

EXPERT
REVIEWS

Atopy and the gastrointestinal tract – a review of a common association in unexplained gastrointestinal disease

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In addition to diseases conventionally associated with atopy there is increasing recognition that atopy is also linked to a spectrum of gastrointestinal (GI) manifestations, including food allergy, primary eosinophilic GI disease, functional gastrointestinal disorders, gluten interactions, gastroesophageal reflux disease and inflammatory bowel disease. These associations may be underpinned by shared genetic susceptibilities, initiation of related immune pathways and common patterns of exposure to environmental cues, including allergen/pathogen encounters and variations in the composition of the intestinal microbiota. Further scrutiny of GI diseases with prominent allergic-type immune responses may yet redefine treatment paradigms for these common and important atopy-associated diseases. Looking forward, interventions by manipulation of the microbiota or host immune responses hold promise, but there is still room for further exploration of this novel field of host susceptibility, host-microbe interactions and atopy-associated GI diseases.

KEYWORDS: allergy • atopy • eosinophilic gastrointestinal disease • food allergy • gastrointestinal inflammation • intestinal microbiota

Atopy

Atopy is defined as a personal and/or familial tendency to produce IgE antibodies in response to ordinary exposure to allergens, usually proteins, with sensitization typically occurring in childhood [1]. Consequently, those with this predisposition may develop typical symptoms of recognized atopic diseases, including asthma, rhinoconjunctivitis or eczema. 'Allergy' specifically denotes the development of a hypersensitivity reaction initiated by immune mechanisms, including antibody and cell-mediated responses. Allergic symptoms in those with an atopic predisposition are frequently referred to as 'atopic', as in atopic rhinitis. In Western societies the prevalence of atopy is increasing. Between 1990 and 1998, in Denmark, there was an increase in the prevalence of atopy from 26.5 to 33.9%, a relative increase of 28% [2]. In the UK, in the timeframe 1975–1998, a relative increase of 40% was found in adults [3]. While there is strong evidence of a genetic component in

atopy, these rapid increases in prevalence show that environmental factors are important, and therefore, it is likely that atopic diseases arise as a consequence of gene–environment interactions. The GI tract provides unparalleled access to environmental signals. As well as interfacing with the greatest density of commensal microbes (>10¹⁴ organisms [4]), it is constantly exposed to a dynamic and ever changing repertoire of food antigens, including >60 g of dietary foreign protein every day [5]. Accordingly, it is unsurprising that the GI tract is intimately linked to, and associated with, atopic disease.

The immunopathology of atopic disease

The immune mechanisms responsible for causing atopic diseases are complex, with prominent roles played by both adaptive and innate immunity. The kinetics of allergic responses can be subdivided into early- or late-phase reactions in allergen challenge experiments [6]. For instance, in appropriately sensitized atopic asthmatic patients inhalation challenge with

specific allergen provokes immediate, but transient bronchospasm. This early phase reaction represents the prototypical immediate hypersensitivity reaction and is caused by allergen-induced cross-linking of allergen-specific IgE bound to the surface of mucosal mast cells through the high-affinity IgE receptor (FcεRI), triggering instant release of histamine and other pre-formed mediators. However, 6 h after allergen exposure, there begins a prolonged period of airflow limitation resulting from airway mucosal swelling. This late-phase response (LPR) is caused by allergen-reactive CD4⁺ T cells and eosinophils recruited to the airways [7]. The LPR mimics features of chronic disease where antigen-specific CD4⁺ helper cells that have differentiated into particular effector lineages play a key functional role. TH2 T cells are strongly implicated since they are enriched at disease sites and produce disease-relevant cytokines, including IL-4 (mast cell activation and immunoglobulin class switching to the pro-allergic IgE subclass), IL-5 (eosinophils recruitment/activation) and IL-13 (class switching and tissue remodeling) [7–11].

Immunoregulatory T cells may also play a role in atopic disease. Foxp3⁺ Tregs are immunosuppressive CD4⁺ T cells, which suppress inflammation. They are also implicated in successful acquisition of oral tolerance [12] and in suppression of TH2-mediated inflammation in atopic disease [13]. Defective Treg suppression of allergen-induced proliferation and TH2 cytokine production by effector T cells has been reported in patients with atopic disease [14,15]. Induction of allergen-responsive Tregs has been proposed to underpin the therapeutic efficacy of peptide-based immunotherapy for atopic disease [16]. Patients with mutations in the Treg lineage defining transcription factor Foxp3 (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) develop multisystem inflammatory disease and have markedly elevated serum IgE levels [17].

Innate immunity also participates in allergic responses. Dendritic cells (DCs) in the airways sample aeroallergens and other inhaled antigens and present them to antigen-specific T cells. Importantly, IgE may also play an important role in driving DC-instructed CD4⁺ T-cell responses. Like mast cells and basophils, DCs express FcεRI allowing them to 'capture' allergens that have been bound by IgE for subsequent presentation to T cells [18]. FcεRI⁺ DCs stimulate T-cell proliferation [18], and in asthma FcεRI⁺ DCs in the lung capture and process inhaled allergens before migrating to the mediastinal lymph nodes where they prime TH2 immunity [19]. In keeping with these observations, anti-IgE (omalizumab) treatment of atopic asthmatic patients diminishes the number of 'inflammatory' FcεRI⁺ DCs in the lung [20], and suppresses DC-dependent allergen-reactive TH2 responses [21].

GI diseases are associated with atopy

Atopic diseases manifesting in the skin and mucosal surfaces of the airways have long been appreciated, only more recently has the reach of atopy been recognized to extend to the other major epithelial barrier, the GI tract. Indeed based on epidemiological associations, overlapping genetic and immunological

characteristics, there is growing enthusiasm for the existence of an atopy/gastrointestinal (GI) disease nexus. The spectrum of disease encompasses well-established links with atopy, such as food allergy (FA), to less established associations, such as inflammatory bowel disease (IBD). More recently, it has been proposed that cells conventionally perceived as mediators of allergic immune responses, such as mast cells and eosinophils, are likely to play a role in the pathogenesis of functional GI disorders (FGIDs).

FA & the gut

FA is a well-recognized association with atopy. Eighty percent of children with egg allergy first present with eczema [22]. Unfortunately, FA in childhood portends more severe atopic disease in the future, such as treatment refractory, life-threatening asthma [23].

Definitions and nomenclature of FA are controversial areas with differing terminology in use in Europe and the USA, although there is universal acceptance that immune mechanisms, especially IgE-mediated responses, play a central role. By contrast, food intolerance, which is non-immune mediated and includes pharmacological effects of food constituents (e.g., tyramine in cheese), or enzyme deficiencies (e.g., lactose intolerance) should be considered a separate entity.

Around 6–8% of children in the UK and the USA are affected by FA and common offending allergens include cow's milk proteins, egg and peanut [24]. Clinical presentations of FA are numerous and varied, and include anaphylaxis, cutaneous manifestations (eczema, urticaria, flushing and angioedema) and respiratory symptoms (wheezing, rhinorrhoea and stridor). GI symptoms are also well recognized and include vomiting, diarrhea and abdominal pain [24]. Many presentations of FA are indicative of immediate IgE-mediated hypersensitivity reactions and may occur within minutes of ingesting the offending allergen. However, non-IgE-mediated food antigen-induced symptoms are recognized in which cutaneous and respiratory symptoms are less prominent and GI symptoms instead predominate, such as primary eosinophilic GI diseases (EGIDs). Although these diseases are linked with atopy, immediate hypersensitivity reactions are uncommon and instead cell-mediated immunity and mucosal eosinophilia is strongly implicated. These 'allergic-type' mucosal inflammatory diseases share striking immunological parallels with the late-phase allergic reactions occurring in the skin, nose and lungs of atopic patients, where antigen-reactive T cells direct recruitment and activation of eosinophils [25]. Celiac disease is another prototypical cell-mediated immune response directed against specific food antigens. Although the classical form of disease is possibly linked to atopy, other aberrant, non-celiac host responses to wheat antigens are clearly associated with atopy. FA-associated GI and non-GI syndromes are listed in TABLE 1.

Atopy & EGIDs

The EGIDs comprise a heterogeneous group of overlapping diseases, which includes eosinophilic esophagitis (EE), eosinophilic gastroenteritis, eosinophilic enteritis and eosinophilic

Table 1. Clinical presentations of food allergy.

GI conditions linked to food allergy	Non-GI presentations seen in food allergy
Eosinophilic esophagitis/gastroenteritis	Angioedema, classic food-related anaphylaxis, laryngeal edema, oral allergy syndrome
Milk protein allergy of infancy, cow's milk allergy syndrome	Asthma, contact dermatitis, eczema, atopic dermatitis, urticaria, rhinoconjunctivitis, conjunctivitis, generalized flushing
Food-associated, exercise-induced syndromes	Milk-induced pulmonary disease in infants (Heiner's syndrome, pulmonary hemosiderosis)
Food-induced enterocolitis syndrome Food-induced proctocolitis syndrome	
GI hypersensitivity (e.g., vomiting, colic, diarrhea) Induced colitis (blood in the stools)	
IBD	
IBS	
GI: Gastrointestinal; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome.	

colitis. There are close associations with a personal (70% of patients) or family history of atopy [26], and a further 10% of patients have a family member with EGID. The incidence of primary EGID is increasing with 'hot zones' of prevalence localizing to urban areas, mirroring the changes seen in other atopic diseases, such as asthma [27].

Patients typically present with overt GI symptoms without systemic features of FA, although severe manifestations, such as anaphylaxis, occur with greater frequency than the general population [28]. Sensitivity to food antigens is a central feature of EGIDs and exclusion of 'sensitizing' foods relieves symptoms in most patients [29]. In one study of 941 children with EE, diagnostic testing for food allergens with skin-prick testing (SPT) and atopy patch testing showed that sensitization to at least one food was present in 77% of patients [28]. Prescriptive food exclusion based on the results of SPT and atopy patch testing induced clinical remission in three-quarters of patients [28].

The EGIDs are characterized immunologically by the accumulation of eosinophils in the relevant mucosal tissue (esophagus in EE, small intestine in eosinophilic gastroenteritis and in the colon in eosinophilic colitis), which may extend through the muscularis [30]. By definition, other causes of tissue eosinophilia are necessarily absent. Although eosinophils are normal constituents of the GI tract, aside from the esophagus [31], in EGIDs eosinophil infiltration of the lamina propria is markedly increased with evidence of degranulation typically present [26]. There is also expansion of T cells [32], B cells [33] and mast cells [32]. In EE, the prototypical EGID, mucosal transcription of TH2 cytokines, including IL-4, IL-5 and IL-13 are markedly enhanced in diseased tissue [32,34]. Notably, food allergens trigger TH2 cytokine production by peripheral blood CD4⁺ T cells from patients with EGIDs [35,36], consistent with an allergen-driven TH2 diathesis being crucial for disease development.

Gluten reactions

Immune-mediated reactions to gluten include conventional FA to wheat, cell-mediated reactions to gliadin (celiac disease,

dermatitis herpetiformis and gluten ataxia) and non-celiac wheat sensitivity [37]. Wheat allergy is an adverse immunologic reaction to wheat proteins and like FA to other food allergens is IgE mediated. It may manifest as baker's asthma, rhinitis, eczema, urticaria and anaphylaxis. Wheat-dependent exercise-induced anaphylaxis is caused by a specific type of grain protein, ω 5-gliadins [37].

Although most studies analyzing potential links between atopy and celiac disease have shown a positive association, this is not universally the case [38–42]. However, there does appear to be a clear link between atopy and non-celiac wheat sensitivity. In one study, 262 patients with atopic diseases (asthma, rhinitis and eczema) and GI symptoms were investigated with duodenal biopsy, celiac serology and HLA testing [43]. Although almost 30% of patients had histological evidence of inflammation resembling celiac disease, none of these patients had anti-gliadin or anti-endomysial antibodies. Similarly, the prevalence of celiac disease-associated HLA haplotypes DQ2 and DQ8 was not increased beyond controls or the background population [43]. These data indicate that symptomatic GI disease characterized by macroscopic and microscopic intestinal inflammation is present in a significant number of patients with atopic disease, even the absence of true celiac disease. Importantly, patients from this cohort who subsequently adhered to a gluten-free diet showed marked symptomatic improvement. In another study, a subset of irritable bowel syndrome (IBS) patients in whom celiac disease was definitely excluded had their symptoms triggered by wheat exposure, even in robust double-blind placebo-controlled challenges, further supporting the existence of non-celiac wheat sensitivity as a true clinical entity [44]. Notably, co-existent atopy in patients with non-celiac wheat sensitivity was three to four times more common than in patients with true celiac disease or IBS [44], reinforcing the likely importance of atopy in this setting.

Inflammatory bowel disease

In parallel to the increasing prevalence of atopy, Crohn's disease (CD) and ulcerative colitis (UC), the major forms of IBD,

Table 2. Inflammatory bowel disease is associated with atopic disease.

Study (year)	Atopic disease prevalence in IBD	Atopic disease prevalence in controls	Ref.
Hammer <i>et al.</i> (1968)	UC (n = 97) Eczema 23% [†] Rhinitis 12% [†] Asthma 5% CD (n = 45) Eczema 33% [†] Rhinitis 18% [†] Asthma 4%	Control (n = 319) Eczema 7% Rhinitis 6% Asthma 3%	[47]
Jewell <i>et al.</i> (1972)	UC (n = 51) Atopic disease 16% [†] CD (n = 30) Atopic disease 13% [†]	Control (n = 86) Atopic disease 1.2%	[48]
Roberts <i>et al.</i> (1978)	UC (n = 300) Eczema 21% [†] Rhinitis 19% [†] Asthma 9% [†]	Control (n = 300) Eczema 8% Rhinitis 11% Asthma 5%	[49]
Myrelid <i>et al.</i> (2004)	CD (n = 280) Eczema 27% [†] Rhinitis 20% Asthma 15%	Control (n = 779) Eczema 16% Rhinitis 19% Asthma 12%	[50]
Bernstein <i>et al.</i> (2005)	UC (n = 3873) Asthma 21% [†] CD (n = 4193) Asthma 20% [†]	Control (n = 38,674) Asthma 16%	[46]

[†]Statistically significant difference in comparison with control group.

CD: Crohn's disease; IBD: Inflammatory bowel disease; UC: Ulcerative colitis.

are also increasing over time and in different regions around the world, indicating their emergence as important global diseases [45]. Several studies have sought to investigate whether there is a link between IBD and atopy, including some from the 1960s and 1970s. In most of these studies, including a large Canadian study of over 8000 IBD patients [46], an increased prevalence of atopic diseases, including eczema, allergic rhinitis and asthma in IBD has been reported (TABLE 2) [46–50]. Indeed, early reports of the histological features of IBD noted that in addition to neutrophils and lymphocytes, the cellular infiltrate present in intestinal lesions often included cells seen in atopic diseases, such as eosinophils, such that CD and UC were sometimes even referred to as 'allergic' diseases [51]. Some reports have shown increased total or food allergen-specific IgE levels in IBD [48,52,53] and a recent study of 117 consecutive IBD patients found increased rates of atopy (by SPT and allergen-specific IgE) in CD in comparison with the UC or the background population [54]. Orofacial granulomatosis is a rare chronic inflammatory disease of the mouth with overlapping features of CD. Atopy is present in >80% of orofacial granulomatosis patients, particularly in those with concurrent CD [54].

The potential role of dietary antigens in IBD has long captured the imagination. Loss of tolerance to food antigens, such as FA, is similar to the loss of tolerance to commensal bacteria

observed in IBD. Food antigens may exacerbate the inflammatory process in CD. 'Elemental diets' in which complex dietary proteins are replaced with their constituent amino acids are therapeutic in CD with efficacy comparable with corticosteroids [55]. Although a role for IgE-mediated FA remains to be conclusively shown in IBD, intestinal responses with aspects reminiscent of the allergic LPR may be seen in IBD, particularly with respect to the presence of mucosal eosinophils. There are conflicting data regarding whether mucosal eosinophils are associated with increased disease severity, tissue restitution or favorable treatment outcomes in IBD [56]. However, studies evaluating eosinophil granule proteins, indicative of eosinophil degranulation/activation, show that these proteins are increased in blood, inflammatory lesions and feces in active IBD [57–61]. The chief eosinophil chemo-attractant eotaxin is also increased in blood [62] and the intestine [63] of IBD patients with active inflammation. Support for a functional role for eosinophils is found in animal studies, where mice lacking eosinophils, eotaxin or eosinophil granule proteins have diminished intestinal inflammation [63–65]. A recent study has

shown that eosinophils, optimally quantified with a specific anti-major basic protein immunostaining, are increased in the lamina propria of IBD patients in numbers correlating with disease severity [66]. Furthermore, a careful morphological description of eosinophil tissue distribution revealed localization to mucosal nerve fibers. Eosinophilic inflammation was also observed to extend into smooth muscle layers, even in UC patients, which is conventionally considered a disease limited to the mucosa. Eosinophil/nerve/smooth muscle interactions in the mucosa of IBD patients offer a plausible mechanistic explanation of how inflammation may impact gut motor function and influence GI symptoms in IBD.

Interestingly, patients with CD [67] and UC [68] have increased eosinophil counts in induced sputum as well as increased airway hyperresponsiveness, hallmark features of asthma, indicating that the IBD/atopy association may be bidirectional, and a shared tendency for mucosal inflammation in the lungs and the gut.

Gastroesophageal reflux disease

The association between asthma and gastroesophageal reflux disease (GERD) is well recognized and has been extensively reviewed [69]. Non-immune mechanisms are proposed, including hyperinflation of the asthmatic chest resulting in gastroesophageal junction failure (and GERD), vagal hypersensitivity

triggering simultaneous bronchial smooth muscle constriction (causing asthma) and gastroesophageal junction relaxation (causing GERD) and aspiration of gastric secretions secondary to excess reflux triggering bronchial spasm. However, a large randomized, placebo-controlled trial demonstrated that even optimal acid suppression with proton pump inhibitors (PPIs) had no therapeutic impact on poorly controlled asthma, even in patients with GERD confirmed by pH monitoring [70]. Immunological mechanisms have also been postulated. Asthma patients have atypical reflux symptoms [71], and atopic patients have esophageal mucosal abnormalities supporting a possible 'allergic' basis for this association. Patients with grass pollen allergy have increased infiltration of the proximal esophagus with eosinophils during seasonal exposure in comparison with control subjects [72]. Furthermore, in a large series of primary care patients, GERD symptoms were more common in patients with allergic rhinitis, even in the absence of co-existent asthma [73], consistent with GERD being linked to atopy rather than just asthma.

A further mechanistic link between atopy and GERD, and indeed other acid-related GI diseases, has been suggested, caused by acid suppressing medications. In mice and humans, acid suppressing drugs such as H₂ blockers or PPIs trigger increased IgE production [74,75]. In some patients, augmented serum IgE levels arising following the institution of PPI therapy persisted beyond 5 months. Serum concentration of ST2 (soluble IL-33 receptor), a TH2-specific marker, is significantly elevated in patients commenced on acid suppression therapy [74]. Immediate hypersensitivity reactions to food proteins are also increased in mice treated with acid suppression therapy, indicating that this phenomenon was functionally relevant [75]. Increased IgE production following acid suppression may be due to resistance of dietary proteins to peptic digestion, which results in altered presentation of these allergens to the host immune system.

Functional gastrointestinal disorders

FGIDs, including IBS and functional dyspepsia (FD) are common diseases defined by a symptom-based classification (the Rome classification), in the absence of other recognized organic pathology. Patients with atopic disease have an increased risk of FGIDs. In a retrospective case-control study of 7235 adult primary care patients, lower GI symptoms were significantly more common in patients with asthma (9.9%) and allergic rhinitis (7.9%) in comparison with patients with other chronic diseases (4.9%) [76]. It has even been proposed that a subgroup of patients with IBS should be defined as 'atopic IBS', who may benefit from specific therapeutic interventions compared with non-atopic cases [77]. A similar trend is seen in the upper GI tract. In another large case-control study of primary care patients, dyspepsia was significantly more common in patients with asthma (21.1%) and allergic rhinitis (15.4%) compared with controls (11.3%) [73]. There are independent associations between bronchial hyperresponsiveness and FGIDs, including FD and IBS [78].

In recent years, new paradigms of FGID pathophysiology have emerged, which cast doubt on labeling of these diseases as 'functional' rather than 'organic'. Indeed, both IBS and FD

have consistently been linked to low-grade inflammation of the GI tract with expansion of cells conventionally associated with atopic disease. In IBS, there is expansion of mast cells throughout the small and large bowel [79–82]. There is now accumulating evidence from different research groups showing increased eosinophils in the duodenum of FD patients [83–85]. Subtle mucosal inflammation in these patients is linked to defective intestinal barrier function [86]. These data tie in with observations made nearly 20 years ago, showing that patients with atopic diseases have increased numbers of activated eosinophils in the small intestine and increased expression of pro-allergic cytokines, such as IL-5 [87].

Common immune pathways linking atopy & GI disease

The respiratory and GI tracts share anatomical and immunological similarities. In the 5–7th week of embryological development, a ventral bud from the proximal esophagus starts to develop into the lungs [88]. The respiratory and GI tracts have analogous mucosal-associated lymphoid tissue, which are key inductive sites of T-cell differentiation into effector subsets. Likewise, dysregulated immune activation at the epithelial barrier surfaces is common to both atopic disease and many GI diseases. Although atopy is defined by a heightened propensity to generate IgE antibodies, it is well established that cell-mediated responses are important in chronic inflammation. Antigen-specific TH2 T-cell responses in the GI tract are strongly reminiscent of T-cell responses apparent in the LPR following experimental allergen-challenge of atopic patients. The profile of cytokines produced by the TH2 CD4⁺ T-cell lineage selectively supports eosinophil recruitment and activation, a key feature of inflammation observed in the GI tract in several distinct pathologies. In both prototypical atopic diseases, such as asthma, and in more recently acknowledged eosinophil/mast cell-associated diseases, including IBD, IBS and FD, the localization of these potent innate effector lineages in close proximity to mucosal nerve fibers offers a plausible mechanism for these cells to potentiate aberrant smooth muscle activation, which may culminate in inappropriate hyperactivity of the airways or indeed gut [66].

Although it is convenient to explain the shared susceptibilities of GI and atopic diseases as mutual TH2-mediated disease, it should be recognized that this paradigm fails to account for all of the immunological pathways operating in either the gut or the airways. It is likely that designating individual mucosal diseases exclusively as TH1 or TH2 diseases is an oversimplification. Indeed, asthma, which is undoubtedly characterized by expansion of TH2 T cells, has also been linked to excessive production of IL-17, the prototypical TH17 cytokine, which supports neutrophil accumulation [89]. Indeed, eosinophils are not the only granulocytes infiltrating the airways and in severe asthma they are often accompanied by neutrophils in numbers correlating with disease severity [90]. Furthermore, a novel subset of effector memory CD4⁺ T cells that co-express TH2 and TH17 cytokines have been defined in patients with asthma [91], further blurring the boundaries between T-helper subsets.

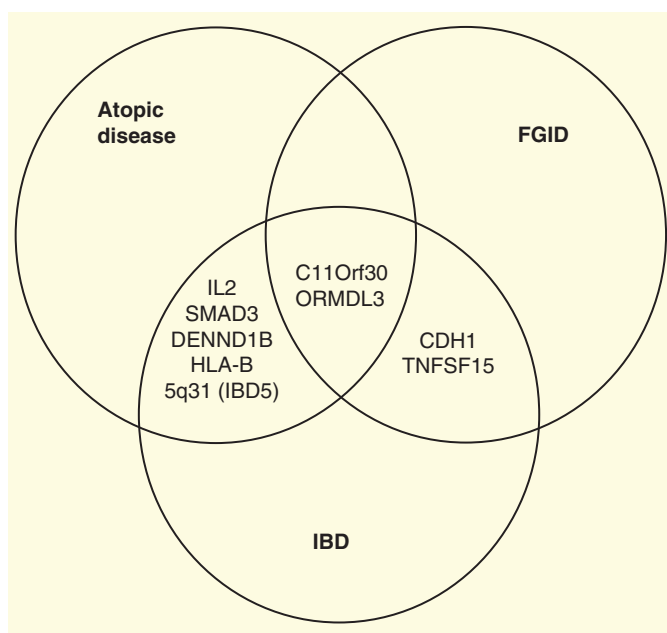


Figure 1. Loci identified by genome-wide association studies or mapping studies overlapping between patients with atopic disease, inflammatory bowel disease and functional gastrointestinal disorders.

FGID: Functional gastrointestinal disorder; IBD: Inflammatory bowel disease.

Data taken from [98–102].

Leukocytes isolated from the lung of asthmatic patients also produce high levels of the TH1 cytokines IFN- γ and TNF- α [92]. Unexpectedly, in an antigen-specific mouse model of asthma, adoptive transfer of antigen-specific TH1 cells exacerbated TH2-mediated airways disease, suggesting that TH1 and TH2 cells can co-operate rather than antagonize each other [93]. Although traditionally associated with macrophage activation, IFN- γ also mediates ‘pro-allergic’ effects. In a mouse model of asthma, it has been shown to stimulate mucosal mast cell activation [94]. Although TH1 and TH17 cells are more strongly implicated in IBD, there is also evidence that TH2 cytokines may also play a role. IL-13 producing natural killer T cells play a key functional role in oxazolone-induced colitis and are present in intestinal lesions of UC patients [95,96]. IL-13 may also play a role in intestinal fibrosis in CD, in which a novel population of innate lymphoid cells have been implicated [97]. Taken together, these studies highlight the dangers of oversimplifying complex disease processes and demonstrate some of the pitfalls of compartmentalizing diseases to fit with immunological paradigms, such as defining diseases as ‘TH1’ or ‘TH2’ mediated. It is likely that overlapping contributions from different effector T-cell lineages co-exist together with innate immune responses in these complex inflammatory responses.

Genetic insights indicative of shared pathways in GI & atopic disease

Population-based genome-wide association studies (GWAS) have revolutionized our understanding of complex genetic

diseases by identifying specific genetic loci significantly associated with disease, in a non-biased, non-hypothesis-driven fashion. GWAS have been performed in many complex diseases, including asthma [98], allergic disease [99] and IBD [100], resulting in the identification of many new disease susceptibility loci, often pin-pointing hitherto unsuspected biological pathways. Following on from these studies suspect loci representing the major signals identified in GWAS have then been sought in other related diseases areas. For example, the major polymorphisms identified in IBD GWAS have subsequently been sought in IBS patients [101]. Together, these studies have identified overlapping genetic susceptibility in atopic diseases and intestinal inflammatory diseases, including FGIDs. There are now at least seven single nucleotide polymorphisms shared between atopic diseases and IBD, some of which are additionally shared with FGIDs (FIGURE 1). Strikingly, these shared genes mostly encode proteins involved in the immune response (*IL-2*, *DENND1B*, *SMAD3*, *ORMDL3*, *HLA B*, *TNFSF15*).

In addition to shared risk variant alleles, there is also clustering of genes implicated in very similar biological processes in these diseases, frequently mapping to pathways involved in innate immune recognition of the microbiota, immune responses and epithelial barrier function. In allergic disease, IBS and IBD, there are increased numbers of patients with polymorphisms at loci encoding innate immune receptors which recognize conserved bacterial molecules, termed pathogen recognition receptors. These include the Toll-like receptors (TLRs) and the NOD family of intracellular pattern recognition receptors. Polymorphisms at loci encoding different pattern recognition receptors are associated with atopic disease (e.g., *TLR1*, *TLR9*, *TLR10*) [99], FGIDs (e.g., *TLR9*) [102] and IBD (e.g., *NOD2*) [100]. It is tempting to speculate that genetic polymorphism at loci involved in innate immune recognition of environmental microbes may influence epidemiological phenomena, such as the hygiene hypothesis (see below). Indeed, children of rural farmers who are exposed to an increased burden of environmental microbes have significant upregulation of some TLRs and reduced incidence of atopic disease [103]. Polymorphisms at loci encoding proteins involved in other immune pathways, including effector cytokines, cytokine receptors and cell signaling molecules also point to a common genetic architecture in these diseases [98–100,102].

Host interaction with intestinal microbial communities impacts host susceptibility to immune-mediated disease

While genetic susceptibility is clearly important for the development of GI disease, environmental factors are arguably at least as important. There are many more healthy individuals with polymorphisms at IBD susceptibility loci than there are IBD patients. Likewise, celiac disease susceptibility HLA haplotypes are present in 20% of the population, while the prevalence of celiac disease is only 1–2% [104]. These data persuasively point to the importance of environmental factors in GI disease susceptibility. The ‘hygiene hypothesis’ contends that reduced exposure to environmental microbes in

industrialized Western societies has contributed to the rapidly rising prevalence of atopic disease by altering the way in which our immune system is educated [105]. Others have postulated that lifestyle changes and modern medical practices, including the widespread use of antibiotics and industrialized food sterilization processes has resulted in a rapid loss of ancestral microorganisms, which have co-evolved with mammalian hosts over millions of years to educate and limit host immune responses to environmental stimuli [106]. Consequently, these ancestral regulatory organisms that help to put the brakes on overly exuberant host immune responses have been forever lost.

It is now recognized that the microbial communities colonizing our epithelial barrier surfaces play a key role influencing host susceptibility to immune-mediated disease, including atopy. Following birth, we become permanently colonized with prodigious numbers of microorganisms, including an estimated 10^{12} bacteria colonizing the skin and 10^{14} bacteria occupying the GI tract of humans [4]. The emergence of culture-independent molecular techniques, such as high-throughput 16S rRNA gene sequencing, has revolutionized the capacity to define the identity and proportional breakdown of the bacterial communities occupying particular ecological niches. The Human Microbiome Project has shown that the community composition of the microbiota colonizing 18 body habitats, including the skin, urogenital and GI tracts of 242 healthy adults is highly variable, both between individuals as well between different body habitats in the same individual [107]. As well as harboring the greatest total number of organisms, the microbiota of the distal GI tract is also one of the most diverse in terms of community membership and inter-individual variation. Collectively in humans, over 1000 bacterial species have been identified in this habitat and each of us harbors approximately 160 different bacterial species. Although neonates are born germ free, they are immediately colonized by maternally derived bacteria that they are exposed to during birth. Vaginally delivered babies are rapidly colonized at different body habitats by taxa present in the mother's vagina, including *Lactobacillus*, *Prevotella* and *Atopobium*, whereas infants delivered by caesarean section are predominantly colonized by skin taxa, such as *Staphylococcus* spp. [108]. However, by 3 years of age the composition of the intestinal microbiota largely evolves to resemble that of adults [109], demonstrating that the environmental conditions of a particular ecological niche strongly influence the ultimate success of microbial colonization.

Using high-throughput 16S rRNA gene sequencing patients with allergic disease, IBD or FGIDs have distorted intestinal microbiota community profiles in comparison with healthy control individuals [110–114]. Differences common to these diseases include reduced bacterial diversity, together with loss of certain phyla or species. These differences may have a significant impact on host immune phenotype, since it is now appreciated that the composition of the intestinal microbiota profoundly impacts key aspects of host immunity, such as the differentiation of effector CD4⁺ T-cell lineages. Intestinal colonization with segmented filamentous bacteria

(SFB) is necessary and sufficient for Th17 responses in mice, not just in the gut, but also at extraintestinal organs [115]. Mice lacking SFB are protected from immune-mediated diseases, including arthritis and demyelination [116,117], yet disease susceptibility can be reinstated following *de novo* colonization with SFB. These data show that intestinal bacteria dictate host generation of effector T-cell responses, both in and beyond the gut, which in turn impacts host susceptibility to immune-mediated disease.

The composition of intestinal microbiota also influences host capacity to generate Tregs. Mucosal Foxp3⁺ Treg induction is strikingly enhanced in mice colonized with particular profiles of bacteria from the genus *Clostridia* (from clusters IV, XIVa and XVIII) [118]. Furthermore, oral administration of these *Clostridia* clusters suppresses mucosal inflammation, including experimental allergic diarrhea. Intriguingly, these clusters of *Clostridia* are selectively depleted in patients with IBD [111] or atopic disease [110], consistent with the possibility that the intestinal microbiota of patients with these inflammatory diseases might have an unfavorable community structure for cultivating mucosal Treg.

Expert commentary

Well-established epidemiological associations and shared patterns of changing prevalence has led to growing enthusiasm for the possibility of an atopy/GI nexus. Only now are these associations starting to be reconciled by plausible biological mechanisms. Overlapping genetic susceptibilities, shared disruptions of key intestinal microbiota communities together with closely linked patterns of immune pathway activation likely underpin these associations. Current insights demonstrate that the genetic architecture of these diseases have related defects in genes involved in the immune response and recognition of environmental microbes. The intestinal microbial profiles of these diseases are distinct from healthy individuals, including perturbation of bacterial communities implicated as modulators of host immunity. Closer scrutiny of effector immune pathways operating at the barrier surfaces, including the skin, lung and gut has shown some overlapping features, and in particular a shared TH2 diathesis and eosinophil recruitment appears to be a recurring theme, although other mechanisms are also likely important.

Five-year view

The continuing parallel increases in prevalence of many of these common related diseases promises to place them at the forefront of concern of healthcare systems globally. The need for improved therapeutics in this important disease area has never been greater and interventions aimed at manipulating environmental variables and modulating host immunity are emerging on the therapeutic horizon. Strategies are likely to include novel probiotics, non-absorbable antibiotics, fecal microbiota transplantation and therapeutic supplementation with selective bacterial clusters, such as *Clostridia*. It is also anticipated that selective targeting of key cytokines/mediators

involved in these related pathologies will appear in the clinic in the coming years. Immunomodulatory cell therapies, such as *ex vivo* expanded Tregs, which are currently being evaluated in clinical trials [119], are likely to find favor in the treatment of related atopic and GI diseases. This exciting area of gene–environment interaction at the host–microbe interface is ripe for exploration.

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Key issues

- Atopic diseases are increasing in prevalence in parallel with numerous gastrointestinal (GI) diseases.
- Epidemiological evidence has highlighted links between atopy and various GI diseases, including functional GI disorders, eosinophilic GI diseases and inflammatory bowel disease.
- These associations may be underpinned by shared genetic susceptibilities, initiation of similar immune response networks and dysregulated host–microbe interactions.
- Patterns of immune pathway activation may be common to these diseases, including triggering of TH2 immunity and inappropriate mobilization of eosinophils and mast cells.
- The genetic architecture of these linked diseases overlap with some shared risk alleles and involvement of similar immune pathways, such as innate immune recognition molecules.
- The composition of the microbial communities colonizing the gut profoundly impacts host immunity and may be dysregulated in these diseases.
- Manipulation of the intestinal microbiota with probiotics, antibiotics, fecal microbiota transplantation and supplementation with bacteria, which selectively induce Treg cells hold therapeutic promise in this disease area.
- Selective targeting of key cytokines/mediators involved in these related pathologies will appear in the clinic in coming years.

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