

REVIEW

Lung–gut cross-talk: evidence, mechanisms and implications for the mucosal inflammatory diseases

M. K. Tulic^{1,2}, T. Piche^{1,3} and V. Verhasselt^{1,2}

¹Université de Nice Sophia-Antipolis, EA 6302 Tolérance Immunitaire, Nice, France, ²The International Inflammation 'in-FLAME' Network, Worldwide Universities Network, Perth, WA, Australia and ³Department of Gastroenterology and Nutrition, Hôpital de l'Archet 2, CHU de Nice, Nice, France

Clinical & Experimental Allergy

Summary

The mucosal immune system (including airway, intestinal, oral and cervical epithelium) is an integrated network of tissues, cells and effector molecules that protect the host from environmental insults and infections at mucous membrane surfaces. Dysregulation of immunity at mucosal surfaces is thought to be responsible for the alarming global increase in mucosal inflammatory diseases such as those affecting the gastrointestinal (Crohn's disease, ulcerative colitis and irritable bowel syndrome) and respiratory (asthma, allergy and chronic obstructive pulmonary disorder) system. Although immune regulation has been well-studied in isolated mucosal sites, the extent of the immune interaction between anatomically distant mucosal sites has been mostly circumstantial and the focus of much debate. With novel technology and more precise tools to examine histological and functional changes in tissues, today there is increased appreciation of the 'common mucosal immunological system' originally proposed by Bienenstock nearly 40 years ago. Evidence is amounting which shows that stimulation of one mucosal compartment can directly and significantly impact distant mucosal site, however the mechanisms are unknown. Today, we are only beginning to understand the complexity of relationships and communications that exist between different mucosal compartments. A holistic approach to studying the mucosal immune system as an integrated global organ is imperative for future advances in understanding mucosal immunology and for future treatment of chronic diseases. In this review, we particularly focus on the latest evidence and the mechanisms operational in driving the lung–gut cross-talk.

Correspondence:

Meri K Tulic, EA 6302 "Tolérance Immunitaire" Université de Nice Sophia-Antipolis, Hôpital de l'Archet, Route Saint Antoine de Ginestière BP3079, 06202 Nice Cedex 03, France. E-mail: meri.tulic@unice.fr

Cite this as: M. K. Tulic, T. Piche, V. Verhasselt. *Clinical & Experimental Allergy*, 2016 (46) 519–528.

Introduction

Evidence for mucosal immune system as a system-wide organ

Since 1978 [1], we have been introduced to the common mucosal immunological system; however, it is not until recently we have started to understand the importance of this concept. The concept suggests that different mucosal sites of the body function together as a system-wide organ to protect the host against foreign invading organisms. Over the last 30 years, there have been a multitude of studies showing cross-mucosal interaction between distant mucosal sites. Various studies demonstrating vaccinations at one mucosal site leading to protection in another [2], infection with a virus resulting in high concentrations of virus-specific immunoglobulins in other mucosal secretions [3] or greater risk of allergic lung disease in neonates who

take oral antibiotics [4] are to list a few. This interaction between distinct mucosal sites is further complicated by one's genetic predisposition (particularly in cystic fibrosis) as well as the influences of the external environment, as recently demonstrated that dietary fibre (in the gut) influences immune responses in the lungs and severity of allergic inflammation in mice [5]. It is perhaps not surprising that there may exist a lung–gut axis as these two mucosal sites are structurally and functionally similar organs with the same embryonic origin. According to Chinese medicine, the lung and the intestine are a pair of related organ systems (Biao-Li) [6]. Both of these tissues have an enormous surface area exposed to external environment and therefore act as the primary defence against the invading foreign pathogens, playing a crucial role in innate and adaptive immunity. It is often the case that respiratory and intestinal mucosal disease present with overlapping pathological changes. Perhaps this is not surprising

considering that the gastrointestinal tract will ultimately be exposed to the same pathogens or antigens that are introduced into the respiratory system [7] and gut mucosal system may serve as a primary sensor of foreign antigens from the environment. Just as the revelation that asthma is simply not a disease of the large airways (but small airways and the parenchyma) has revolutionized the treatment of asthma, recognition of mucosal immune system as a system-wide organ may be the critical step in future treatment of debilitating chronic inflammatory diseases such as inflammatory bowel disease (IBD), allergies and asthma which are increasing at an alarming rate.

Lung-gut cross-talk in inflammatory bowel diseases (IBD)

The first evidence of pulmonary-intestinal cross-talk was reported nearly 50 years ago by Turner-Warwick [8] and later by Kraft and colleagues in 1976 [9] who have noted development of severe, chronic broncho-pulmonary disease in patients with IBD, years after onset of their diagnosis. Using CT scans, the authors found a correlation between individual's pulmonary symptoms and the severity of their intestinal disease. Early epidemiological evidence for pulmonary involvement in IBD is rather controversial. Some reported only a few cases of pulmonary complications in IBD patients [10], others no associations at all [11]. It was not until more recently with more sensitive technology and advances in imaging methods (including high-resolution computed tomography, sensitive pulmonary function tests, bronchoscopies and histological examinations) that the extent and severity of pulmonary function abnormalities have been recognized in clinical literature. These new studies have demonstrated a wide spectrum and severity of pulmonary involvement in otherwise lung asymptomatic IBD patients; up to 48% adult IBD patients and 71% of IBD children and adolescents to have bronchial hyper-reactivity [12, 13]. Changes were not only seen in large but small airways, changes in bronchial epithelium itself (including basal cell hyperplasia, basement membrane thickening, sub-mucosal inflammation, small airway fibrosis and increase in epithelial thickness), as well as inflammation of pulmonary parenchyma. In fact, in a large population-based Canadian study performed 15 years ago, it was reported that pulmonary complications were the most common concomitant chronic disorder in patients with IBD [12] and that pulmonary involvement was more pronounced in patients with active disease compared to those in remission [13]. Only a few years later it was recommended [14] that physicians must take a broader approach when treating patients with concomitant gastrointestinal and pulmonary disease.

IBD, which includes Crohn's disease (CD) and ulcerative colitis (UC) are good examples to study cross-talk between the gut and the lungs. Although the gastrointestinal tract is the main affected site, both CD and UC are systemic inflammatory disorders that can affect almost all organs. In the lungs, the symptoms manifest as increased numbers of alveolar lymphocytes, interstitial lung disease and a reduction in the diffusion capacity of the lung. Today, it is believed that almost half of UC [15, 16] and half of CD [15, 17] patients have sub-clinical pulmonary abnormalities and that even in the absence of broncho-symptoms and presence of normal lung function, there exists low-grade inflammation in their airways [18]. In agreement with those statistics, a literature survey which identified 55 articles citing thoracic disorders in IBD patients, have shown large airway involvement accounting for 39% of these associations [19]. This year, a large cohort study in Taiwan ($n = 26\,300$) have shown IBD to be associated with a higher subsequent risk of asthma [20]. Pulmonary impairment is not only seen in adults but also in children with gut dysfunction [21]. Unfortunately, only a few basic research studies have been performed looking at mechanisms of the inflammatory cross-talk between the intestine and the lungs and clearly this area of research warrants further exploration to influence clinical practice where in general, lungs and gut are still treated as separate mucosal sites.

Lung-gut cross-talk in allergic disease

Allergic disease including asthma, rhinitis and food allergy are on the increase, they are occurring at an earlier age and children are less likely to outgrow their disease by childhood. The most common manifestation of allergic responses to food involve the gut and gastrointestinal allergy to ingested foods often precedes or coexists with respiratory tract symptoms including nasal congestion, rhinorrhea, sneezing, coughing and wheezing [22]. In asthmatics, the incidence of respiratory symptoms induced by food ranges between 2% and 8% [22]. Asthmatics and those with allergic rhinitis have been shown to have high levels of eosinophils in both airways and in their intestines [14]. Moreover, some asthmatic patients commonly suffer from gastrointestinal disorders such as primary eosinophilic gastrointestinal disease, gastro-oesophageal reflux disease (GERD) or the more severe eosinophilic esophagitis (EE); an overlapping lung-gut conditions. In these conditions, eosinophils, which are hallmark cells of the allergic disease, are significantly elevated and are also thought to be responsible for disease pathogenesis in the gut. Eosinophils may hold a key in understanding the inflammation process between the two mucosal sites and it may simply be that allergic symptoms run from

one end of the gut to the other [14]. Moreover, just as there are different types of asthma, it has been proposed that there may also exist different types of gut disease that may be related to presence or absence of eosinophils [14].

It has been well-known for some time that prior exposure to a pathogen in the lungs has a significant effect on the subsequent development of allergic or respiratory disease at the same site, however, whether it has an effect on a distant site remained unanswered until recently. Brandt and colleagues have shown that experimental gastrointestinal allergy to OVA enhances pulmonary responses to OVA but also to an unrelated allergen (house dust mite, HDM) [23]. That is, an established inflammation in the gastrointestinal tract pre-disposes mice to specific and non-specific allergic airway responses. Williams and colleagues have shown that the immune response generated after colonic bacterial infection with a gut-restricted-pathogen such as *Citrobacter rodentium* can abrogate eosinophilic pulmonary disease to an unrelated pathogen (*Citrobacter neoformans*) in the lungs of mice [24]. Similar cross-protection was demonstrated by Verhasselt and colleagues showing administration of food antigen to the neonatal mice gut protects against future development of respiratory allergic disease [25]. Moreover, it has been shown that T cells primed with reovirus in the murine intestine confer protection to reovirus infection of the respiratory tract [26]. Together these results suggest that modification in the gut compartment has a profound effect on lung responses; however modulation from lungs to the gut can also be achieved. Ruane et al. have demonstrated that murine lung dendritic cells (DCs) up-regulate the expression of gut-homing molecules (integrin $\alpha 4\beta 7$ and CCR9) on T cells allowing them to migrate to the GI tract to induce protection against intestinal pathogens [27]. Together these results suggest that the allergic reactions at one mucosal site can prime for similar responses in distant mucosal sites. That is, responses in the lung may be indirectly modified by direct effect in the gut and *vice versa*. Intestinal priming leading to protection of respiratory tract may provide a powerful tool for future modification and/or manipulation of responses in these two compartments. In this context, the use of allergen-specific desensitization for allergic disease in humans is a highly-relevant mechanism in gut-lung cross-talk. In general, sublingual immunotherapy (SLIT) and oral immunotherapy (or specific oral tolerance induction, SOTI) initially involve local and peripheral generation of regulatory T cells which migrate to the distant effective sites such as the lungs and nose, resulting in down-regulation of Th2-driven effector responses in allergic individuals (reviewed in [28]). Sustained and disease-modifying effects of SLIT, in particular, have been confirmed in

large, randomized, double-blind, placebo-controlled trials in adults and children [29–32]

Lung-gut cross-talk in chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD), which includes emphysema and chronic bronchitis, is a progressive disease characterized by prolonged airflow obstruction and reduced lung function. Cigarette smoking is the leading cause of COPD however other lung irritants such as air pollution, chemical fumes or dust can contribute to the disease; not to mention genetic predisposition [33]. Although 80% of COPD patients are smokers, only 15–50% of smokers develop the disease [34], suggesting that other environmental and/or genetic factors are involved.

There exists strong epidemiological evidence for association between the incidence of COPD and IBD [35, 36] and COPD is a significant mortality factor among CD patients [35, 36]. A population-based cohort study showed that CD was more prevalent in COPD patients than in healthy controls (2.72 OR) and CD a greater risk than smoking alone [35]. Intestinal manifestations of COPD include malabsorption and chronic TNF-driven inflammation, which are further exacerbated with disease severity [37, 38]. We know that in COPD, smoke drives bronchitis as it damages airway epithelia and epithelial tight-junctions [39], however smoking has also been positively associated with CD [40]. It is therefore likely that the toxic effect of smoke extends systemically to the intestine. Whether this is a result of direct or indirect smoke ingestion and/or smoke-induced loss of intestinal permeability as seen in COPD patients [41] is currently unknown.

Role of microbiota in lung-gut cross-talk

The recent important advance in the field of mucosal immunology has been the recognition of microbial gut microbiota in contribution to health or disease of the host. The millions of commensal bacteria, called the 'microbiota' has become a subject of extensive research. Now referred to as a metabolic organ, the microbiota is important in not only host nutrition, metabolism, and defense against foreign pathogens [42] but also in epithelial homeostasis and ontogeny of innate and adaptive immunity (reviewed in [43]). Our gut microbiome is a personalized signature which evolves with us. Changes in its composition and/or diversity can have dramatic consequences for the host. High-throughput sequencing technologies over the last 10 years have given us some important information with respect to what constitutes a 'healthy gut microbiota' however this is still very much a debate as diverse arrays of healthy microbiota are

found in different healthy people [44] and dysbiosis of the resident microbiota has been linked with an ever-growing number of disorders including cancers, cardiovascular and respiratory disease, obesity and IBD [18, 45–48]. Extensive epidemiological evidence of the role of altered commensal microbiota in IBD is provided by the observation that the incidence of this inflammatory pathology is tripled in children treated with five or more courses of antibiotics [49]. Using novel fecal microbiota transplantation (FMT) therapy, early promising results have recently shown that restoration of a healthy microbiota may be possible by transplanting the microbiome of a healthy subject into a patient with IBD [50] however this technique is in its infancy and its therapeutic usefulness and efficacy remains to be proven [51].

We have known for some time the influence of commensal microbiota on lung injury [52] and development of allergies [53, 54] and more recently, of its critical and direct role in promotion of tolerance to aeroallergens in neonates [55]. Furthermore, evidence from mice suggests that changes in maternal [56, 57] or infants [4, 58, 59] gut microbiota composition or diversity (modified by diet or antibiotics) can have profound, long-term impact on subsequent development of allergic disease in progeny. In humans, evidence points to low diversity of the gut microbiota in early infancy as an important risk factor for subsequent development of allergy and asthma [60–62]. Although the exact mechanism(s) involved are poorly understood, it is believed that gut microbiota metabolism of dietary fibre (which increases circulating short-fatty acids) can shape the immunological environment in the lung [5] and when given to pregnant mice, such high-fibre/acetate diet prevents development of allergic airway disease in adult offspring by epigenetic modification of the *Foxp3* promoter [56]. In addition, perhaps this diet yields a distinctive gut microbiota, which plays an important protective role in lung inflammation *via* activation of innate pathways including toll-like receptor (TLR)-4 as previously shown for *pneumonia*-induced inflammation in mice [63].

In the last 5 years, there has been a significant new discovery in the microbiota field. Human lungs are no longer considered sterile environments. We now know that bacteria as well as non-bacterial organisms including viruses (virome) and fungi (mycobiome) are also found in healthy human lungs [64–66] and evidence is starting to emerge which suggest changes in the number and/or diversity of indigenous microbiota in the diseased lungs [64, 65, 67]. We know that in intestinal microbiota load and diversity stabilizers at around 3 years of age to resemble those of adults [68, 69] and similar pattern of community maturation can be seen in the microbiota of the upper respiratory tract of infants [70], however, similar studies are yet to be performed in

the microbiota of the lower respiratory tract. These results suggest that the first 3 years are likely to be an important period for reprogramming or an opportunity to intervene. Early changes in lung microbiota can shape the local immunological environment in the lungs and influence the outcome and severity of lung function and lung disease (reviewed in [71]). We now know that there is a cross-regulation of lung–gut immunity and intestinal microbiota has been shown to directly immunomodulate pulmonary responses to invading pathogens [72, 73].

These results suggest that healthy lung microbiome is critical to respiratory health and that manipulation of microbiota may be an attractive tool for future exploration for treatment of not only gastrointestinal but also respiratory diseases such as asthma. This manipulation may be achieved with diet high in fibre/acetate which directly influences airway responses in mice [56, 71] or the use of pre- or postnatal probiotics (particularly the *Lactobacillus* and *Bifidobacterium* species) which are thought to be effective in preventing atopic eczema [74–76] but not asthma development (reviewed in [51, 77]). To date, the primary outcome in these probiotic prevention studies has been eczema and studies which are sufficiently powered to effectively examine asthma as a primary outcome are urgently needed [51]. We can hypothesize that perhaps there is a continuum of microbiota lining the entire length of the mucosal membrane; the dominant species and diversity varying in different mucosal compartments. If this was the case, dysbiosis in one compartment may impact the homeostasis of another and the nature of the gut–lung cross-talk might be an underlying factor for the development, maintenance, and exacerbation of chronic inflammatory diseases. This remains to be proven.

Proposed mechanism(s) of lung–gut cross-talk

As respiratory and intestinal mucosal disease present with overlapping pathological changes it is likely that similar immune components drive the underlying pathological changes and that the local mucosal inflammation drives distant mucosal inflammation and *vice versa*. Associations between the gut and lung seems specific to the two organs in the rat model of UC as no pathological or functional changes were seen in other organs [78]. This lung–intestine specificity is well known in traditional Chinese medicine and postulates that the disruption of ‘social’ networks between these two related organ systems (Biao–Li) may disrupt the bidirectional gut–lung communications leading to onset of disease.

In the literature, the general consensus is that there is a shift in the inflammatory process from the bowel to the lungs, however the mechanisms are poorly

understood. High resolution computed tomography (HRCT) images have clearly demonstrated that there are multiple centres of airway responses and that in fact, airway respiratory epithelium is directly affected and epithelial cells are thought to be the primary target of inflammation. After activation, the epithelial cells release large quantities of pro-inflammatory mediators that attract inflammatory cells. Increased number of neutrophils, eosinophils and T cells have been reported in broncho-alveolar lavage (BAL) fluid [79] and sputum [80] of IBD patients. In experimental model of colitis, colonic eosinophilic inflammation is thought to be driven by CD11b+CCR2+Ly6Chigh inflammatory monocytes in the colon of mice which express eosinophil chemoattractant CCL11 [81]. Whether same phenotype of cells exist in man and are also responsible for lung eosinophilia or whether these cells migrate from gut to the lung is currently unknown. In light of recent literature suggesting a link between IBD and asthma [20], it is becoming increasingly evident to examine the role of eosinophils in the link between these two chronic diseases. Along with eosinophils, neutrophils may also be implicated in gut–lung cross-talk as primed neutrophils (which are characteristic of patients with active IBD) may re-enter the circulatory system and migrate to the lung where they can induce pathology, however this is yet to be confirmed.

Along with inflammation, the physical destruction of epithelial barrier has been proposed as a potential mechanism as it's a common feature of both respiratory and gastrointestinal diseases. Overproduction of proteases during excessive inflammation is thought to play an integral role in its destruction. It has been known for over 15 years that *Dermatophagoides Pteronyssinus* (*Der p 1*), an ubiquitous environmental respiratory antigen from house dust mite (HDM), has potent protease activity in the lungs [82, 83] and is considered to be the most important cause of allergic respiratory disease such as asthma [84]. In line of this evidence, our latest data showing presence of *Der p 1* in human gastrointestinal tract and its detrimental effect on gut epithelial barrier, warrants further exploration of its potential link between gut and lung disease [85].

Another mechanism that can modify lung–gut cross-talk and is likely to contribute to etiology of mucosal inflammatory disease is the altered homing properties of intestinal and/or lung lymphocytes. In normal, non-inflamed state, lymphocytes are thought to migrate preferentially to the same tissue where they first encountered the antigen and therefore their homing receptors are specific for the ligands on their target tissues [86]. However, intestinal lymphocytes from IBD patients are known to lack tissue specificity [87] which may explain presence of inflammation in number of organs in IBD and not only in the gut. The

lymphocyte-mediated pathology in both compartments during IBD may be a result of non-specific homing receptors expressed under inflammatory conditions. Ruane and colleagues [27] have recently challenged this long-standing dogma that only gut-resident dendritic cells (DCs) can recruit antigen-specific T cells back to the gut. They have shown the presence of an alternative pathway for cellular migration in mice, showing that both gut and lung DCs can up-regulate gut-specific homing molecules integrin $\alpha 4\beta 7$ and chemokine receptor (CCR9) and recruit antigen-specific T cells to the gut. Importantly, targeting lung DCs by immunizing the mice intranasally with *Salmonella typhimurium* was able to induce protective gut immunity against the vaccine. Of course, the homing properties of intestinal and/or lung effector lymphocytes are likely to be influenced by their expression of chemokine receptors or integrins. For example, orally induced IgA-producing B cells express CCR9 and CCR10, as well as $\alpha 4\beta 7$ and $\alpha 4\beta 1$ integrins, which allow these cells to migrate to the intestine and the airways as they express CCL25 and CCL28 [88]. Furthermore, oral probiotics in mice promote the development of protective IL-10 producing Tregs in the intestinal lamina propria, and due to their high expression of CCR9 they can migrate to the airway where they inhibit allergic airway inflammation [89]. In this context, we know that certain bacterial strains are known to favour the development of non allergen-specific Tregs in the gut which can influence distal effector T cells to an unrelated allergen, as shown by *Clostridia* strain which protects mice against OVA-induced allergy [90–92]; however, the exact mechanisms are poorly understood [93].

Finally, we cannot talk about mechanisms of gut-mediated lung immunity without a mention of pattern-recognition-receptors of the innate immune system, toll-like receptors (TLRs). TLRs recognize microbial components and trigger activation of NF κ B transcription factor, which is required for expression of genes involved in innate immunity and inflammation [63, 94]. Microbiota is crucial for maintaining normal TLR innate signalling. It has been shown that intestinal-initiated TLR signalling can induce responses in the lung and a local gut injection of TLR ligands can fully restore lung function in germ-free mice [95]. Whether restoration of gut function can be achieved following injection of TLR ligands in the lungs is currently unknown and may be an avenue to explore for treatment of mucosal diseases. Disruption of the intestinal or lung microbiota (dysbiosis), whether it is induced by dietary, pathological or physical insults (such as environmental exposure to toxins and cigarette smoke), results in inappropriate innate immunity, increased inflammation and loss or imbalance of bacterial

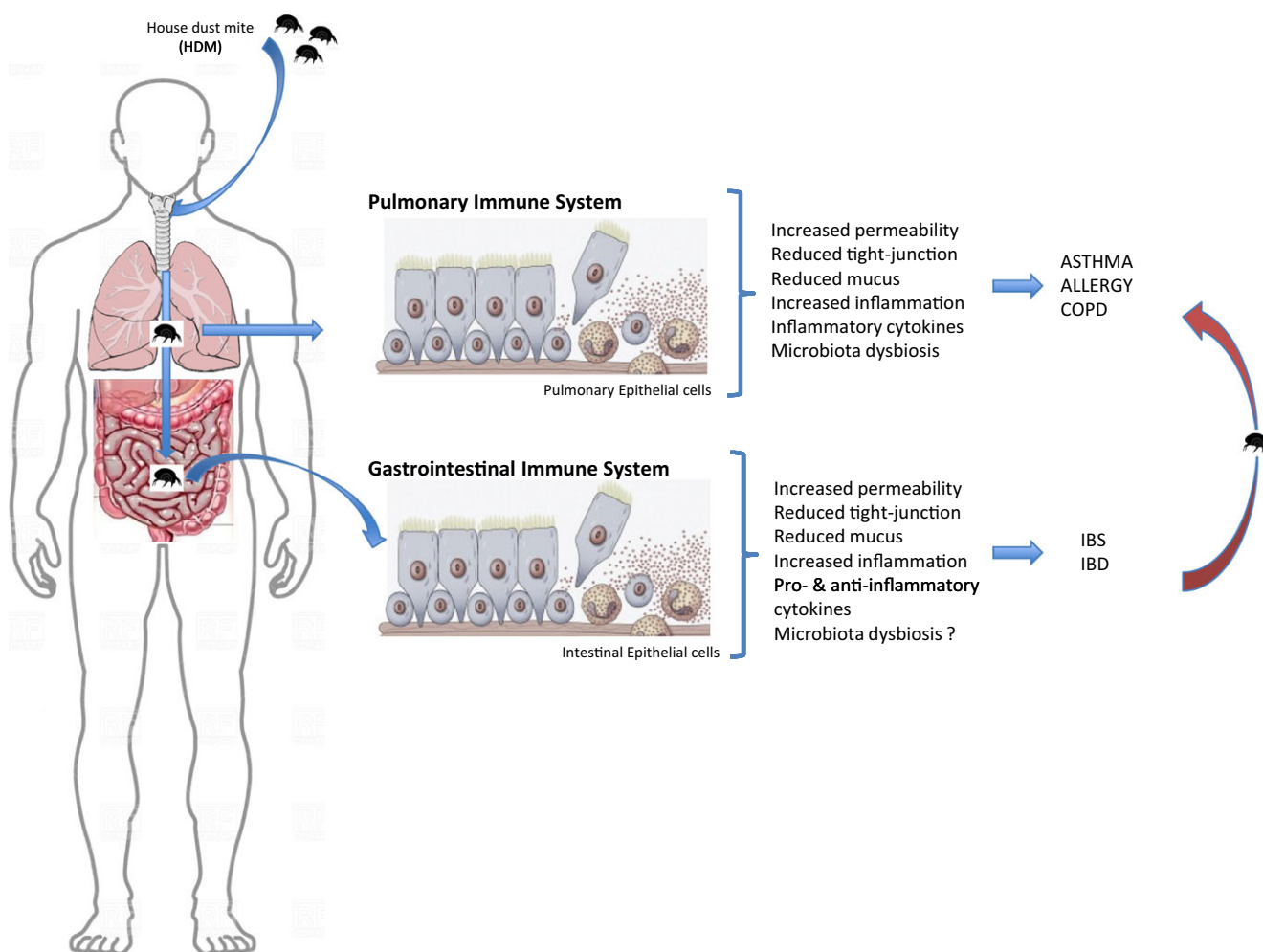


Fig. 1. Proposed hypothesis: The potential role of house dust mite (HDM) in lung–gut cross-talk. Intestinal and respiratory mucosal diseases present with overlapping pathological changes and there is a consensus in the literature that there is a shift in inflammation from the gut to the lungs. One of the candidates which may be responsible for driving disease in both compartments is an aero-allergen and cysteine-protease *Der p 1* found in house dust mite (HDM). Recently, we found HDM in the healthy human gut mucosa where it can have detrimental effect on gut permeability and barrier function (Tulic *et al.*, 2015). In healthy individuals, HDM favours production of anti-inflammatory IL-10 whilst this is not seen in patients with IBS. Excessive inflammation in susceptible individuals may trigger a parallel inflammatory cascade in distal mucosal site to initiate allergic disease.

metabolites; together which have a negative impact on systemic immune response.

Molecules as candidates for lung–gut cross-talk

As discussed above, respiratory and intestinal mucosal diseases share many overlapping pathologies and we may envisage the possibility that the same molecule(s) may drive these changes in the two compartments. Both are considered to be systemic inflammatory diseases. Bronchus associated lymphoid tissue (BALT) regulates lymphocyte trafficking from lung tissue through general circulation and mirrors the role of gut associated lymphoid tissue (GALT) which traffics lymphocytes from the gut. To date we have no firm evidence of a

single mediator, allergen or an enzyme as a linkage between the gut and the lungs (or any other extraintestinal organs). However, one of the emerging candidates which may drive the bi-directional gut–lung cross-talk is thymic stromal lymphopoietin (TSLP). TSLP is a critical factor linking responses at interface between the body and the environment (mucosa, skin and ocular tissue) to Th2-driven allergic responses [96, 97]; a master regulator of both skin and airway inflammation. Increased TSLP production in skin keratinocytes leads to atopic dermatitis in skin and concomitant allergic inflammation in the lungs of mice [98]. It is thought that prior sensitization and allergen challenge in the lung is required for activation of multiple centres although we have recently shown that HDM exposure

in the gut impairs gut epithelial function irrespective of individuals atopic status [85]. Originally shown to be produced by pulmonary epithelial cells and epidermal keratinocytes, we now know that TSLP is also *constitutively* expressed by intestinal epithelial cells from healthy subjects (highest level in colonic epithelia) where it is thought to be involved in tolerance to commensal microbiota through its modulation of DC function [99]. Breakdown of this pathway is observed in patients with Crohn disease, resulting in initiation of Th2 cytokines, IgE production and Th2-mediated allergic diseases [100]. Whether initiation and/or amplification of this TSLP-induced response in the gut is the trigger for lung disease is yet to be examined.

The other candidates for lung-gut cross-talk include growth factors and cytokines such as vascular endothelial growth factor (VEGF), TGF-beta, TNF, IL-6 and IL-13. All of these cytokines have been strongly implicated in both IBD and respiratory disease [101–103]. VEGF is known for its intimate involvement in pathogenesis of IBD [101] but it also promotes pulmonary angiogenesis, leucocyte extravasation, inflammation and decreased endothelial barrier function in the lungs [78]. Systemic IL-6, with local TGF-beta production are major triggers in development of Th17 subset of T cells which may drive cross-organ Th17 polarized inflammation [102]. The other plausible candidates are proteases [104]. Increased protease activity leading to a defective epithelial barrier and excessive inflammation is a common feature of both COPD and IBD and recent advances have shown mast cell restricted protease to be involved in pathogenesis of both experimental colitis and COPD [105]. Our own data has shown presence of another functionally active cysteine protease in human gut, *Der p 1* (the major respiratory allergen from HDM) [85], which has detrimental effect in the healthy gut and may initiate distant inflammation in the lungs (Fig. 1). Whether this cysteine protease directly impacts lung function in IBD patients is currently unknown. Finally, we have to account for cigarette smoke exposure as a plausible trigger for both intestinal and respiratory diseases. Cigarette smoke is undoubtedly a common risk factor

for both COPD and IBD; known to damage airway epithelia, affect maturation of lung DCs, lymphocyte homing and trafficking, and selectively inhibit bacterial growth (reviewed in [106]). It is not unreasonable to envisage that these toxic effects may spread to neighbouring mucosa and promote similar pathology in the gut. Research is needed to examine its direct role in bi-directional lung-gut cross-talk.

Conclusion

Although we have made much progress over the last 10 years in understanding the role of gut microbiota in host immunity there remain many unanswered questions. Unravelling the mechanisms of lung-gut cross-talk is critical in our understanding of the aetiology of incredibly complex mucosal inflammatory diseases, such as IBD, COPD and allergy. These diseases are multi-faceted and involve not only environmental and genetic host factors but often present and manifest with multi-organ damage. It is envisaged that organs with the same embryonic origin may share the same pathological specificities in a disease. Promising recent research have demonstrated that immunity may be transferrable across different mucosal sites and have stressed the importance of microbiota on not only gut but also lung homeostasis. Current research is exploring the best ways to target intestinal microbiota for treatment of lung-related infectious and respiratory diseases which include the use of probiotics, oral vaccines against respiratory pathogens and probiotic coupled vaccines whereby probiotics are commonly used as adjuvants (reviewed in [72]). The key is not to overlook the impact of environmental triggers such as ubiquitous antigens such as those found in the house dust to which we are constantly exposed to on daily basis. This area of research is in its infancy and holds much promise in future discovery of better treatment for mucosal inflammatory diseases.

Conflict of interests

The authors declare no conflict of interest.

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