered under airway inflammatory conditions [41]. Interestingly, TAS2R-mediated ASM relaxation is unaffected despite tachyphylaxis of $\beta_2$AR-mediated ASM relaxation due to chronic agonist treatment suggesting that in the conditions where asthmatics are refractory to beta agonist treatment, TAS2R agonists can be useful for stimulating bronchodilation. Further, ASM cells express multiple subtypes of TAS2Rs (at least 3–4 of them at a level higher than $\beta_2$AR), all of which are known to relax ASM. This presents an opportunity to explore multiple subtypes of TAS2R either singularly or in combination for drug development (as opposed to the $\beta_2$AR, which has only one subtype). Finally, in preclinical models of allergen-induced asthma (house dust mite and ovalbumin), mice treated with TAS2R agonists significantly inhibit the development of AHR [20••]. Thus, TAS2Rs based on their ability to relax ASM are a novel target for direct bronchodilation.

TAS2Rs belong to the superfamily of class A GPCRs (rhodopsin-like receptors) which is the largest group of GPCRs. Other class A GPCRs include the well-described $\beta_2$ adrenergic receptor, muscarinic receptors, and cysteinyl leukotriene receptors. There are 25 distinct TAS2R subtypes expressed in humans (35 in mice) that demonstrate significant overlap in ligand binding [42, 43]. The nuances in signaling differences between TAS2R subtypes, if any, are unclear due to (1) lack of receptor subtype–specific ligands and (2) expression of multiple TAS2R subtypes on an individual cell. While activation of class A GPCRs typically results in coupling to heterotrimeric G proteins (Gs, Gq, or Gi) and activation or inhibition of second messengers (cAMP or $Ca^{2+}$), ligand binding to TAS2Rs results in signaling mediated via heterotrimeric G protein gustducin. However, the role of gustducin as a G protein in TAS2R signaling in non-gustatory cells such as airway cells is not clear. A recent study established that G proteins Gαi1, Gαi2, and Gαi3 are involved in TAS2R-mediated signaling in ASM cells [44]. It is worth noting that gustducin has a very high amino acid homology with other Gi family G proteins. Interestingly, βγ subunit of the

heterotrimeric G protein mediates signaling downstream of G proteins upon activation of TAS2Rs in both taste and non-gustatory cells [17••, 45]. In other class A GPCRs, the primary signaling is mediated via α subunit of heterotrimeric G protein. However, TAS2Rs differ from the prototypical Gq-coupled GPCRs in the physiologically distinct outcomes following receptor activation in non-gustatory cells.

The intracellular signaling and mechanism(s) by which bitter tastants induce ASM relaxation are an active area of investigation. Three different mechanisms have been proposed from studies published so far. First, initial rise in intracellular $Ca^{2+}$ levels by bitter tastants leads to activation of large conductance potassium channels ($BK_{Ca}$) opening of which leads to membrane hyperpolarization and ASM relaxation [17••]. Second, activation of TAS2R with its cognate ligand leads to separation of βγ subunit of the heterotrimeric G protein of TAS2R that binds and inhibits voltage-dependent $Ca^{2+}$ channel (VDCC) activity, thereby attenuate intracellular $Ca^{2+}$ flux by contractile agonists that is needed for sustained contraction of ASM [45]. Third, activation of TAS2Rs by agonists leads to inhibition of $Ca^{2+}$ release from $IP_3R$ induced by contractile agonists thereby inhibiting $Ca^{2+}$ elevation and contraction [46]. Collectively, these findings suggest that TAS2R agonists use multiple mechanisms to inhibit airway tone.

**b) Airway remodeling (AR):** AR is the progressive alterations in lung architecture that can severely constrain airflow (both fixed and dynamic airway resistance) in asthmatics. Multiple cell types including epithelial cells and ASM can contribute towards the development and maintenance of AR [31, 32, 47]. Most importantly, no medications are currently available that specifically address this pathophysiological feature of asthma, thus underscoring a critical unmet clinical need [47, 48].

One important feature of AR is increased proliferation of ASM cells and accumulation of smooth muscle mass around the airways. GPCR agonists, cytokines, chemokines, and growth factors released in the airways due to allergen-induced airway inflammation can collectively induce ASM cell proliferation [32, 47, 49]. Our studies using primary human (normal and asthmatic) ASM cells in culture determined the effect of three different TAS2R agonists namely, chloroquine, quinine, and saccharine on PDGF-, EGF-, and FBS-induced growth [19]. The findings establish the concentration-dependent anti-mitogenic effect of TAS2R agonists on ASM. Further, our findings demonstrate that TAS2R agonists inhibit cell cycle progression by inhibiting PI3 kinase–mediated pro-mitogenic signaling in ASM cells [19]. A recent study similarly demonstrated the anti-mitogenic effect of bitter tastants on human ASM cells. The specificity of TAS2R in mitigating ASM proliferation was confirmed by using siRNA-mediated downregulation of different subtypes of TAS2R in human ASM cells [50]. In addition, we also established the role of autophagy in TAS2R agonists–mediated inhibition of ASM cell growth [18]. Our findings demonstrate that TAS2R agonists, chloroquine and quinine, modulate mitochondrial structure and function resulting in excessive autophagy and ASM cell death. Furthermore, Bnip3 (a member of the apoptotic Bcl-2 family of proteins) plays a central role in TAS2R agonist–induced ASM functional changes via a mitochondrial pathway. These findings are significant as the current anti-asthma drugs do not effectively mitigate features of AR and particularly do not inhibit ASM proliferation effectively [48]. TAS2R agonists may provide an opportunity to explore a therapeutic target that can effectively mitigate ASM remodeling as well as induce efficacious bronchodilation.

**c) Airway inflammation:** Immune cells play a central role in orchestrating the inflammatory response in the lungs and collectively their function/dysfunction impacts the disease outcome [51]. Inhaled corticosteroids have been particularly helpful in limiting airway inflammation and are the first line of treatment to this pathology in asthma, although a small population of asthmatics develop resistance to this therapy [52–54]. More recently, anti-cytokine monoclonal antibody (biologics)–based therapies have gained significant interest owing to their efficacy in limiting recruitment of inflammatory cells such as eosinophils into the airways [55–57].

Recent studies have indicated ectopic expression of TAS2Rs in distinct cell types (myeloid and mesenchymal origin) in the airways [17••, 58, 59••]. TAS2Rs have been shown to regulate immune function in airways in response to inhaled allergens, and microbial or toxic exposures. In vertebrates, activation of TAS2Rs in airways can stimulate immune and non-immune cells to produce a variety of anti-microbial products such as defensins, reactive oxygen species (ROS), nitric oxide (NO) [60], and increased ciliary beat frequency to clear mucus entrapped foreign material [1].

## Epithelial TAS2Rs in Immunity: Tuft Cells and Solitary Chemosensory Cells

Along with immune cells, epithelial cells can also contribute actively to the development and exacerbation of asthma [61]. In vertebrate airways, members of the TAS2R family are expressed (along with the essential components for signaling) by multiple epithelial cell types in the upper respiratory and lower respiratory tracts [1, 62–65]. However, this distribution pattern is not diffusive and is restricted to specialized regions.

**Tuft Cells** TAS2Rs can function as pattern recognition receptors (PRRs) and are activated by binding of microbial N-acyl L-homoserine lactones (AHLs) and are suggested to regulate

type I and type II immune responses [20••, 59••, 66••, 67]. The role of TAS2Rs in the regulation of Th2 immune response is evident in intestinal tract, wherein innate immune response is mediated by a type of sparsely populated cell with a "tuft" (tuft cell or brush cell) of apically located microvilli. The intestinal tuft cell expresses multiple subtypes of bitter taste receptors on its surface and the expression of these receptors can be altered under pathological conditions. In a murine model of helminth (*Trichinella spiralis*) infection, genes for multiple TAS2R genes (*Tas2r108*, *Tas2r110*, *Tas2r117*, *Tas2r122*, *Tas2r130*, *Tas2r136*, and *Tas2r143*) are upregulated in tuft cells [8••]. Metabolic products from *T. spiralis* can stimulate T2R143 on tuft cells and stimulate intracellular $Ca^{2+}$ mobilization. The physiological consequence of this increase in intracellular $Ca^{2+}$ results in the secretion of the cytokine IL-25 and the upregulation of goblet cell and tuft cell markers. The subsequent expansion of tuft cells results in a "weep and sweep" response where a type 2 response generated by mucus-producing cells results in secretion of excess mucus and synchronized movement of tuft cells to push the invader to be expelled from the GI tract. In the context of airway diseases such as asthma, the ability to expel harmful inhaled agents such as allergens and microbes could protect the lung from inflammatory conditions. However, additional studies are needed to establish this phenomenon using animal models. Since endogenous ligands of TAS2Rs are largely unknown, it is postulated that these receptors have evolutionarily developed as part of broader host defense mechanism for expulsion of harmful compounds from human body.

**Solitary Chemosensory Cells** Solitary chemosensory cells (SCCs) are a highly specialized epithelial cell type that are present in very small numbers in the airways yet are capable of functioning as a focal point in airways for engagement of antimicrobial action [1]. Similar to the SCCs in the nasal cavity and vomeronasal organ, SCCs within the trachea are also receptive to bitter taste compounds. SCCs share many morphological and chemoperceptive biochemical features with oral taste cells. These cells are in close proximity to the parasympathetic innervations that connect to the trigeminal nerve [1, 58, 63]. SCCs express transcripts for multiple TAS2Rs [63], and multiple studies have shown that SCCs are able to regulate the respiratory rate by releasing acetylcholine and influencing nerves in proximity [58, 68, 69]. This results in a neurogenic inflammation and depression of respiration rate, which in turn limits inhalation of foreign material including potential allergens such as molds. In addition to these cells, other epithelial cell types have been shown to express TAS2Rs. Specifically, cholinergic brush cells (BCs) in the trachea are similar to SCCs in their distribution frequency and chemoperceptive abilities [58, 64, 68]. In summation, epithelial cells that express TAS2Rs and exert chemoperception-based anti-microbial actions are strategically placed in airways to counter toxic foreign insults. However, very little is understood about these cell types in the context of asthma. Indeed, allergenic molds such as *Aspergillus* and *Alternaria* may produce secondary metabolites that could potentially activate TAS2Rs on epithelial cells resulting in their subsequent removal from airways. This protective effect imparted by TAS2Rs could particularly benefit a subset of severe asthmatics in whom fungal allergens are common drivers of exacerbation (severe asthmatics with fungal sensitization) [70]. However, the therapeutic potential of targeting TAS2Rs to improve outcomes in this niche group of asthmatics needs systematic investigation.

## TAS2Rs on Immune Cells

**Macrophages** TAS2Rs have been reported in tissue resident macrophages and infiltrating immune cells such as monocytes and neutrophils [67, 71]. These cells are essential in maintaining tissue homeostasis and are typically the first responders to a foreign insult. Agonists of TAS2Rs have been shown to inhibit release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in LPS-induced inflammation models using tissue macrophages, macrophage cell lines, circulating myeloid progenitor cells, and in monocyte-derived macrophages and dendritic cells in vitro and in vivo [72–77]. Consistent with the ability of TAS2R agonists to promote anti-inflammatory responses, stimulation of J774 macrophage cell line with LPS in presence of bitter compounds resulted in significant reduction in activation of LPS-induced iNOS (inducible nitric oxide synthase) and $NO_2^-$ generation [73]. Recent studies have provided some mechanistic insights into how TAS2Rs promote anti-inflammatory actions. Schierbeck and colleagues have shown that bitter taste receptor agonists such as chloroquine may exert anti-inflammatory actions on monocytes (stimulated with LPS/IFN-γ) by inhibiting the release of HMBG1 (high mobility group protein B1) [75]. HMBG1 is a multifunctional redox sensor and mediator of inflammatory responses, which acts as a damage-associated molecular pattern (DAMP) and is actively secreted during inflammation as a cytokine. Elsewhere, it has been shown that TAS2R agonists such as the macrolide antibiotic azithromycin can promote a phenotypic shift in macrophages from an M1 (classical, pro-inflammatory) to M2 (alternative, anti-inflammatory/reparative) phenotype [77].

**Granulocytes** In addition to mononuclear cells, TAS2Rs are expressed in mast cells, neutrophils, and eosinophils [20••, 66••]. Mast cells are critical mediators of type II immune responses that are activated on IgE binding to the cognate high affinity FcεRI expressed on mast cell surface, and the activation of mast cells is marked by a degranulation response releasing inflammatory mediators. This response is crucial for innate defense against parasitic pathogens such as helminths. Multiple TAS2R subtypes such as TA2R4, TAS2R46, and TAS2R14 have been reported on mast cells [66••].

Stimulation of activated human mast cells with TAS2R agonists has been shown to regulate release of pro-inflammatory mediators such as histamine and eicosanoids. This is particularly important, since mast cells are often recruited into ASM regions in asthmatics wherein they exert stimulation of contractile responses [29, 78, 79]. Studies in our lab have shown that stimulation of TAS2Rs can inhibit migration of neutrophils *in vitro* [20••]. Whether this mechanism results in inhibition of migration of eosinophils and mast cells to the asthmatic lungs remains to be objectively evaluated.

TAS2R expression has also been reported in circulating leukocytes from severe asthmatics [59••]. The expression of multiple TAS2R subtypes including TAS2R4, TAS2R10, and TAS2R14 is relatively higher in isolated lymphocytes compared with other immune cell populations [59••]. Elsewhere, it has been reported that TAS2R38 expression is significantly higher especially in activated or memory $CD4^+$ T cell lymphocytes (relative to naïve populations) [80]. The clinical significance of increased expression of TAS2R subtypes in lymphocytes and its correlation with disease severity needs additional investigation.

### TAS2Rs in Ciliary Functions

TAS2Rs on ciliated epithelial cells (CECs) and solitary chemosensory cells (SCCs) have been extensively studied for their role in recognizing inhaled toxins and microbial (bacterial and fungal) acyl-homoserine lactones (AHLs) that serve as ligands for this family of receptors. Ciliated epithelial cells express motile cilia that sense presence of foreign particles such as bacteria and allergenic molds in the respiratory tract and mediate their removal via mucociliary clearance. CECs express a variety of receptors for bitter compounds including TAS2R4, TAS2R43, TAS2R38, and TAS2R46 [62]. Interestingly, these receptors have been shown to localize to specific locations within the cilia as well as the apical surface on CECs [81]. In CECs, the activation of TAS2Rs culminates in increased ciliary beat frequency, which likely enhances mucociliary clearance [1, 62]. In addition to regulating ciliary function, stimulation of TAS2Rs on CECs can also release anti-microbial agents directly into the airway surface liquid. The activation of TRPM5 from the sudden increase in $[Ca^{2+}]_i$ activates nitric oxide synthase and subsequently, production of anti-microbial nitric oxide [60].

Collectively, we now understand that TAS2Rs are differentially expressed in distinct immune cell types and their respective activation states. Further, their expression and function are altered with underlying disease states. Although stimulation of TAS2Rs on leukocytes broadly promotes immune tolerance and inhibition of inflammatory networks induced by microbial products and allergens, more studies are needed to understand the clinical essentiality of the spectrum of immune function modulation provided by TAS2Rs.

## Paradigm Shifting TAS2Rs in Asthma Therapy: Where Do We Go from Here?

As evidenced here, TAS2Rs demonstrate multimodal functional versatility in the context of different tissue environments and disease states while retaining core cellular signaling pathways. In integrative animal models of obstructive lung diseases that are marked by type II immune responses, our studies have suggested that targeting TAS2Rs can provide bronchodilatory effects by promoting relaxation of airway smooth muscle and mitigate other pathological features including airway remodeling and airway inflammation, thus underscoring the potential of targeting TAS2Rs for therapeutic relief. This is facilitated by expression of TAS2R subtypes on multiple effector cells (immune cells, epithelial cells, and ASM cells) involved in asthma pathology. The potential for TAS2Rs to regulate migration of immune cells (particularly eosinophils) provides an alternative to anti-cytokine biologics that are very expensive. Finally, the ability of TAS2Rs to inhibit the development of airway remodeling features makes them a suitable candidate to develop comprehensive anti-asthma therapies.

One major challenge in development of TAS2Rs as therapeutic targets is the dearth of receptor subtype–specific agonists with refined pharmacological profile. Although we have access to a substantial library of pharmacologically well-characterized bitter compounds at our disposal, agonist-receptor subtype promiscuity has forestalled progression to clinical trials. Future research into development of TAS2R agonists with increased specificity to receptor subtypes will provide a much-required boost for the field to advance. To this effect, developing crystal structures and computational models to ascertain the agonist binding and receptor activation properties are essential to fully elucidate the pharmacology of TAS2Rs. Furthermore, given the strong evidence that TAS2Rs are involved in ASM relaxation, it is logical to assume that one or more TAS2R genes regulate airway tone. The next critical step in TAS2R research is to determine which specific TAS2R subtypes are most important with respect to asthma pathogenesis and for potential anti-asthma therapy. TAS2R expression and agonist sensitivity vary significantly across species posing additional challenge in translating findings from animal model studies to humans. This is particularly significant considering the fact that TAS2Rs have emerged as novel therapeutic target in human asthma. Notwithstanding the limitations of the current experimental approaches and basic understanding of TAS2Rs, the clinical utility of TAS2Rs in asthma is intriguing.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance


1. Workman AD, Palmer JN, Adappa ND, Cohen NA. The role of bitter and sweet taste receptors in upper airway immunity. Curr Allergy Asthma Rep. 2015;15(12):72.
2. Lee RJ, Cohen NA. Taste receptors in innate immunity. Cell Mol Life Sci. 2015;72(2):217–36.
3. Finger TE, Danilova V, Barrows J, Bartel DL, Vigers AJ, Stone L, et al. ATP signaling is crucial for communication from taste buds to gustatory nerves. Science. 2005;310(5753):1495–9.
4. Sternini C, Anselmi L, Rozengurt E. Enteroendocrine cells: a site of 'taste' in gastrointestinal chemosensing. Curr Opin Endocrinol Diabetes Obes. 2008;15(1):73–8.
5. Sternini C. Taste receptors in the gastrointestinal tract. IV. Functional implications of bitter taste receptors in gastrointestinal chemosensing. Am J Physiol Gastrointest Liver Physiol. 2007;292(2):G457–61.
6. Rozengurt E. Taste receptors in the gastrointestinal tract. I. Bitter taste receptors and alpha-gustducin in the mammalian gut. Am J Physiol Gastrointest Liver Physiol. 2006;291(2):G171–7.
7. Wu S, Rozengurt N, Yang M, Young SH, Sinnett-Smith J, Rozengurt E. Expression of bitter taste receptors of the T2R family in the gastrointestinal tract and enteroendocrine STC-1 cells. Proc Natl Acad Sci U S A. 2012;99(4):2392–7.
8.•• Luo XC, Chen ZH, Xue JB, Zhao DX, Lu C, Li YH, et al. Infection by the parasitic helminth Trichinella spiralis activates a Tas2r-mediated signaling pathway in intestinal tuft cells. Proc Natl Acad Sci U S A. 2019;116(12):5564–9. **Study demostrated the role of TAS2Rs in orchestrating parasite-induced Th2 immune response.**
9. Braman SS. The global burden of asthma. Chest. 2006;130(1 Suppl):4S–12S.
10. Skloot GS. Asthma phenotypes and endotypes: a personalized approach to treatment. Curr Opin Pulm Med. 2016;22(1):3–9.
11. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med. 2012;18(5):716–25.
12. Wenzel SE. Asthma: defining of the persistent adult phenotypes. Lancet. 2006;368(9537):804–13.
13. Drazen JM, Silverman EK, Lee TH. Heterogeneity of therapeutic responses in asthma. Br Med Bull. 2000;56(4):1054–70.
14. Demoly P, Paggiaro P, Plaza V, Bolge SC, Kannan H, Sohier B, et al. Prevalence of asthma control among adults in France, Germany, Italy, Spain and the UK. Eur Respir Rev. 2009;18(112):105–12.
15. Chapman KR, Boulet LP, Rea RM, Franssen E. Suboptimal asthma control: prevalence, detection and consequences in general practice. Eur Respir J. 2008;31(2):320–5.
16. Salpeter SR, Wall AJ, Buckley NS. Long-acting beta-agonists with and without inhaled corticosteroids and catastrophic asthma events. Am J Med. 2010;123(4):322–8 e2.
17.•• Deshpande DA, Wang WC, McIlmoyle EL, Robinett KS, Schillinger RM, An SS, et al. Bitter taste receptors on airway smooth muscle bronchodilate by localized calcium signaling and reverse obstruction. Nat Med. 2010;16(11):1299–304. **Study for the first time demostrated the expression and functional effect of TAS2Rs on human ASM cells.**
18. Pan S, Sharma P, Shah SD, Deshpande DA. Bitter taste receptor agonists alter mitochondrial function and induce autophagy in airway smooth muscle cells. Am J Physiol Lung Cell Mol Physiol. 2017;313(1):L154–L65.
19. Sharma P, Panebra A, Pera T, Tiegs BC, Hershfeld A, Kenyon LC, et al. Antimitogenic effect of bitter taste receptor agonists on airway smooth muscle cells. Am J Physiol Lung Cell Mol Physiol. 2016;310(4):L365–76.
20.•• Sharma P, Yi R, Nayak AP, Wang N, Tang F, Knight MJ, et al. Bitter taste receptor agonists mitigate features of allergic asthma in mice. Sci Rep. 2017;7:46166. **This study demonstrated the in vivo effectiveness of TAS2R agonists on features of asthma in multiple murine models.**
21. Kuperman DA, Huang X, Koth LL, Chang GH, Dolganov GM, Zhu Z, et al. Direct effects of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma. Nat Med. 2002;8(8):885–9.
22. Risse PA, Jo T, Suarez F, Hirota N, Tolloczko B, Ferraro P, et al. Interleukin-13 inhibits proliferation and enhances contractility of human airway smooth muscle cells without change in contractile phenotype. Am J Physiol Lung Cell Mol Physiol. 2011;300(6):L958–66.
23. Chiba Y, Nakazawa S, Todoroki M, Shinozaki K, Sakai H, Misawa M. Interleukin-13 augments bronchial smooth muscle contractility with an up-regulation of RhoA protein. Am J Respir Cell Mol Biol. 2009;40(2):159–67.
24. White TA, Xue A, Chini EN, Thompson M, Sieck GC, Wylam ME. Role of transient receptor potential C3 in TNF-alpha-enhanced calcium influx in human airway myocytes. Am J Respir Cell Mol Biol. 2006;35(2):243–51.
25. Kuyper LM, Pare PD, Hogg JC, Lambert RK, Ionescu D, Woods R, et al. Characterization of airway plugging in fatal asthma. Am J Med. 2003;115(1):6–11.
26. Ordonez CL, Khashayar R, Wong HH, Ferrando R, Wu R, Hyde DM, et al. Mild and moderate asthma is associated with airway goblet cell hyperplasia and abnormalities in mucin gene expression. Am J Respir Crit Care Med. 2001;163(2):517–23.
27. Damera G, Tliba O, Panettieri RA Jr. Airway smooth muscle as an immunomodulatory cell. Pulm Pharmacol Ther. 2009;22(5):353–9.
28. Panettieri RA Jr. Airway smooth muscle: an immunomodulatory cell. J Allergy Clin Immunol. 2002;110(6 Suppl):S269–74.
29. Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-cell infiltration of airway smooth muscle in asthma. N Engl J Med. 2002;346(22):1699–705.
30. Lauzon AM, and Martin JG. Airway hyperresponsiveness; smooth muscle as the principal actor. F1000Res. 2016;5.
31. Prakash YS. Emerging concepts in smooth muscle contributions to airway structure and function: implications for health and disease. Am J Physiol Lung Cell Mol Physiol. 2016;311(6):L1113–L40.
32. Prakash YS. Airway smooth muscle in airway reactivity and remodeling: what have we learned? Am J Physiol Lung Cell Mol Physiol. 2013;305(12):L912–33.
33. Billington CK, Penn RB. Signaling and regulation of G protein-coupled receptors in airway smooth muscle. Respir Res. 2003;4:2.
34. Deshpande DA, Penn RB. Targeting G protein-coupled receptor signaling in asthma. Cell Signal. 2006;18(12):2105–20.
35. Pera T, Penn RB. Bronchoprotection and bronchorelaxation in asthma: new targets, and new ways to target the old ones. Pharmacol Ther. 2016;164:82–96.

36. Chaudhari N, Roper SD. The cell biology of taste. J Cell Biol. 2010;190(3):285–96.
37. Roper SD, Chaudhari N. Taste buds: cells, signals and synapses. Nat Rev Neurosci. 2017;18(8):485–97.
38. Zhang CH, Chen C, Lifshitz LM, Fogarty KE, Zhu MS, ZhuGe R. Activation of BK channels may not be required for bitter tastant-induced bronchodilation. Nat Med. 2012;18(5):648–50 author reply 50-1.
39. Belvisi MG, Dale N, Birrell MA, Canning BJ. Bronchodilator activity of bitter tastants in human tissue. Nat Med. 2011;17(7):776.
40. Pulkkinen V, Manson ML, Safholm J, Adner M, Dahlen SE. The bitter taste receptor (TAS2R) agonists denatonium and chloroquine display distinct patterns of relaxation of the guinea pig trachea. Am J Physiol Lung Cell Mol Physiol. 2012;303(11):L956–66.
41. Robinett KS, Koziol-White CJ, Akoluk A, An SS, Panettieri RA Jr, Liggett SB. Bitter taste receptor function in asthmatic and nonasthmatic human airway smooth muscle cells. Am J Respir Cell Mol Biol. 2014;50(4):678–83.
42. Shi P, Zhang J, Yang H, Zhang YP. Adaptive diversification of bitter taste receptor genes in mammalian evolution. Mol Biol Evol. 2003;20(5):805–14.
43. Chandrashekar J, Hoon MA, Ryba NJ, Zuker CS. The receptors and cells for mammalian taste. Nature. 2006;444(7117):288–94.
44. Kim D, Woo JA, Geffken E, An SS, Liggett SB. Coupling of airway smooth muscle bitter taste receptors to intracellular signaling and relaxation is via Galphai1, 2,3. Am J Respir Cell Mol Biol. 2017;56(6):762–71.
45. Zhang CH, Lifshitz LM, Uy KF, Ikebe M, Fogarty KE, ZhuGe R. The cellular and molecular basis of bitter tastant-induced bronchodilation. PLoS Biol. 2013;11(3):e1001501.
46. Camoretti-Mercado B, Pauer SH, Yong HM, Smith DC, Deshpande DA, An SS, et al. Pleiotropic effects of bitter taste receptors on [Ca2+]i mobilization, hyperpolarization, and relaxation of human airway smooth muscle cells. PLoS One. 2015;10(6):e0131582.
47. Prakash YS, Halayko AJ, Gosens R, Panettieri RA Jr, Camoretti-Mercado B, Penn RB, et al. An Official American Thoracic Society Research statement: current challenges facing research and therapeutic advances in airway remodeling. Am J Respir Crit Care Med. 2017;195(2):e4–e19.
48. Nayak AP, Deshpande DA, and Penn RB. New targets for resolution of airway remodeling in obstructive lung diseases. F1000Res. 2018;7.
49. Lloyd CM, Robinson DS. Allergen-induced airway remodelling. Eur Respir J. 2007;29(5):1020–32.
50. Kim D, Cho S, Castano MA, Panettieri RA, Woo JA, Liggett SB. Biased TAS2R bronchodilators inhibit airway smooth muscle growth by downregulating phosphorylated extracellular signal-regulated kinase 1/2. Am J Respir Cell Mol Biol. 2019;60(5):532–40.
51. Locksley RM. Asthma and allergic inflammation. Cell. 2010;140(6):777–83.
52. Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. Report of a workshop held in Eze, France, October 1992. Am Rev Respir Dis. 1993;148(4 Pt 2):S1–26.
53. Barnes PJ. Efficacy of inhaled corticosteroids in asthma. J Allergy Clin Immunol. 1998;102(4 Pt 1):531–8.
54. Barnes PJ. Current issues for establishing inhaled corticosteroids as the antiinflammatory agents of choice in asthma. J Allergy Clin Immunol. 1998;101(4 Pt 2):S427–33.
55. McCracken JL, Tripple JW, Calhoun WJ. Biologic therapy in the management of asthma. Curr Opin Allergy Clin Immunol. 2016;16(4):375–82.
56. McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. Am J Respir Crit Care Med. 2019;199(4):433–45.
57. Pepper AN, Renz H, Casale TB, Garn H. Biologic therapy and novel molecular targets of severe asthma. J Allergy Clin Immunol Pract. 2017;5(4):909–16.
58. Krasteva G, Canning BJ, Papadakis T, Kummer W. Cholinergic brush cells in the trachea mediate respiratory responses to quorum sensing molecules. Life Sci. 2012;91(21–22):992–6.
59.•• Orsmark-Pietras C, James A, Konradsen JR, Nordlund B, Soderhall C, Pulkkinen V, et al. Transcriptome analysis reveals upregulation of bitter taste receptors in severe asthmatics. Eur Respir J. 2013;42(1):65–78. **This is a clinical study demonstrating the expression changes in peripheral blood leukocytes TAS2Rs in asthmatics.**
60. Lee RJ, Chen B, Redding KM, Margolskee RF, Cohen NA. Mouse nasal epithelial innate immune responses to Pseudomonas aeruginosa quorum-sensing molecules require taste signaling components. Innate Immun. 2014;20(6):606–17.
61. Lambrecht BN, Hammad H. The airway epithelium in asthma. Nat Med. 2012;18(5):684–92.
62. Shah AS, Ben-Shahar Y, Moninger TO, Kline JN, Welsh MJ. Motile cilia of human airway epithelia are chemosensory. Science. 2009;325(5944):1131–4.
63. Finger TE, Bottger B, Hansen A, Anderson KT, Alimohammadi H, Silver WL. Solitary chemoreceptor cells in the nasal cavity serve as sentinels of respiration. Proc Natl Acad Sci U S A. 2003;100(15):8981–6.
64. Saunders CJ, Reynolds SD, Finger TE. Chemosensory brush cells of the trachea. A stable population in a dynamic epithelium. Am J Respir Cell Mol Biol. 2013;49(2):190–6.
65. Tizzano M, Cristofoletti M, Sbarbati A, Finger TE. Expression of taste receptors in solitary chemosensory cells of rodent airways. BMC Pulm Med. 2011;11:3.
66.•• Ekoff M, Choi JH, James A, Dahlen B, Nilsson G, Dahlen SE. Bitter taste receptor (TAS2R) agonists inhibit IgE-dependent mast cell activation. J Allergy Clin Immunol. 2014;134(2):475–8. **This study demonstrated the functional effect of TAS2R activation in mast cells obtained from human subjects.**
67. Maurer S, Wabnitz GH, Kahle NA, Stegmaier S, Prior B, Giese T, et al. Tasting Pseudomonas aeruginosa biofilms: human neutrophils express the bitter receptor T2R38 as sensor for the quorum sensing molecule N-(3-oxododecanoyl)-l-homoserine lactone. Front Immunol. 2015;6:369.
68. Krasteva G, Canning BJ, Hartmann P, Veres TZ, Papadakis T, Muhlfeld C, et al. Cholinergic chemosensory cells in the trachea regulate breathing. Proc Natl Acad Sci U S A. 2011;108(23):9478–83.
69. Tizzano M, Gulbransen BD, Vandenbeuch A, Clapp TR, Herman JP, Sibhatu HM, et al. Nasal chemosensory cells use bitter taste signaling to detect irritants and bacterial signals. Proc Natl Acad Sci U S A. 2010;107(7):3210–5.
70. Denning DW, Pashley C, Hartl D, Wardlaw A, Godet C, Del Giacco S, et al. Fungal allergy in asthma-state of the art and research needs. Clin Transl Allergy. 2014;4:14.
71. Gaida MM, Dapunt U, and Hansch GM. Sensing developing biofilms: the bitter receptor T2R38 on myeloid cells. Pathog Dis. 2016;74(3).
72. Ogino H, Fujii M, Ono M, Maezawa K, Hori S, Kizu J. In vivo and in vitro effects of fluoroquinolones on lipopolysaccharide-induced pro-inflammatory cytokine production. J Infect Chemother. 2009;15(3):168–73.
73. Ianaro A, Ialenti A, Maffia P, Sautebin L, Rombola L, Carnuccio R, et al. Anti-inflammatory activity of macrolide antibiotics. J Pharmacol Exp Ther. 2000;292(1):156–63.
74. Jeong JY, Jue DM. Chloroquine inhibits processing of tumor necrosis factor in lipopolysaccharide-stimulated RAW 264.7 macrophages. J Immunol. 1997;158(10):4901–7.

75. Schierbeck H, Wahamaa H, Andersson U, Harris HE. Immunomodulatory drugs regulate HMGB1 release from activated human monocytes. Mol Med. 2010;16(9–10):343–51.
76. Yasutomi M, Ohshima Y, Omata N, Yamada A, Iwasaki H, Urasaki Y, et al. Erythromycin differentially inhibits lipopolysaccharide- or poly(I:C)-induced but not peptidoglycan-induced activation of human monocyte-derived dendritic cells. J Immunol. 2005;175(12): 8069–76.
77. Vrancic M, Banjanac M, Nujic K, Bosnar M, Murati T, Munic V, et al. Azithromycin distinctively modulates classical activation of human monocytes in vitro. Br J Pharmacol. 2012;165(5):1348–60.
78. Woodman L, Siddiqui S, Cruse G, Sutcliffe A, Saunders R, Kaur D, et al. Mast cells promote airway smooth muscle cell differentiation via autocrine up-regulation of TGF-beta 1. J Immunol. 2008;181(7):5001–7.
79. Page S, Ammit AJ, Black JL, Armour CL. Human mast cell and airway smooth muscle cell interactions: implications for asthma. Am J Physiol Lung Cell Mol Physiol. 2001;281(6):L1313–23.
80. Tran HTT, Herz C, Ruf P, Stetter R, Lamy E. Human T2R38 bitter taste receptor expression in resting and activated lymphocytes. Front Immunol. 2018;9:2949.
81. Salathe M. Regulation of mammalian ciliary beating. Annu Rev Physiol. 2007;69:401–22.