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Review

Follow up on atopy and the gastrointestinal tract – a review of a common association 2018

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Abstract

Introduction: Primary atopic disorders can be classified as heritable genetic disorders presenting with deregulated pathogenic allergic effector responses irrespective of sensitization. In the last decade, there are parallel rises in the burden of atopic and gastrointestinal (GI) diseases.

Areas covered: There is increasing recognition of an association between atopy and GI disease through immune dysregulation, the microbiome and shared genetic pathways. Since the first article on atopy and the GI tract in 2014 in this journal, many more studies have shed light on the shared pathways in these diseases, particularly in the field of eosinophilic GI disease, functional GI disorders and inflammatory bowel disease.

Expert opinion: Understanding the links with common mechanisms in atopy and GI diseases that may lead to better targeting of treatment through manipulation of immune mechanisms, the microbiome, genetics, food allergens and specific GI diseases such as inflammatory bowel disease, functional GI disorders.

Keywords

Gastrointestinal Inflammation, Atopy, Eosinophilic Gastrointestinal Disease, Food Allergy, Microbiome, Genetics

Article highlights

- **Gastrointestinal diseases are associated with atopy** - Atopy is defined as the tendency to become sensitized and express IgE to environmental allergens after ordinary exposure. Parallel rises in the burden of GI disease and atopic diseases in the last decade, including eosinophilic esophagitis, food allergy, inflammatory bowel disease and functional gastrointestinal disorders
- **Common immune pathways in atopy and GI disease** - Recently described, innate lymphoid cells (ILCs) residing in the GI tract play critical roles in maintaining intestinal homeostasis, driving inflammatory pathology promoting allergic responses, these cells likely provide an immunological link between GI dysfunction and atopy.
- **Microbiome and atopy** - the microbiota actively contributes to maintaining immune homeostasis, a fine balance which when disrupted by overgrowth or loss of diversity can promote disease, for example loss of key digestive enzymes through microbial alterations may promote increased exposure to antigenic moieties on otherwise harmless foods.
- **Inflammatory Bowel Disease (IBD) and Atopy** – there is a strong association between IBD and the development of extra-intestinal atopic disease, including atopic dermatitis and asthma both of which themselves are linked to dysbiosis. Associations between IBD and atopic disease are bidirectional as asthma and atopic dermatitis are associated with an increased risk of subsequent IBD diagnosis
- **Food Allergy and Functional Gastrointestinal Disorders** – the immunology of food allergy shares similarities to other GI diseases such as eosinophilic oesophagitis, and the functional GI disorders (FGIDs); functional dyspepsia and the irritable bowel syndrome associated with traditionally type-2 immune responses
- **Genetics, Atopy and Gastrointestinal Disease** - genome wide association studies show overlap of genetic linkage of autoimmune disorders, asthma and inflammatory bowel disease

1. Introduction - Atopy and Gastrointestinal Disease

Atopy is defined as the tendency to become sensitized and express immunoglobulin E (IgE) to environmental allergens after “ordinary exposure” [1]. A recent review of primary atopic disorders classifies these as “heritable genetic disorders which present with deregulated pathogenic allergic effector responses irrespective of sensitization, which includes genetic disorders which result in abnormal mast cell degranulation, chronic type 2 T helper (Th2)- and eosinophil-mediated allergic inflammation, and exuberant IgE expression”, a broader definition which encompasses many allergic phenotypes [2]. Hypersensitivity and allergy are defined slightly differently, hypersensitivity as a condition resembling allergy with symptoms and signs that are reproducible which is induced by a defined stimulus at a dose tolerated by normal subjects (ordinary exposure) and allergy defined by a hypersensitivity reaction to verified or strongly suspected immunological mechanisms [3]. Whilst these definitions seem superficially similar, it is important in the context of the new ICD-11 codes, implemented June 2018, as these include system based clearly defined allergy and hypersensitivity conditions, which can be used to provide important morbidity and mortality statistics for use in disseminating scant health care resources [4].

1.1 Burden of Atopy in Society

There is a high burden of asthma in childhood, globally 11% [5], with highest rates in England, 38% [6], USA 20% and Oceania 29% [5]. Asthma is known to be associated with other atopic diatheses, allergic rhinitis and eczema [6]. The major determinants of developing an atopic disease is genetic predisposition and concomitant exposure to provocative environmental agents. Asthma is increasing globally, particularly in urban environments, for example, in migrant children in Italy, the prevalence also increased with the number of years of residence, gaining a lifetime risk similar to Italian children, emphasising environmental exposure as primary importance [7].

1.2 Atopy and Environment

Environment includes food consumption and interaction with the gut microbiome. The microbiome refers to the collective genomes of the microorganisms in a particular environment, and microbiota is the community of microorganisms themselves.

Approximately 10^{12} bacteria, viruses, fungi, and protozoa reside in the human gastrointestinal tract [8]. It is known that the microbiome is different in atopic versus non-atopic individuals, and this occurs in the first few months after birth [9].

Thus there are likely shared pathways between atopy and the gut, this review aims to build on the previous atopy - gut review in this journal in 2014 [10].

2. Gastrointestinal Diseases are associated with Atopy, Evidence from Epidemiology Studies

It is noteworthy that there are parallel rises in the burden of gastrointestinal (GI) disease and atopic diseases in the last decade [10].

2.1. *Eosinophilic Oesophagitis*

The major example of the association with atopy is eosinophilic oesophagitis (EoE). Both the incidence and prevalence of EoE have increased dramatically over time, and causes of this condition are blamed on food allergen changes, increase in aeroallergens and early life exposures which may affect the microbiome [11]. A systematic review of 53,592 adult and pediatric EoE patients showed a significantly higher rate of comorbid asthma, eczema and allergic rhinitis with odds ratios (ORs) ranging from 2.8 to 5.1 times greater in asthma [12]. Whilst there is good evidence that asthma and EoE occur together, there is sparse evidence characterising this association [13]. Of note in children and adults with EoE, whilst both show a high prevalence of comorbid atopy and food allergy, children show a higher sensitivity to food allergens with higher rates of asthma than adults [14].

2.2 *Food Allergy*

Food allergy is common, with up to 10% of the population affected, mainly those in developed countries and more common in children compared to adults and allergy to cow's milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish constitutes the majority of food allergy reactions [15] [16]. Fortunately, some food allergies resolve in late childhood – milk, egg and wheat (50% resolution), soy (45%) whereas peanut and tree nut allergy are much lower, 10-20% and allergies to seeds, fish and shellfish are considered persistent [16].

2.3 *Inflammatory Bowel Disease*

Inflammatory bowel disease (IBD), ulcerative colitis and Crohn's disease are also associated with atopy [10]. For example, cow's milk allergy is a risk factor for paediatric IBD and asthma, paediatric Crohn's disease [17]. A systematic review of 18 studies concludes that asthma is associated with both ulcerative colitis and Crohn's disease, although there was variation by geographical region and study design may also have contributed to some difference in results [18].

2.4 *Coeliac Disease*

A link with coeliac disease and atopy is also well established. Those with coeliac disease and also those on a gluten free diet without a doctor diagnosis of coeliac disease - non-coeliac wheat sensitivity (NCWS) have comorbidities of autoimmune and allergy related

disorders as shown in a large population study of 22,277 participants in the National Health and Nutrition Examination Survey [19]. Coeliac disease confers an excess risk of asthma, up to 1.6 fold in Swedish children and adults [20]. In children, those with a positive asthma predictive index (API) [21] were more likely to have coeliac disease, (19% versus 8%) with a strong association with family history of asthma and that there are asthma-related genetic factors in common with coeliac disease [22]. Whilst antibiotic exposure in the first year of life increases the risk of early diagnosis of coeliac disease in infancy, however concurrence of the two disorders is not explained by this exposure and other shared risk factors such as environment and genetics may account for this association [23].

2.5 Functional Gastrointestinal Disorders

Functional gastrointestinal disorders (FGIDs) are common (13% with irritable bowel syndrome (IBS) and 16% with functional dyspepsia (FD) in an Australian population study in 2018 [24]. Atopy and FGIDs has been explored in population studies of over 23, 000 patients in primary care, in the UK [25]. This study showed that FGIDs and atopic conditions (asthma, eczema, allergic rhinitis/ hay fever and allergic conjunctivitis) are linked, and share a connection partly explained through mood disorders of anxiety and depression, and this heterogeneity was proposed to be explained by a genetic- environmental link [25]. A recent study from Australia also showed atopy and autoimmune disease are linked to FD and IBS, although in this general population. not linked to psychological distress [26]. This suggests that different peripheral pathways may be triggered in different geographical environments. The events in early life such as non IgE mediated food allergies can impact with presentation of symptoms of FGIDs in later life and gastroenterologists should be aware of this link when taking a history and making a diagnosis in GI disease [27] .

2.6 Gastro-oesophageal reflux disease

In gastro-oesophageal reflux disease (GORD) an association of reflux with symptoms of asthma is well known particularly so in severe asthma, with reported prevalence rates from 17% to 74% [28]. A recent review whilst controversial, suggested that, treating GORD in this subset of asthma patients may improve asthma control [29].

2.7 A Holistic Approach to Diagnosis in GI Disease

Whilst association does not imply causality it is the initial step to understanding common pathology pathways in disease [30] and from a clinical standpoint we should rigorously phenotype patients based on known clinicopathological characteristics with expert consensus backing, such as in coeliac disease [31] and eosinophilic oesophagitis [32]. The work up of patients should include a careful structured clinical history, biopsy, and in future

microbiome and genetic studies, dietary inquiry and intervention. Utilising a holistic approach to GI disease [33] we can then unravel the links with atopy and GI disease, and importantly diagnose and treat disease comorbidity as an increased risk of coronary heart disease and diabetes mellitus has been noted with asthma [34].

3. Common Immune Pathways in Atopy and GI Disease.

The GI tract is a site of complex immune homeostasis, where the local mucosal immune system regulates the balance between tolerance of the intestinal microbiota and luminal contents (such as food), and the surveillance and elimination of pathogens and expanding pathobiont populations. Our understanding of mucosal immune regulation has been significantly changed by the recognition of innate lymphoid cells (ILCs)[35]. ILCs are broadly classified into three subsets (ILC1, ILC2 and ILC3) based on their transcriptional regulation and their effector functions, which are analogous to T- helper (Th)1, Th2 and Th17 cells. While relatively low in abundance, ILCs are extremely potent, and play critical roles in maintaining intestinal homeostasis, driving inflammatory pathology in promoting allergic responses[36,37].

ILCs contribute to homeostasis in the intestinal mucosa through limitation of CD4+ T cell responses to the normal intestinal microflora. Conversely, the absence of specific ILC subsets, such as ROR γ t+ Group 3 ILCs (ILC3s), can drive a dysregulation of gut homeostasis [38]. ILC3s produce IL-17 and IL-22 in the presence of IL-23 and IL-1 β [35] and maintain the balance between intestinal homeostasis and responses to extracellular bacterial pathogens. This balance appears to be at least partially dependant on the balance of IL-22 and IL-17 produced by ILCs [39] where loss of IL-22 promotes a Th17 response. In the context of atopy, recent animal studies have suggested that eosinophil recruitment and activation [40] can be facilitated by Th17 responses. Eosinophils are generally considered to be indicative of a Th2 allergic phenotype, but here, the pathway is driven by an axis of IL-23/Th17 and GM-CSF [41,42]

These events may promote a cyclic escalation of type 2 responses whereby secretion of IL-33, activates local eosinophils and further drives the maturation of ILC2s [43], which themselves are regulators eosinophil homeostasis [44]. ILC2s, are largely analogous to the classical atopic Th2 response and have been identified as early facilitators of allergic responses. Mast cells, which are abundant in atopy, functional GI disease and inflammation release serine proteases promoting the expansion of eosinophils and IL-5 and IL-13 producing ILC2s [45,46]. The respective Th2 and Th1 cytokines, IL-33 and IFN- γ , act as counter-regulators of ILC2 homeostasis [47]. Infection or dysbiosis, may be sufficient to tip the balance of these cytokine responses and disrupt intestinal homeostasis. For example, during micronutrient deficiency (e.g. with infection) ILC2 populations expand within the GI

tract [48]. Because GI resident ILC2 may be recruited to other sites in the body[49], this may provide an immunological link between GI dysfunction and atopy.

4. Microbiome and Atopy

While our understanding of the mechanistic interactions of the microbiota with the host is still expanding, it is clear that the microbiota is crucial for metabolic regulation, protection against invading pathogens and the immune maturation of the host. Thus the microbiota actively contributes to maintaining immune homeostasis and given the variance in microbiome compositions observed between individuals and geographies, it is likely that specific host-microbiome homeostasis develops throughout childhood [54]. Alteration to this homeostasis manifests as a reduced microbial diversity that is commonly observed in inflammatory, autoimmune and metabolic diseases [55-57]. Although the mechanism behind these disease-associated changes is unclear, it is commonly believed that reduced microbial diversity allows the outgrowth of pathobionts that aggravate the immune system to promote disease. Associations between increased populations of *Clostridium difficile* and *Escherichia coli* and childhood atopic disease supports this hypothesis [58], as does the observation that the use of antibiotics during childhood increases the risk of atopy[59-61]. However, an alternative explanation may be that the loss of important immuno-modulatory species, such as *Clostridia spp.* and *Bacteroides spp.*, impacts immune homeostasis which allows outgrowth of intestinal pathobionts. Animal studies demonstrate the importance of *Clostridia spp.* in the regulation of intestinal ILC and T cell populations, whereby antibiotic elimination of *Clostridia spp.* leads to a decrease in IL-22 production by mucosal innate lymphoid cells (ILCs) and a loss of and T regulatory cell (Treg) populations within the GIT [51,62-64]. This likely results from a loss of microbial metabolites such as short chain fatty acids, which increase the immunosuppressive activity and number of Tregs cells in the GIT [65].

Tregs play a number of key roles in maintaining gut homeostasis, limiting the expansion of effector T cell populations and controlling tolerance responses specific antigens. Tregs also control the intestinal microbiota through secretion of TGF- β , facilitating B cell class-switching to produce IgA. Secretory IgA (sIgA) is released at skin and mucosal surfaces and prohibits the binding of pathogens, and pathogen related products, to the GIT epithelium. As specific microbiota populations influence Treg abundance, host Treg-microbiota balance may be co-regulatory [66,67] promoting tolerance towards some populations while controlling pathobionts through IgA secretion[68,69] This is reflected in the fact that IgA deficiency is commonly associated with atopy and autoimmune disorders but is not a key driver of severe infection[70]. Patients with atopic dermatitis and asthma both show reduced levels of local sIgA [71,72] and studies in infant cohorts suggests that reduced IgA responses to the gut

microbiome precede the development of asthma and allergic disease[73]. Thus, dysbiosis may be an initiating factor in atopic individuals through loss of Treg homeostasis and an associated reduction in systemic sIgA capacity. This would also explain observational studies linking early life antibiotic use with food allergy[74,75] and inflammatory bowel disease[76]. In the context of commensal and pathobiont - pathological (disease-causing) organism -balance, a seminal study looking at the colon microbiome in discordant twins, found that an abundance of *Ruminococcus gnavus* was associated with respiratory allergies [77] Mice fed *R. gnavus* developed respiratory inflammation characterised by Th2 biased immune reactions in the colon and lung [77]. Further immune characterisation of these models may provide insight into how alterations in the intestinal microbiota may lead to systemic manifestations of atopic and allergic disease.

See Figure 1.

5. Inflammatory Bowel Disease and Atopy

Inflammatory bowel diseases (IBD) is an extremely heterogeneous group of diseases manifesting as chronic inflammation of the GI tract [78]. Of the different IBD endotypes, Crohn's disease is broadly driven by Th1/Th17 immune responses while ulcerative colitis has features reflective of Th2 and Th17 pathology. Both diseases are associated with an imbalance in the intestinal microbiota [79,80] and immune responses against the microbiota are considered an underlying feature of both diseases.

Like food allergy, there is evidence that early life use of antibiotics is a risk factor for early onset IBD[76,81]. This risk is greater with pre-partum use of antibiotics, suggesting that colonisation of a newborn and subsequent establishment of the microbiota is a critical factor in developing immune health[76]. Parallel to this, there is a strong association between IBD and the development of extra-intestinal atopic disease, including atopic dermatitis[82] and asthma[83,84], both of which themselves are linked to dysbiosis[73]. Given the evidence from germ free animals suggesting that a microbiota is essential for development of a healthy immune system[57], both IBD and atopy may be linked through under-development or defects in the immune system arising from early life dysbiosis. Recent reports of gut-lung trafficking of immune cells[49,85] may shed light on the mechanisms that drive asthma and allergic disease outside of the GI tract of IBD patients. Of note, is the finding that ILC2, active in the lungs and circulatory system, may arise from resting cell populations in the GI tract[49]. ILCs play broadly analogous roles to adaptive T cells. In particular, ILC2s, like their Type 2 T helper cell counterparts, secrete type-2 cytokines including IL-5 and IL-13. ILC2 populations have been identified in patients with asthma, allergic rhinitis and atopic

dermatitis[86] and IL-33, an epithelial cytokine broadly associated with allergic disease is a potent activator and mobiliser of ILC2s[87,88]. Whether disturbances in the GI tract interfere with the homeostasis of gut-resident ILC2s remains to be determined, but systemic dissemination of gut bacteria, common in IBD[85], may be a causal factor. The associations between IBD and atopic disease are also bidirectional with both asthma and atopic dermatitis associated with an increased risk of subsequent IBD diagnosis[89,90]. In the case of lung disease, clinical and small animal studies suggest that reduced lung capacity can drive bowel dysfunction through systemic ischemia[85,91], which in turn promotes increased intestinal permeability and inappropriate angiogenesis which predisposes to IBD.

6. Food Allergy

The GI tract operates in a state of homeostasis, surveilling the lumen for potential threats while maintaining active tolerance, as it is exposed to a vast array of food and microbial antigens. This tolerance is largely facilitated by mucosal T cell populations, which produce IL-10 and TGF- β maintaining Treg populations, IgA production and ultimately driving anergy [92]. Food allergy occurs due to a poorly understood breakdown of this immune tolerance, and in many respects, the immunology of food allergy shares similarities to other GI diseases such as eosinophilic oesophagitis, and the functional GI disorders (FGIDs); functional dyspepsia and the irritable bowel syndrome. All of these conditions are associated with traditionally type-2 immune responses [93] and a breakdown of immune homeostasis in the intestinal mucosa. Immunologically, food allergy is facilitated by expansion of allergen-specific Th2 cells that produce interleukin IL-4 and IL-13, promoting B-cell class switching to allergen-specific IgE which mediates mast cell, basophil and eosinophil degranulation and thereby allergic disease. The activation of Th2 cells leads to release of IL-25 and IL-33, which are potent activators of eosinophils and ILC2s [94]. Here again, ILC2s play an important role and recent mechanistic studies suggest that IgE production drives expansion of intestinal ILC2 reserves[95] Once activated IL-4 secreted from ILC2s enhance mast cell activity[95] and actively suppress Tregs[96], augmenting the allergic response. It is unclear what causes the initial sensitisation to food antigens, but alterations in the microbiota, commonly associated with food allergies, may hold the key[97]. Because the microbiome accounts for enzymes responsible for the digestion of certain proteins and absorption of dietary components that otherwise would not be digestible [98,99] loss of key digestive enzymes through microbial alterations may promote increased exposure to antigenic moieties on otherwise harmless foods. For example, gliadin, the immunogenic gluten derivative involved in the pathogenesis of coeliac disease, is not readily digestible by host enzymes, but is readily degraded by intestinal microbes[24]. Thus impaired microbial

digestion, as a result of dysbiosis, could facilitate food allergies and related disorders such as non-coeliac wheat sensitivity.

7. Functional Gastrointestinal Disorders

Functional GI disorders (FGIDs) are a group of unexplained chronic gastrointestinal conditions which manifest with no obvious structural or biochemical pathology. The two most common forms of FGIDs are functional dyspepsia and the irritable bowel syndrome, although these two conditions manifest heterogeneous symptoms and likely represent several distinct conditions[101,102]. There is growing consensus that FGIDs are a result of low-grade intestinal inflammation, or loss of immune homeostasis, as increases in mast cells, eosinophils and gut homing T cells are observed in these conditions, accompanied by regional changes in the microbiota corresponding to where the symptoms manifest. While a Th2 response has been associated with the pathophysiology of FGID, largely due to the presence of mast cells, eosinophils and *ex vivo* cell stimulation assays[103], there is little *in vivo* evidence for this and very poor consensus on the immune endotypes involved in FGIDs [104].

There is significant overlap between FGID and atopic diseases, most commonly eczema, asthma, allergic rhinitis and allergic conjunctivitis [25]. In addition, IBS patients are 10-times more likely to suffer from pulmonary hypersensitivity than healthy individuals [105].

Epidemiological studies support a link between FGIDs and atopy, with a study of over 23,000 patients in primary care demonstrating a 25% overlap between atopy and FGID [25]. Observations of increased duodenal eosinophil numbers in FGID patients presenting with dyspepsia and post-infectious IBS may offer insight into the link between atopy and FGIDs[106-108] although the clinical significance and link to atopic disease remains to be determined.

While there is a clear link between FGIDs and atopy, it is unclear whether FGIDs promote allergic disease, or vice versa. A recent case study highlighting a case of “atopic IBS” occurring with severe asthma, reported that ongoing treatment with omalizumab, an anti-IgE monoclonal antibody, not only reduced the burden of asthma symptoms, but also maintained complete remission from IBS symptoms for 4 years[109]. A subsequent study in a Japanese cohort identified a population of IBS patients with diarrhoea, characterised by an IgE-mediated serological food hypersensitivity[110]. There has been some suggestions that FGIDs, or at least some FGID subtypes may represent a mild allergic or hypersensitivity reaction to food[33,111,112]. While FGIDs may be managed by dietary intervention [113,114], reports of elevated IgE are surprisingly sparse and FGIDs have largely been considered distinct from food allergy.

Nevertheless, there is sufficient evidence to suggest that a proportion of FGID patients are subject to an atopic phenotype and distinguishing these groups will be important in the overall understanding and management of FGIDs.

8. Genetics, Atopy and Gastrointestinal Disease

The concept of atopy as a heritable genetic disorder presenting with dysregulation of allergic effector responses has led to the search for shared genetic and other pathways in GI disease[2]. It is apparent from genome wide association studies that there is overlap of genetic linkage of autoimmune disorders, asthma and inflammatory bowel disease – common gene loci for example include DENN Domain Containing 1B (*DENND1B*), Mothers against decapentaplegic homolog 3 (*SMAD3*) and Solute carrier family 22, members 4 and 5 (*SLC22A4/5* (5q31/IBD5)) present in both asthma and Crohn's disease[115] and in the case of *SLC22A4*, also coeliac disease [116]. Genetic factors are implicated in food allergy and associations with variations and mutations in the Filaggrin (*FLG*) gene and HLA haplotypes are important and there is a complex interplay with genetics and the microbiome[117]. Recently identified associations of *HLA-C1* genotype associations with Crohn's disease in separate Korean and Spanish populations [118,119] are of particular interest given that genome wide association studies have previously associated HLA-C region genotypes with psoriasis [120], asthma[121] and IgE regulation [122]. Linking single nucleotide polymorphisms to biological dysfunction is not always straightforward, but these studies do at least suggest that common pathways may be involved across disorders.

Expert Opinion

The burden of both GI disease and atopy, which may be environment dependent, is increasing in society. It is now well established from recent epidemiology studies, that there are links with atopy and GI disease particularly in eosinophilic oesophagitis with food allergies and also the functional GI disorders functional dyspepsia and irritable bowel syndrome, . These and other GI diseases are also linked to dysbiosis of the microbiome with subsequent or independent immune dysregulation. In addition, there is genetic predisposition to these diseases, - for example, coeliac disease only occurs in those with a permissive genetic profile.

Accurate diagnosis of disease is all-important for effective treatment – it must become the norm to take a holistic approach to patients as currently for symptoms and examination. In future microbiome and genetic profiling and assessing serology biomarkers for disease and disease biotype, as occurs in eosinophilic versus neutrophilic asthma will become all important. It is known that childhood treated asthma and coeliac disease are significantly

associated and therefore coeliac disease in asthmatics should be considered and vice versa with coeliac disease, family history being important here also. Overlap in disease of different specialities must be addressed sensibly. Recognition of the vulnerability to overlap is important as early recognition may prevent lasting damage.

The treatment of functional GI disease is rarely successful, based on alleviation of symptoms and not cure. The current hope is that there may be overlap of successful atopy treatments with that can improve therapy for functional GI disorders, trials of this approach are warranted. Targeted treatments in this area may alleviate for example, atopic IBS and allow understanding of duodenal eosinophilia – is this “asthma of the duodenum”?

Common immune pathways in atopy and GI disease are recently described and innate lymphoid cells (ILCs) residing in the GI tract play critical roles in maintaining intestinal homeostasis, driving inflammatory pathology promoting allergic responses, these cells likely provide an immunological link between GI dysfunction and atopy.

The microbiota actively contributes to maintaining immune homeostasis, a fine balance which when disrupted by overgrowth or loss of diversity can promote disease, for example loss of key digestive enzymes through microbial alterations may promote increased exposure to antigenic moieties on otherwise harmless foods. Targeting the microbiome to modulate immune atopic reactions is an exciting prospect as new technologies delve deeper into identifying all the microbes present in the gut and which -or more likely which combinations and which species - are specifically linked to GI diseases and atopy. If the microbiome is mapped out alongside genetic profiling for GI disease and atopic tendencies, we can personalise an individual's proclivities and possibly avert GI and atopic disease expression from an early stage. Genetics, atopy and GI disease are known to be linked and genome wide association studies show overlap of genetic linkage of autoimmune disorders, asthma and inflammatory bowel disease. There is- a strong association between IBD and the development of extra-intestinal atopic disease, including atopic dermatitis and asthma both of which themselves are linked to dysbiosis. Associations between IBD and atopic disease are bidirectional as asthma and atopic dermatitis are associated with an increased risk of subsequent IBD diagnosis

Five year view

Atopic GI disease and disease are both rising in prevalence and the evidence linking these two conditions should continue to make them a priority issue for Health Services. A continuing search for cost effective therapeutic measures must continue, including immunomodulation and likely antibiotic/ probiotic microbiome manipulation for exploration. Finding effective approaches to reprogram GI immune systems may prevent future gut

diseases, however in the short-term attention to healthier diets and curtailing antibiotic exposures may optimize public health in terms of atopic disease risk [123].

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Legend to Figure 1

Figure 1: Immune mechanisms linking GI Disease and Atopy:

Intestinal dysbiosis can lead to loss of Regulatory T cell (T_{reg}) populations and may result in loss of systemic Immunoglobulin A (IgA) production. Dysbiosis also influences type 3 innate lymphoid cell (ILC3) homeostasis, leading to an increase in interleukin (IL-) 17 at the expense of IL-22. T helper (Th) 17 responses facilitated by IL-17, may, in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) recruit eosinophils. Interplay between mast cells and eosinophils, facilitated by IL-25 and IL-33 or by IgE, can drive the expansion of type 2 ILCs (ILC2s), which in turn, can further enhance eosinophil recruitment. IL-4 secretion from ILC2s can suppress T_{reg} populations, while extra-intestinal signalling can recruit expanded ILC2 populations from the gastrointestinal tract to distal organs.

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Immune mechanisms linking GI Disease and Atopy

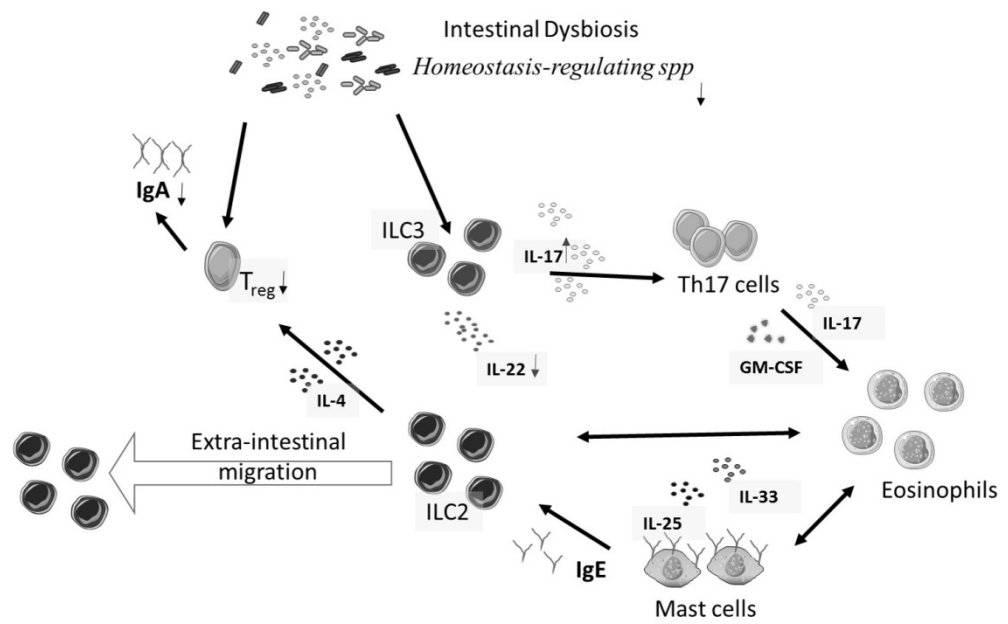


Figure 1

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