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Interactions between taste receptors and the gastrointestinal microbiome in inflammatory bowel disease

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HIGHLIGHTS

- Taste genetics, and oral receptor expression levels, determine dietary preferences and intake which is linked to IBD risk.
- The risk for IBD may be linked to specific taste genotypes.
- Extra-oral taste receptors may detect and respond to a range of microbial components.
- These receptors modulate metabolic and gastrointestinal functions, which may influence microbial environments and IBD risk.

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ABSTRACT

Incidence rates of inflammatory bowel disease (IBD) are increasing worldwide. This correlates with increased consumption of red meats, alcohol, refined sugars, oils and animal fats, typical of a "Western" diet. Poor dietary habits are the most ubiquitous environmental factor implicated in IBD, along with gastrointestinal dysbiosis. Taste genetics and oral receptor expression levels determine dietary preferences and therefore, nutritional intake. Taste receptors (TRs) are also expressed throughout the gastrointestinal tract, where they are involved in modulating metabolic processes and gastrointestinal function. Importantly, these receptors are known to be involved in the modulation of inflammatory processes in the respiratory tract. In this system, TRs detect and respond to bacteria and bacterial signalling molecules and initiate protective responses. We propose that TRs play a similar role in the gastrointestinal tract, thereby modulating risk for IBD. TRs may indirectly affect risk for IBD by altering dietary intake, and therefore microbial composition and function. Alternatively, TRs may directly detect and respond to gastrointestinal bacterial components. Overall, there is evidence to suggest an emerging role for TRs in the aetiology of IBD. Furthermore, targeting these receptors via dietary modulation may have therapeutic potential.

1. Introduction

Inflammatory bowel disease (IBD) is an umbrella term used to describe disorders involving chronic inflammation of the gastrointestinal tract. The two most common forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). IBD is particularly prevalent in the developed world, with the highest incidence rates in Western Europe, North America, Australia and New Zealand. However, incidence rates are also increasing in less-industrialised countries [1]. While the different forms of IBD, such as CD and UC, share common symptoms, they are distinct

Abbreviations: AHL, acyl homoserine lactone; CD, Crohn's disease; GLP-1, glucagon-like peptide-1; IBD, inflammatory bowel disease; LPS, lipopolysaccharide; SCFA, short chain fatty acid; SCFAR, short chain fatty acid receptor; SNP, single nucleotide polymorphism; TR, G protein-coupled taste receptor; TLR, Toll-like receptor; UC, ulcerative colitis

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disorders. CD causes transmural inflammation, which can occur along the entire length of the gastrointestinal tract, or portions of it, with areas of healthy tissues. In UC, the inflammation is restricted to the mucosal layers and is limited to the colon and rectum. The aetiology of IBD is not completely understood. However, it is thought to be related to interactions between genetic, microbial, immunological and environmental factors [2]. Nutrition is a major environmental factor determining risk for IBD. Interestingly, increased incidence rates correlate with the increased consumption of red meats, alcohol and refined sugars, oils and animal fats [3]. These foods are typical of a "Western" diet. This style of diet is tightly linked to IBD [4–6] and has been reported as the most relevant environmental factor [7].

Dietary intake is directly associated with risk for IBD [4], and can also indirectly affect risk by modulating the composition and function of the intestinal microbiome [8]. TRs detect key dietary components and play a critical role in determining dietary preferences. These receptors are expressed throughout the gastrointestinal tract, where they are involved in regulating dietary intake and altering the microbial environment [9–11]. This review will explore the interactions between nutrition and microbial function in the gastrointestinal tract and the role of taste genetics in modulating these processes. Furthermore, TRs are involved in modulating inflammation in the respiratory tract [12–16]. Therefore, this review will also explore a potential role for TRs in regulating gastrointestinal inflammation. Overall, the aetiology of IBD may be related to interactions between diet, the gut microbiome and taste genetics.

2. Diet and the gastrointestinal microbiome in IBD pathogenesis

Diet is a major modifiable risk factor in inflammatory diseases and is closely linked to a healthy gut microbiome. Development of IBD is positively associated with high intakes of total fats, polyunsaturated fatty acids, omega-6 fatty acids, refined sugars, meat, alcohol and smoking. Conversely, high fibre and fruit intake reduce risk for CD, and high vegetable intake may reduce risk for UC [4–6,17–19]. Furthermore, multiple exclusionary diets exist that have been effective in inducing and maintaining remission during IBD [6,20,21]. However, dietary recommendations are unique for each individual IBD case, making broad recommendations particularly difficult [19,22]. While the mechanisms explaining the associations between diet and IBD remain to be fully elucidated, it is likely that dietary modulation of the gastrointestinal microbiota plays a major role [6,8].

IBD typically develops due to a genetic predisposition to respond aberrantly to commensal microflora [23]. Over 231 individual polymorphisms have been associated with IBD risk [24,25]. However, genetic factors are more influential in CD, than UC [26]. Interestingly, many of these genetic risk factors influence the microflora. The intestinal microbiota modulates barrier function and host immunity. Alterations to these processes are crucial in IBD development [8]. The first molecular characterisation of the gut microbiome during IBD was published over ten years ago [27]. Since then, extensive IBD-associated microbial patterns have been determined. These include decreases in short chain fatty acid (SCFA)-producing Firmicutes, decreases in some Bacteroidetes, increases in mucolytic species, increases in sulfate-reducing bacteria, increases in pathogenic bacteria and an overall reduction of microbial diversity [2].

As well as being directly involved, diet may also indirectly modify IBD risk by modulating the composition and function of the intestinal microbiome (Fig. 1). For example, in a gnotobiotic mouse model colonised with human microbiota, depletion of dietary fibre leads to disruption of the mucous layer, compromised barrier function, tissue damage and immune activation [28], all of which are conditions associated with IBD. This study eloquently highlighted the effects of diet on IBD pathogenicity via the modulation of microbial composition in mice. However, whether dietary interventions are as effective in humans remains uncertain [29].

Dietary fibre is essential for the production of SCFAs by commensal bacteria. SCFAs have key roles in modulating inflammatory processes, and both CD and UC are characterised by SCFA deficiencies [6,30]. As well as SCFAs, bacteria produce a variety of components that can trigger inflammatory pathways, including lipopolysaccharides (LPS; cell wall components) and acyl homoserine lactones (AHLs; bacterial quorum-sensing molecules) [31,32]. Overall, "Western" dietary patterns have detrimental effects on the composition of the gut microbiome, which may relate to disease pathogenicity [8] (Fig. 1). Because of the importance of diet in IBD aetiology, dietary interventions, such as elimination diets, are often used to reduce acute IBD symptoms [6].

While CD and UC share many common features, they have distinct microbial signatures [33]. The differences in microbial structure between CD and healthy participants is more dramatic than the differences between UC and healthy participants [34]. Even though intestinal dysbiosis has been implicated in the development of IBD [25,35], there is no causal link between any particular pathogen or microbial signature and IBD [35]. However, a highly volatile microbiota is common in IBD [33,36]. This changeable environment during IBD disrupts host immune pathways and mucosal integrity, which are key factors in IBD pathogenesis.

3. Taste regulates dietary intake and is altered during IBD

Taste is important in determining dietary preferences and therefore, nutritional intake, which are key components in IBD pathogenesis and management. There are five modalities of taste: Bitter, sweet, umami, salty and sour. Three of these are facilitated by G protein-coupled TRs (TRs). In humans, the *TAS1R* gene family encodes three receptors (T1Rs) involved in the detection of sugars, carbohydrates and proteins. The *TAS2R* gene family includes genes for 25 functional receptors (T2Rs) that are involved in the detection of bitter compounds [37].

Genetic variation in these TRs may be implicated in the modulation of IBD risk. For example, single nucleotide polymorphisms (SNPs) of the *TAS1R2* gene (rs12033832; rs35874116) are associated with reduced sensitivity to sweet, and corresponding increased sugar intake in individuals with a BMI $\geq$ 25 [38,39]. Carriage of these variant alleles is yet to be examined directly in relation to IBD risk; However, in a case-control study, sugar consumption was positively associated with risk for CD [17]. *TAS2R* polymorphisms are also implicated in dietary preference and intake of foods and nutrients that may alter IBD risk. *TAS2R38* SNPs (including rs713598, rs1726866 and rs10246939) have been linked to alcohol consumption, vegetable intake, smoking habits, coffee consumption and sugar intake [40,41]. Overall, taste genotypes influence dietary intake, which is a key factor in the development of IBD (Fig. 2). However, additional research is needed to determine if there is a direct association between *TAS1R* and *TAS2R* genetics and risk for IBD via modulation of dietary preferences.

Taste preferences can also be affected by altered TR expression. For example, T1R2 has been shown to be under-expressed on the tongues of mice with diet-induced obesity compared to lean mice [42]. This may lead to subsequent sugar overconsumption in obese mice due to a decreased sensitivity to sugar. Furthermore, relative expression levels of a form of T2R38 was positively correlated with the percieved bitterness of PROP and broccoli juice [43]. This suggests that altered oral TR expression levels may determine dietary preferences and intake, subsequently altering IBD risk (Fig. 2).

Alteration of taste sensitivity has been observed in concurrence with IBD. In a human IBD case-control study, taste sensitivity was significantly reduced in IBD patients compared to healthy controls and standardised data [44]. This is in line with two previous studies that identified reduced taste sensitivity in CD patients compared to healthy subjects [45,46]. These studies suggest a correlation between bitter and sweet sensitivity and IBD, however, whether reduced gustatory function is a cause, or a consequence of IBD remains unclear. Overall, reduced taste sensitivity may lead to increased intake of sweet and/or

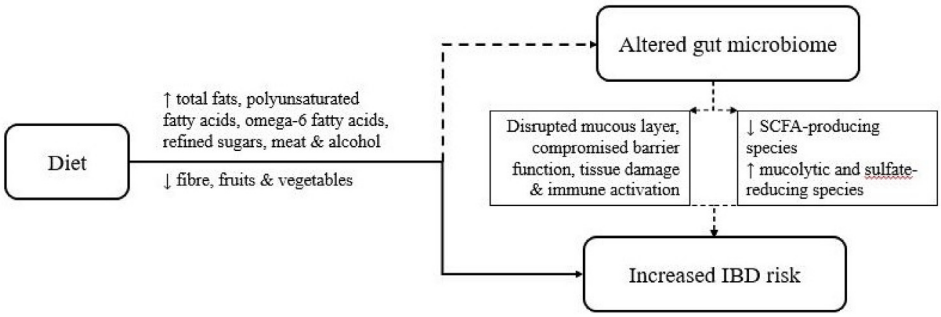

Fig. 1. Dietary factors are directly associated with IBD risk. Diet may also indirectly effect IBD risk via alteration of the function and composition of the intestinal microbiota.

fatty foods. These foods are strongly linked to inflammation [4,5,19,47,48] and may therefore alter risk for IBD. Furthermore, IBD appears to bi-directionally alter taste sensitivity and dietary intake.

3.1. Extra-oral taste receptors

Recently, chemosensory roles for TRs have been identified outside the oral cavity. Their expression has been identified in a wide range of organs, including the brain, lungs and gastrointestinal tract. In extra-oral systems, TRs have established modulatory roles in metabolism in the gastrointestinal tract, and inflammation in the airways [11,12,15,49–51].

TRs are expressed throughout the entire gastrointestinal tract, where they have extensive roles in metabolic regulation. This includes processes such as appetite regulation, gut motility and glucose homeostasis [9–11]. TRs are expressed in enteroendocrine cells, which are chemosensory cells that secrete metabolic hormones in response to luminal contents (Fig. 3). For example, ghrelin secretion, in response to T2R activation, has been demonstrated *in vivo* [52]. Furthermore, in STC-1 enteroendocrine cells, it was demonstrated that bitter stimuli induced cholecystokinin secretion [53]. These studies suggest that TRs are involved in the modulation of food intake and gut motility, which has direct effects on microbial composition and function, subsequently altering risk for IBD (Fig. 2).

Extra-oral TRs are also involved in the modulation of glucose homeostasis, which may be associated with IBD risk. T1Rs detect luminal glucose and regulate the secretion of the incretin hormones, including glucagon-like peptide-1 (GLP-1) [54]. Interestingly, T2Rs are also involved in the regulation of blood glucose levels. In a case-control study, four *TAS2R* SNPs (rs2588350, rs619381, rs3741845 and rs6488334) were significantly associated with type 2 diabetes. Furthermore, rs3741845 (a *TAS2R9* SNP) was also associated with glucose and insulin dysregulation in non-diabetics [55]. This is of interest as type 2 diabetes and IBD are interrelated conditions that commonly co-exist. These conditions share common signalling pathways and dysbiotic microbial signatures [56]. Therefore, TRs may act as a link between the two conditions by modulating sugar intake, glucose metabolism and related inflammation. Additionally, GLP-1 has been shown to attenuate gastrointestinal inflammation *in vivo* [57]. Therefore, altered GLP-1 secretion (modulated by *TASR* variants) may reduce or amplify inflammation during IBD.

Results from two recent mouse studies suggest that TRs may be directly involved in the modulation of gastrointestinal inflammation (Fig. 2). One study investigated the metabolic benefits of treatment with a tas2r108 agonist on mice with diet-induced obesity. Along with weight loss, improved insulin sensitivity and normalised plasma lipids, this study reported reduced levels of inflammatory cytokines that were elevated in obese mice [51]. The second study found that α-gustducin (a key taste signalling molecule) knockout mice are more susceptible to colitis and exhibited more aggressive IBD symptoms. These mice also displayed increased expression of TNF and interferon-γ and decreased expression of IL-13 and IL-5 in the colon [58]. Together, these studies suggest a critical role for taste signalling components in the regulation of inflammation. Overall, gastrointestinal TRs and signalling molecules appear to have a role in the regulation of intestinal inflammation. Importantly, targeting these receptors (potentially via dietary intervention) may present a new means for reducing IBD symptoms.

4. Taste receptors can directly detect bacteria and modulate inflammatory responses

TRs may be directly involved in the modulation of inflammation via interaction with bacterial metabolites and cell wall components [50]. This has been demonstrated in the respiratory tract where TRs interact with, and respond to, noxious substances and bacterial molecules [12–14,16,49,59]. The upper airways contain solitary chemosensory

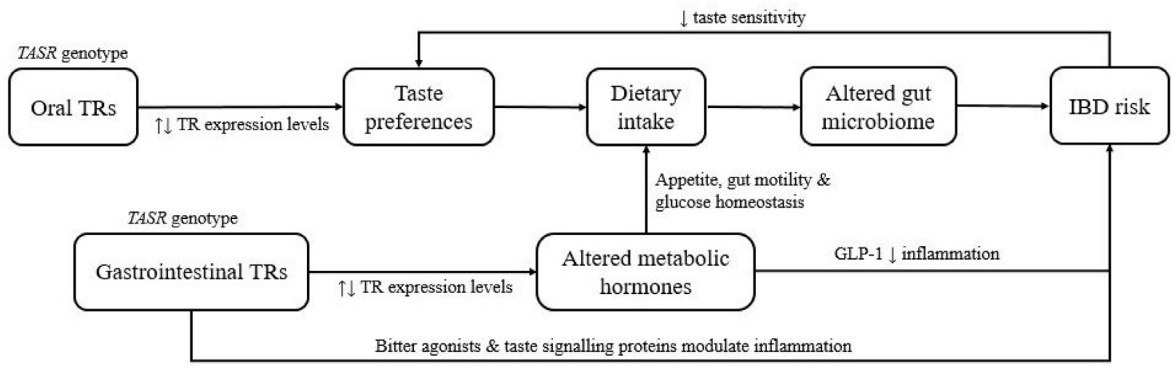

Fig. 2. Oral taste regulates dietary intake and is altered during IBD. Extra-oral taste receptors alter food intake and gut motility, which effects microbiome composition and therefore IBD risk. Bitter agonists, taste signalling components and GLP-1 may also modulate inflammation.

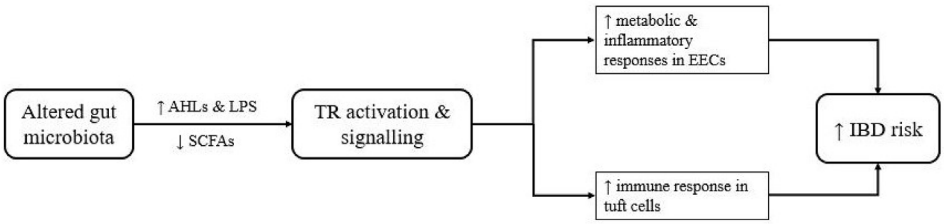

Fig. 3. Gastrointestinal taste receptors may be implicated in IBD pathogenesis. These receptors can detect bacteria and may modulate inflammatory responses by intestinal enteroendocrine and tuft cells in reponse to perturbations of the intestinal microbiota.

cells, involved in the modulation of innate immune responses; these cells express both T1Rs and T2Rs [12,15,60]. Furthermore, these cells respond to bitter ligands and bacterial signals in a protective manner. In humans, stimulation of T2Rs results in the release of anti-microbial peptides β-defensin 1 and 2 [15]. In sinonasal cells, T2R38 has been shown to be activated by AHLs and to generate nitric oxide in response [13].

Interestingly, T1Rs are also involved in this response. Following infection, sweet receptors are de-activated as bacteria reduce glucose concentrations. This increases the T2R-mediated release of anti-microbial compounds [61]. Furthermore, it was found that genetic knockout of α-gustducin or TrpM5 (transient receptor potential channel 5; essential for transduction of bitter, sweet and umami tastes) eliminated protective responses like sneezing and neurogenic inflammation in mice [62]. Altogether, these studies highlight a critical role for extra-oral TRs, and taste signalling molecules, in the modulation of respiratory, immune functions and inflammation. Therefore, it is likely that gastrointestinal TRs are similarly involved in regulating inflammation in the gastrointestinal tract. If this is the case, then TRs may have a key role in modulating inflammation during IBD.

It is widely established that TRs are involved in the regulation of airway immunity [13,49,62]. Because of this, it has recently been suggested that TRs may also have a role in the regulation of gut inflammatory responses [58]. Due to the nature of the interaction between bacteria and TRs in the upper airways, TR activation in the gastrointestinal tract may have similar anti-inflammatory functions. Interestingly, IBD shares environmental, genetic, immunological and microbial risk factors with inflammatory respiratory disorders. This has lead to the notion that there is crosstalk between inflammatory conditions of the respiratory and gastrointestinal tracts [63]. *TASR* mutations, and associated altered inflammatory pathways may be one potential cofactor explaining this phenomenon. Overall, TRs may have a role in modulating inflammatory responses that are implicated in IBD.

5. Gastrointestinal taste receptors may directly modulate inflammatory processes implicated in IBD

The aetiology of IBD is strongly related to diet, the gastrointestinal microbiota and the genes relating to microbiome function. It appears that dysbiosis precedes the onset of IBD [25]. Intestinal TRs may indirectly affect the gastrointestinal microbiome via the modulation of gastrointestinal functions, or by altering dietary intake. Interestingly, there are multiple bacterial components, including AHLs, SCFAs and LPS that may interact with gastrointestinal TRs to directly modulate inflammation during IBD (Fig. 3). In the respiratory tract, AHLs act as T2R agonists and trigger inflammation. These compounds have also been shown to suppress the proliferation of colonic epithelial cells and disrupt barrier function in colonic tissues [64]. We propose that T2Rs in the colon may similarly detect bacterial AHLs and therefore be directly implicated in the progression of IBD.

TRs are expressed in enteroendocrine cells of the gastrointestinal tract. In response to pathogens and bacterial metabolites, enteroendocrine cells release peptide hormones and cytokines [65]. Additionally, several hormones secreted by enteroendocrine cells act directly on nearby immune cells to reduce or amplify inflammatory responses [57]. Enteroendocrine cells also produce specific interleukins (ILs) involved in the pathogenesis of IBD [66,67], and display altered patterns of hormone secretion during IBD [68]. The coexpression of TRs in enteroendocrine cells indicates that they may be involved in modulating gastrointestinal inflammation. However, the potential role for TRs in IBD remains to be identified.

As well as TRs, there are other receptors expressed in gastrointestinal enteroendocrine cells that detect and respond to bacterial components [69]. Importantly, these receptors are involved in the inflammatory response. GPR43 activation by SCFAs results in the secretion of TNF [70] and toll-like receptors (TLRs) are activated by LPS to secrete inflammatory cytokines. Furthermore, it was shown that like TRs, TLR activation was associated with a rapid calcium flux [71]. This flux was followed by cholecystokinin secretion by enteroendocrine cells, which inhibits the production of TNF and IL-6 in rats [72]. This supports the idea that receptors within enteroendocrine cells may work together to regulate inflammation and alter IBD risk.

Due to the expression of TRs in enteroendocrine cells, and their involvement in the immune response in the respiratory system, we suggest that TRs may work in conjunction with TLRs and SCFA receptors (SCFARs), to detect perturbations in the intestinal gut bacteria and modulate inflammatory responses. SCFARs detect bacterial metabolites, and TLRs detect bacterial components, including LPS, to initiate immune responses. While TLR activation generates a sustained immune response over a period of hours, antimicrobial peptide secretion following TR activation in the respiratory tract is immediate [15]. This suggests that T2Rs and TLRs in enteroendocrine cells may also work together to produce immediate versus sustained immune responses.

Interestingly, intestinal tuft cells also express taste signalling proteins [73–76], and share morphological characteristics with taste bud sensory cells [77,78]. These cells are another type of intestinal chemosensory cell (distinct from enteroendorine cells) involved in regulating immune responses to parasites and microbes [79–82]. Importantly, reduced tuft cell numbers are correlated with active IBD in humans and mice [83–85]. Therefore, tuft cells may have a protective function in IBD (Fig. 3). The involvement of taste signalling pathways in tuft cells, and their role in immune regulation, suggests potential crosstalk between enteroendocrine and tuft cells. This may be relevant in the development and pathogenesis of IBD. Overall, there is evidence to suggest that gastrointestinal TRs, and taste signalling pathways, may have direct modulatory roles in inflammation during IBD.

6. Conclusion

There is growing evidence to suggest that TRs may be involved in the aetiology of IBD. This may occur via direct interactions between TRs and bacteria as occurs in the respiratory tract, or via modulation of metabolic function. Indirectly, *TASR* genotype may modulate dietary preferences and habits, impacting development and symptoms. Taste receptor expression may also be altered in response to inflammation or dietary changes, which may further compound risk or symptoms.

Overall, there is evidence to suggest a role for TRs in the development and severity of IBD. However, this role remains to be characterised, and further research is needed.

Author statement

A.T., E.C., M.V., S.K., C.S., M.L. and E.B. contributed to the formulation and revision of this paper. All authors approved the final version of the manuscript.

Declaration of competing interest

The authors declare no conflicts of interest.

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