Pulmonary-intestinal cross-talk in mucosal inflammatory disease

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Chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases (IBDs) are chronic inflammatory diseases of mucosal tissues that affect the respiratory and gastrointestinal tracts, respectively. They share many similarities in epidemiological and clinical characteristics, as well as in inflammatory pathologies. Importantly, both conditions are accompanied by systemic comorbidities that are largely overlooked in both basic and clinical research. Therefore, consideration of these complications may maximize the efficacy of prevention and treatment approaches. Here, we examine both the intestinal involvement in COPD and the pulmonary manifestations of IBD. We also review the evidence for inflammatory organ cross-talk that may drive these associations, and discuss the current frontiers of research into these issues.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases (IBDs) are mucosal inflammatory diseases affecting the respiratory system and gastrointestinal tract, respectively. COPD affects 64 million people worldwide and is the fourth leading cause of death.[1] IBD has a prevalence of >300/100,000 globally and there has been a dramatic increase in the incidence of IBD over the last 50 years.[2,3] COPD and IBD are both chronic diseases, which are driven by recurrent cycles of inflammation that lead to tissue damage and remodeling, which progressively worsen symptoms. There are no cures for either disease and both require lifelong health maintenance, for which current therapies are suboptimal.[4–6] Many of the similarities in the pathological features of COPD and IBD are a result of the common physiology of the respiratory and gastrointestinal systems.

Common physiology of the respiratory and gastrointestinal tracts

Structurally, the respiratory and gastrointestinal tracts have many similarities.[7,8] Both have an extensive, highly vascularized, luminal surface area,[9–12] which is protected by a selective epithelial barrier[13–15] and an overlying mucus-gel layer[16,17] from commensal bacteria, pathogens, and foreign antigens. These epithelial surfaces cover a submucosal layer of loose connective tissue and mucosa-associated lymphoid tissue, composed of resident lymphocytes. This lymphoid tissue regulates antigen sampling, lymphocyte trafficking, and mucosal host defense.[18,19] Respiratory and gastrointestinal epithelia share a common embryonic origin in the primitive foregut,[20,21] which may account for their similarities. However, it is most likely that it is the similar inflammatory and immune components of these organs that are the cause of the overlap in pathological changes in respiratory and intestinal mucosal diseases.

Chronic obstructive pulmonary disease

COPD is an umbrella term describing a group of conditions characterized by prolonged airflow obstruction and loss of the functional capacity of the lungs. Patients suffer from chronic bronchitis and emphysema that lead to breathing difficulties (dyspnea).[22] Symptoms are induced by exaggerated and chronic inflammatory responses to the noxious insult of smoke exposure, with periodic exacerbations of disease typically caused by bacterial or viral infection.[23] Smoking is the major causal risk factor in COPD in westernized countries, but wood smoke and pollution are important in other areas, and there are genetic and epigenetic components.[24] Recent studies have shown that exposure to respiratory infections or hyperoxia in early life may also contribute to the development of COPD.[25,26]

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Inflammatory bowel disease

IBD is a term that describes a group of inflammatory diseases of the gastrointestinal tract. Ulcerative colitis (UC) and Crohn's disease (CD) are the two most common forms of IBD.[27] Physiologically, UC and CD are quite distinct. UC is characterized by continuous, superficial ulceration of the colon, whereas CD manifests with transmural, sporadic (skip) lesions and may occur at any point along the digestive tract.[28,29] Both conditions are associated with excessive daily bowel movements, severe abdominal pain, diarrhea, weight loss, malnutrition, and intestinal bleeding. The causes of IBD are unclear; however, several factors are known to contribute to the onset of the disease including genetic risk, environmental stress, the intestinal microbiome, and inflammatory dysfunction.[30]

Inflammatory organ cross-talk in COPD and IBD

It is widely accepted that secondary organ disease occurs in both COPD and IBD.[31–37] There is much recent clinical interest in intestinal manifestations of COPD, and an increasing number of studies has highlighted the prevalence of pulmonary inflammation in IBD. At an epidemiological level, there is a strong association between the incidence of COPD and CD.[38–40] A population-based cohort study performed by Ekbom *et al.*,[39] showed that the risk of CD in COPD sufferers was 2.72 times higher than that in healthy controls and greater than the risk reported for smoking alone. There is also a familial risk factor, with an increased risk of CD among the first-degree blood relatives of COPD sufferers, although shared environmental factors may account for this. Specific intestinal manifestations of COPD include atrophic gastritis and nutritional absorption deficiency in the small intestine.[34,41]

Conversely, COPD has been shown to be a significant mortality factor among CD sufferers,[38,40] with standardized mortality ratios of 2.5–3.5 for COPD in the CD population. Kuzela *et al.*[42] demonstrated a high incidence of abnormal pulmonary function in both CD and UC patients, despite a lack of radiological abnormalities. Similar findings by Tzanakis *et al.*[31,43,44] led them to propose that patients suffering from IBD should undergo pulmonary evaluation including physical examination, chest X-ray, and pulmonary function testing. Black *et al.*[33] performed a literature survey that identified 55 articles citing thoracic disorders in IBD patients, with large airway involvement accounting for 39% of these associations. Three more specific studies of randomly selected IBD patients showed incidence rates of pulmonary organ involvement at 44,[45] 48,[46] and 50%.[47] The symptoms manifested as interstitial lung disease, increased numbers of alveolar lymphocytes, and a reduction in the diffusion capacity of the lung. Pulmonary involvement was more likely in UC, but was still significant in CD.

Hence, there is a clear but undefined link between inflammatory diseases in the respiratory and intestinal systems. Although the associations have been clearly identified in the clinical literature, there have been few basic research studies that have investigated the mechanisms of the inflammatory cross-talk involved.

COMMON RISK FACTORS IN COPD AND IBD

Both COPD and IBD are multifactorial diseases and share many aspects of the classical "triad" of risk factors: environmental factors, genetic susceptibility, and microbial involvement. In addition, both conditions exhibit clear signs of immunological dysfunction in their pathologies. However, although smoke or particulate inhalation is a critical environmental factor for COPD, the corresponding factors for IBD are ill-defined. Conversely, although there is a clear link between the intestinal microbiome and IBD, the potential of an intrinsic lung microbiome as a risk factor in COPD has only recently emerged.

Smoking as a risk factor for COPD and IBD

Cigarette smoking is the single most important risk factor in COPD. Approximately 80% of people with COPD are past or present smokers. Toxins and particulate matter in inhaled smoke induce acute inflammation in the airways. With repeated insult, inflammation becomes chronic and damages the airway epithelium and lung tissue.[48–50] Eventually this leads to remodeling of the respiratory epithelium, emphysema, and chronic disease. However, only between 15 and 50% of all smokers develop COPD, indicating that smoke inhalation alone is not sufficient to induce disease[51,52] and that other risk factors are likely contribute to the development of COPD. Twin and familial studies have suggested the involvement of genetic factors, with first-degree relatives of COPD sufferers at increased risk.[53,54]

Smoking is also a risk factor for IBD and significantly increases the risk of developing CD by threefold.[55–59] In contrast, and surprisingly, the prevalence of UC among smokers is low, with smoking alleviating symptoms of disease.[59,60] This is exemplified by familial studies of siblings who are genetically susceptible to IBD. In these studies, smokers were shown to be more likely to develop CD and non-smokers to develop UC.[61] Nevertheless, ex-smokers seem to be at increased risk of UC than those who have never smoked.[62–64]

The issue is further complicated when incidences of smokers and IBD are correlated as a whole. Eastern countries tend to have a much higher smoking rate than do western countries;[1] yet western countries have a higher incidence of CD, but not UC, compared with eastern countries.[65,66] The lack of epidemiological correlation between smoking and CD incidence in the east–west divide suggests that, like COPD, smoking by itself is not sufficient to induce IBD. Studies in animal models of CD-like colitis have demonstrated that smoke exposure exacerbates existing colitis in wild-type animals.[67–69] This suggests that smoking can augment existing mucosal inflammation, although no consensus on mechanism has been achieved. Thus, although smoking has an obvious impact on both respiratory and gastrointestinal health, the nature of these phenomena is poorly understood.

Genetic risk of COPD and IBD

Both COPD and IBD have known genetic risk factors. To date, four genetic risk factors have been formally identified for COPD. Deficiency of α_1 anti-trypsin (A1AT), an enzyme and a serum trypsin inhibitor that protects against protease remodeling in the airway, accounts for 2% of COPD in the population.[70,71] Recently, genes for α-nicotinic acetylcholine receptor (*CHRNA3/5*),[72] hedgehog-interacting protein (*HHIP*),[73,74] and iron-regulatory protein 2 (*IREB2*)[75,76] have been shown to be potential susceptibility loci for COPD. However, functional end points have yet to be determined for how these genes influence the development of COPD.

Both CD and UC are known to have genetic risk factors, and both ethnic and familial associations have been shown.[54,77,78] Mutations in genes for nucleotide-binding oligomerization domain containing 2 (*NOD2*),[79–81] autophagy-related protein 16-1 (*ATG16L1*),[82,83] interleukin-23 receptor (*IL23R*),[84,85] and immunity-related guanosine-5′-triphosphatase family M protein (*IRGM*[86]) have been shown to dramatically increase the risk of CD. A recent study has also identified a NOD2 mutation in COPD populations offering a possible link between this condition and CD.[87] These genes code for proteins that control responses to infection at the intestinal mucosa and regulate autophagy. Thus, a paradigm has developed that a defect in bacterial clearance in CD may be one of the key triggers for disease onset. Polymorphisms of human leukocyte antigen class II genes also have a strong association with UC, suggesting that lymphocyte regulation is an important factor in its development.[88,89] Recent studies have made substantial progress in understanding gene associations with UC. Among the new susceptibility loci identified are laminin subunit β-1 (*LAMB1*),[90] extracellular matrix protein 1 (*ECM1*),[91] hepatocyte nuclear factor 4-α (*HNF4A*),[90] and cadherin-1 and cadherin-3 (*CDH1* and *CDH3*, respectively).[90] These genes are involved in maintaining epithelial barrier integrity,[78] suggesting that a dysfunction in the epithelial barrier may predispose to UC.

It is possible that genetic risk factors may also contribute to the association between COPD and IBD. *HHIP* is also important in the development of the intestinal crypt axis,[92] and further studies are required to identify whether this gene contributes to disease overlap between COPD and IBD. The diversity of gene susceptibility loci for both COPD and IBD suggests that susceptibility to these conditions may involve multiple genes and alleles that couple with environmental triggers to induce disease in some individuals.

Disruption of the microbiome

Bacterial colonization of the lower respiratory tract, although once controversial, is now known to influence the pathogenesis of COPD.[93,94] The controversy was due to the classical view, borne largely from culture-based studies, of healthy lungs as a sterile environment.[95,96] Advances in culture-independent techniques for microbial analysis have shown that the healthy lung is host to its own microbiome, which changes significantly during disease.[97,98] Nevertheless, the precise role of the lung microbiome in COPD pathogenesis and the mechanisms that underpin infection-induced COPD exacerbations are poorly understood.[94]

It is also known that changes in the intestinal microbiome are associated with IBD;[30,99,100] however, again, the nature of the shift in commensal populations is not well established. Indeed, it is certain that the microbiome contributes to both the initial inflammation and the chronic nature of IBD, but it is unclear whether commensals are the initiating factor.[101] Regardless of the role in the initiation of IBD, chronic inflammation contributes to a loss of diversity in the microbiome, which seems to perpetuate the disease.[99,101,102] In both COPD and IBD, the microbiomes of the lung and intestine have changes in the dominant species and a reduction in diversity,[103] without decreases in microbial numbers.[104] Whether these changes are a mechanism or consequence of inflammation is not understood, but clearly a healthy microbiome is important to both respiratory and gastrointestinal health.

Epithelial barrier dysfunction

Maintenance of epithelial barrier function is critical for maintaining the healthy state of the respiratory and gastrointestinal mucosa. This is because the epithelial barrier separates the interstitium and the underlying tissues from the milieu of antigenic material in the mucosal lumen. Consequently, loss-of-barrier function as a result of mucosal inflammation contributes to the chronic nature of these conditions, although it is not yet understood whether loss of function is a causative factor or a consequence of disease. COPD patients are particularly susceptible to bronchitis (inflammation of the bronchial mucosa), which develops as smoke exposure damages the airway epithelial barrier. Shaykhiev *et al.*[105] have shown that smoking leads to downregulation of genes coding for tight junction and adherence proteins, which was more pronounced in smokers with COPD. *In vitro* studies examining the effect of cigarette smoke extract on primary bronchial epithelial cells have shown that the endogenous protease calpain, mediates degradation of tight junction complexes.[106] Thus, smoking, the major environmental risk factor for COPD, promotes dysregulation of the pulmonary epithelial barrier.

Epithelial barrier dysfunction is a common feature of IBD.[107] However, although this is well established, like COPD, it is unknown whether barrier dysfunction is a causative or a consequential factor.[108,109] Certainly, in IBD, increased epithelial permeability promotes the progression of chronic inflammation. Soderholm *et al.*[110] demonstrated that the epithelial tight junctions of non-inflamed intestinal tissues from CD patients were more susceptible to breakdown upon luminal antigenic stimulation. Epithelial breakdown allows the establishment of invasive bacterial infections, which are more characteristic of CD than UC.[111] However, both UC and CD patients have high IgG titers against intestinal microbes,[112] and both diseases show histopathological evidence for the loss of tight-junctional integrity,[113–115] suggesting that epithelial dysfunction is important in both conditions.

Pattern recognition receptors

Pattern recognition receptors are a family of highly conserved proteins that are expressed by cells of the innate immune system. They recognize components termed "pattern-associated molecular patterns" of microorganisms, cellular stress signals, and damaged tissues. They may be membrane bound or cytoplasmic and, when activated, induce production and secretion of inflammatory mediators and signaling molecules. Two pattern recognition receptors families known to be important in the mucosal inflammatory response are the cytoplasmic NOD family of receptors and the membrane-bound Toll-like receptor (TLR) family.[116–118]

COPD patients are known to be at an increased risk of pulmonary infection, leading to inflammatory exacerbations of their disease; however, the mechanisms that underlie this increased risk are not well understood.[119] Kinose *et al.*[87] have recently identified increases in the prevalence of the *NOD2* rs1077861 single-nucleotide polymorphism (SNP) in COPD patients. NOD2 recognizes muramyl dipeptide, an element of peptidoglycan, which is an important component of the cell wall of virtually all bacteria. This SNP causes a conformational change in NOD2 and leads to a series of downstream interactions that culminate in nuclear factor-κB activation and an enhanced inflammatory cytokine response upon stimulation. Although baseline *NOD2* expression was unaltered in COPD patients, the SNP was associated with increased COPD disease severity measured by reduced lung function.[87] The mechanism for the involvement of the SNP in COPD pathology has yet to be fully characterized.

NOD2 is also strongly associated with CD, whereby a defect in NOD2 signaling leads to impaired epithelial barrier function, increased IL-1β, and an overcompensating TLR2 response, and promotes increases in serum IL-12.[79,117] *NOD2* mutations are present in 15% of the CD population, and a *NOD2* SNP has recently been associated with smoking and CD.[120] Although Kinose *et al.* did not examine TLR2 or IL-12 in the COPD study, IL-12 has been shown to be associated with increased CD8 cytotoxic T-cell and natural killer (NK) cell activation in COPD patients and mouse models,[121,122] although whether this is related to *NOD2* polymorphisms, requires further investigation. NOD2 may therefore be a common link between COPD and CD, with polymorphisms identified in COPD and CD populations, including an association with smoking and CD.

TLRs that recognize viral and bacterial proteins maintain mucosal homeostasis, and genetic variants of TLRs have been identified in COPD and IBD.[118,123–126] Certainly, infection has a prominent role in COPD pathogenesis, and TLR2, which recognizes a range of bacterial and yeast proteins, has reduced expression and responsiveness to lipopolysaccharide (LPS) in alveolar macrophages from COPD patients and smokers.[127] This suggests that there is a defect in the mucosal innate response in COPD. Conversely, TLR2 was shown to be upregulated in peripheral blood monocytes from COPD patients compared with healthy controls,[124] perhaps indicating the presence of systemic inflammation in these patients. Although certain TLR2 polymorphisms are linked to increased infection, they do not seem to be associated with COPD.[128] Thus, the exact nature and defects of TLR2 responses in COPD remain unclear. TLR4, which recognizes LPS, promotes COPD pathogenesis, although the pathways involved seem to be complex.[126] Investigation of murine models indicates that TLR4 is involved in the development of smoke-induced inflammatory responses.[129] This inflammatory response was driven by IL-1β secretion from macrophages and neutrophil recruitment to lung tissue. Smoke exposure also drives TLR4-dependent IL-8 production in monocyte-derived macrophages.[130] In both of these studies, smoke-induced TLR4 activation was independent of LPS.

Both TLR2 and TLR4 were found to be induced in the colonic mucosa of pediatric IBD patients.[131] Furthermore, Canto *et al.*[132] identified an increase in TLR2 expression on peripheral blood monocytes, which was associated with elevated circulating tumor necrosis factor-α (TNF-α) concentrations in active UC and CD. This suggests that, like COPD, systemic inflammation may be involved is IBD pathogenesis. The D299G and T399I SNPs of TLR4 have been shown to be associated with both UC and CD,[133–135] whereas T399I has also been identified in COPD patients,[136] suggesting a possible common link. Although the functional consequences of these gene variants are not yet fully appreciated, it is known that inflammatory cytokine signaling results in increased TLR4 expression on macrophages from the intestinal epithelium and lamina propria in both UC and CD resulting in increased responsiveness to LPS.[137,138] Thus, TLR4 may have a common role in mucosal inflammatory disease, whereby an inflammatory insult coupled with TLR4 gene variations results in hypersensitivity to LPS and an exaggerated immune response in the lung or intestine.

POTENTIAL MECHANISMS OF ORGAN CROSS-TALK

Despite the similarities in the physiology of the respiratory and gastrointestinal mucosal organs, the common risk factors involved in the development of COPD and IBD and the incidences of inflammatory cross-talk between the two organs in disease, no mechanism has been identified for pulmonary-intestinal organ cross-talk. Although the respiratory and gastrointestinal tracts both share components of the common mucosal immune system, the pathways involved in cross-talk may be multifactorial, like COPD and IBD themselves (**Figure 1**).

Protease regulation in COPD and IBD

There is evidence that dysregulation of protease activity may have a role in both COPD and IBD. Increased levels of the proteases that break down connective tissue components have been identified in COPD patients and modeled in animals.[139] Of particular interest is the matrix metalloproteinase (MMP) family of proteases, which has a role in the digestion of collagen, elastin, fibronectin, and gelatin, key components in mucosal structural integrity.[140] Increased levels of epithelial and leukocyte MMP-2, MMP-9, and MMP-12 have been associated with the pathogenesis of COPD[139,141,142] and IBD,[143–146] which may contribute to a “runaway remodeling” process.

The role of A1AT in COPD is established; however, the prevalence of A1AT in IBD is debatable. A1AT neutralizes proteases

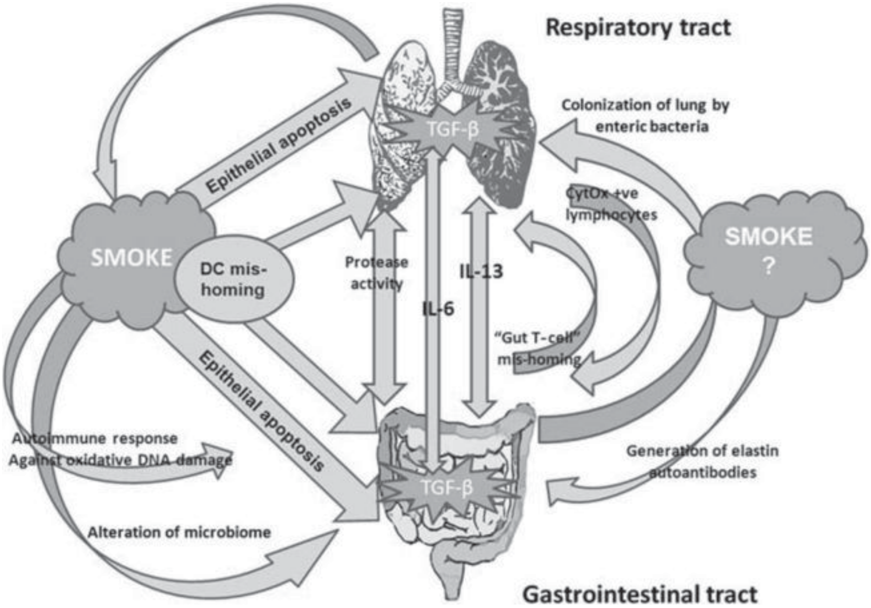

Figure 1 Possible mechanisms of respiratory–gastrointestinal cross-talk include overproduction of proteases during excessive inflammation, changes in immune cell function, including increases in cytochrome oxidase (CytOx) expressing lymphocytes and gut-originating T-cell mis-homing. Cigarette smoke exposure may have a role in organ cross-talk by affecting these processes, and/or by causing mis-homing of dendritic cells (DCs) and epithelial cell apoptosis in respiratory or gastrointestinal tissues. Smoke exposure may also lead to changes in the microbiome, promoting growth of enteric bacteria in the lung or altering the microbiome in the intestine that induces inflammatory responses. Inflammation may lead to the production of autoimmune antibodies against the ubiquitous mucosal protein elastin or autoimmune responses against antigens produced during smoke-induced oxidative DNA damage. Systemic IL-6, in conjunction with localized TGF-β, may drive cross-organ Th17-polarized inflammation. Systemic IL-13 may drive aberrant NKT and macrophage responses across organs. IL-6, interleukin-6; TGF-β, transforming growth factor-β.

involved in tissue remodeling, such as neutrophil elastase[147] and MMP-12.[148] Deficiencies in A1AT production promotes extensive tissue damage during mucosal inflammation as the tissue remodeling process progresses unchecked. Deficiency of A1AT leads to the development of emphysema and COPD.[149,150] Owing to its role in the remodeling of inflamed tissue, fecal A1AT levels are commonly used as a marker for disease severity in CD patients.[151,152] This suggests that that lack of A1AT does not promote the development of CD. Although some studies have suggested higher levels of A1AT in UC patients,[153,154] there is a higher prevalence of the allele linked to A1AT deficiency (PiZ) among the UC population,[153] and UC patients with this allele develop more severe forms of colitis.[154] Further work is required to address this divergence.

Immune cell homing and systemic factors

Both COPD and IBD are considered to be systemic inflammatory diseases and peripheral lymphocyte activity may contribute to pathogenesis.[36,155–158] During inflammation, the bronchus-associated lymphoid tissue regulates lymphocyte trafficking from the lung tissue through the general circulation.[18] This mirrors the role of the gut-associated lymphoid tissue and both lung and intestinal lymphocytes migrate to other mucosal sites as part of the common mucosal immune system.[159] It is possible that this trafficking, although functioning primarily as a common host mucosal defense, may be responsible for extra-organ inflammation associated with COPD and IBD.

In the healthy state, lymphocytes continuously migrate through the circulatory system, entering and exiting the tissue in response to antigen exposure. To control trafficking of lymphocytes through tissues, these cells express unique homing receptors, which are specific for corresponding ligands on their target tissues. Thus, through a combination of homing molecules and specific receptor–ligand interactions, lymphocytes will return to their tissue of origin during an immune response.[160,161] The subtype and phenotype of circulating lymphocytes in COPD patients have not been well characterized.[155] However, there is evidence of abnormal function in peripheral lymphocytes that may contribute to extrapulmonary disease in COPD patients. Sauleda *et al.*[162] showed increased cytochrome oxidase (CytOx) activity in the circulating lymphocytes of COPD patients, which correlated with increased CytOx detected in wasting skeletal muscle that is commonly associated with COPD. Interestingly, this increased oxidative response in circulating lymphocytes is also observed in other chronic inflammatory diseases, such as asthma and rheumatoid arthritis, but whether these same responses occur in IBD is unknown.

For IBD patients, the selectivity of lymphocyte–endothelial interaction is lost. Salmi *et al.*[163] showed that in IBD patients, the expression of homing receptors in intestinal lymphocytes did not confer tissue specificity. These altered homing properties may contribute to the extraintestinal manifestations of IBD. It is known that gut-derived lymphocytes possess the capacity to bind to synovial[164] and hepatic[165] tissue, possibly accounting for the manifestations of IBD observed in these organs. This mis-homing of lymphocytes is believed to contribute to ocular and dermatological extraintestinal manifestations of IBD.[161] Whether this same phenomenon contributes to the lung pathologies observed in IBD is unknown. Increased lymphocyte populations have been observed in the bronchoalveolar lavage (BAL) of IBD patients,[166,167] and analysis of the sputum of IBD patients showed that 65% had an increased CD4/CD8 T-cell ratio in the lung tissue.[168] Whether this represents a further example of lymphocyte mis-homing involved in the pulmonary manifestations of IBD has yet to be confirmed.

It is possible that inhalation of smoke affects gut lymphocyte homing and promotes an inappropriate immune response. Smoke exposure is known to affect T-cell trafficking through altered chemotactic chemokine levels.[169,170] Smoke inhalation also seems to affect the homing properties and maturation of myeloid dendritic cells (DCs),[171–174] which are key antigen-presenting cells in mucosal immune responses. The result is a rapid accumulation of myeloid DCs in the airways of smokers,[171] which may be a result of a reduced capacity of myeloid DCs to migrate to the lymph node.[171,172] A recent animal study has similarly shown that smoke inhalation results in the accumulation of DCs in the intestinal Peyer's patches of wild-type mice, although unlike the airways, this does not seem to be dependent on changes in the expression of the DC-homing molecule CCR6.[175] The increase in DCs was accompanied by a similar accumulation of CD4+ T cells and an apparent increase in apoptosis of the cells overlying the follicle-associated epithelial tissue of the intestine.

This loss in epithelial barrier may lead to increased antigen presentation and promote an intestinal inflammatory response. A caveat to this study was the use of a whole body smoke exposure model, which may not induce the same physiological consequence as inhaled smoke. Erosion of the epithelial layer overlying the follicle-associated epithelial tissue has been observed in CD patient biopsies.[176] Although no data on smoking status of these patients exist, smoke-induced epithelial apoptosis is one possible mechanism for the development of these erosions. Thus, smoking may induce an overall increase in antigenic presentation in the intestines, which may contribute to IBD pathogenesis.

Circulating TNF-α has been strongly implicated in comorbidities associated with COPD[51] and has a central role in the progression of CD.[177] Although anti-TNF therapies do not seem to provide therapeutic relief in COPD,[51] they have been relatively successful for inducing remission in CD.[178–180] Whether this is due to the nature of the damage in COPD or the efficacy of TNF therapy requires further investigation. Studies in transgenic mouse models that overexpress TNF-α, the TNFΔARE mouse model, have shown the development of spontaneous Crohn's-like ileitis and proximal colitis.[181] Although ocular and synovial involvement has been observed, there have been no reports of respiratory disease in this model. However, as with pulmonary manifestations of IBD, the airway involvement may be subclinical and histopathological and lung function studies may be required.

IL-6 has a role in the acute phase response to inflammation and has been implicated in the pathogenesis of both COPD[182,183] and IBD.[184,185] IL-6 is systemically elevated in patients with emphysema and has been shown be associated with apoptosis in the pulmonary tissue.[182,183] Importantly, IL-6, in combination with transforming growth factor-β, is a major factor in the development of the Th17 subset of T-helper cells.[118,186] Th17 cells are a distinct effector T-cell subset that secretes IL-17A, IL-17F, IL-21, IL-22, IL-26, and TNF-α and promote neutrophil chemotaxis.[118,187–190] Recent work has identified increased peripheral Th17 cells in COPD patients.[186]

IL-6 and Th17 cells are also associated with both CD and UC,[185,191] and high levels of IL-6 and Th17-associated cytokines have been identified in both the blood[185] and the inflamed and non-inflamed mucosa[191,192] of IBD patients. Moreover, blockade of the IL-6 pathway is therapeutic in animal models. The fact that IL-6 is elevated in the non-inflamed intestinal mucosa of IBD patients, without causing tissue damage, may suggest that a secondary tissue insult is required. As transforming growth factor-β regulates mucosal tissue remodeling and is strongly associated with COPD and IBD, it is conceivable that increased systemic IL-6, coupled with transforming growth factor-β production at the mucosal surface (due to smoke damage in the lungs of an IBD patient or an intestinal infection in an COPD patients), may lead to the development of a Th17-polarized inflammatory response at a secondary organ.

IL-13 is likely to contribute to COPD progression[193] and mutations in the IL-13 promoter may promote this pathogenesis.[194] T-cell receptor-invariant NK cells or DCs, activated by bacterial or viral infection in the airways, secrete IL-13, which activates macrophages.[193,195–197] This in turn causes further IL-13 production, which leads to STAT (signal-transducer and activator of transcription)6-dependent goblet cell hyperplasia, smooth muscle hyper-responsiveness, and airway remodeling.[188,198]

IL-13 also has a role in the pathogenesis of UC, but does not seem to be involved in CD.[199] In UC, it appears to be the aberrant stimulation of the immune response by the microbiome, which results in direct invariant NK cell cytotoxic action on the epithelium and secretion of IL-13-driving epithelial barrier dysfunction and apoptosis, and enhancement of NKC toxicity.[199,200] Like COPD, STAT6 is an important mediator for the action of IL-13 on the epithelium,[201] and the STAT6 pathway is a potential therapeutic target in both conditions. Whether these pathways act systemically in COPD and IBD is unknown, although serum IL-13 is increased in COPD,[194] possibly driving aberrant NKT and macrophage responses across organs.

Interaction of the respiratory and intestinal microbiomes

COPD sufferers have an altered lung microbiome compared with healthy individuals, including "healthy" smokers.[103] This does not exclude the possibility that smoking influences the lung microbiome. Smoking has been shown to restrict the ability of alveolar macrophages to phagocytose and kill bacteria.[202] This suggests that smoking may lead to a defect in immunoregulation of the lung microbiome. There is evidence that components of the enteric microflora, specifically Gram-negative bacilli, may also make up a component of the lung microflora.[203,204] These bacteria are resistant to cigarette smoke[205] and may contribute to severe exacerbations of COPD.[204] Furthermore, inappropriate immune responses against intestinal microflora are widely accepted to be a critical factor in the ongoing inflammation associated with IBD. Thus, there exists the possibility that the immune response against commensal microflora observed in IBD patients, may not be restricted to the gastrointestinal tract, but may also be directed toward enteric bacteria present in the lung microflora.

There have been no definitive studies on the effect of smoking on the respiratory or intestinal microbiome. This is especially surprising given cigarette smoke is known to selectively inhibit bacterial growth, favoring a Gram-negative bacilli population.[205] It is possible that smoke-induced changes to the intestinal microbiome may promote the increased risk of IBD observed in COPD sufferers. There is growing interest in how diet and nutrition may influence the human microbiome and interplay with the immune system and ultimately human health.[206,207] Fecal bacteriotherapy, whereby the microflora of a healthy patient is transplanted to a colic patient, has shown promise in case studies, as a treatment for UC.[102,208,209] This suggests that the composition of the microbiome has an important role in the intestinal inflammation, and restoration of a "healthy microbiome" can promote remission of disease. Although ultimately conjecture, it is conceivable that smoking may disrupt the "healthy microbiome" and therefore link, smoking and COPD to IBD. This could also account for the familial link of COPD and IBD observed by Ekbom *et al.*[39] as there is a familial link to the make-up of an individuals microbiome and genetics have a role in microbiome development.[210,211]

Autoimmunity

There is some evidence to suggest that COPD has an autoimmune element, which leads to disease progression and relapse.[212] Key to this concept are the observations that only some smokers develop COPD and that the clinical features of COPD continue to increase in severity even after the cessation of smoking. This suggests that ongoing immune responses occur against elements other than cigarette smoke. Smoke-induced emphysema has been shown to generate an autoimmune response against elastins.[140,213] In this proposed model, exposure to smoke antigens promotes an immune response that includes secretion of high levels of elastin proteases (elastases) from neutrophils and macrophages (e.g., neutrophil elastase, MMP-9, and MMP-12).[214] The elastases degrade and fragment elastin proteins, to which the adaptive immune system mounts a response.[140] As elastin is a ubiquitous protein in the mucosal tissue, an autoimmune response could lead to pathologies outside the lung, and may be a mechanism for intestinal pathologies associated with smoking.

Tzortzaki and Siafakas[215] proposed that smoke-induced oxidative epithelial damage initiates the disease process in COPD through the initiation of autoimmune responses. In their proposed model, oxidative DNA damage to epithelial cells leads to phenotypic changes and recognition of these cells as "non-self" by pulmonary DCs. This results in a loss-of-barrier function as a T-cell response is initiated against the epithelium. Such autoimmune responses may affect the intestinal epithelium, or may be driven by smoke exposure at the intestinal mucosa.

It is generally accepted that CD is a disease with an autoimmune component. The prevailing hypothesis for the development of CD is that an initial infection or insult leads to an inappropriate immune response against the intestinal mucosa and/or commensal bacterial population.[30,56] This leads to the recurring cycles of chronic inflammation that characterize CD. UC also has a clear autoimmune element, although different to that of CD.[216,217] Recent work has found that isoforms of human tropomyosin (hTM 1–5) are capable of inducing autoantibodies and T-cell responses in UC.[218] Autoimmunity would also explain some elements of organ cross-talk in inflammatory disease. Immune responses against bacteria or conserved mucosal protein epitopes of the pulmonary and gastrointestinal tracts may explain cross-organ inflammation in COPD and IBD. Expression of hTM on extraintestinal organs may account for cross-organ inflammatory associations in UC, although hTM5, the trypomyosin with the strongest link to UC, has not been identified in the lung tissue.[218]

SUMMARY

Both COPD and IBD are driven by inflammatory processes, are systemic diseases, and are epidemiologically linked. Given the consistent indications of the limited research to date, it is clear that comprehensive studies on the prevalence of intestinal involvement in COPD and pulmonary disease among IBD patients are required. The mechanisms that underpin the development of extra-organ inflammation in COPD and IBD patients are confounded by the complicated etiologies of these conditions. Both conditions share environmental triggers and have similar immune and physiological involvement. However, the diversity of the mechanisms that may be involved in the development of each condition suggests that cross-talk in these diseases may be a multi-faceted process involving multiple pathways (**Figure 1**). Our understanding of this area is largely based on epidemiological and clinical observations and there is a need for basic research to elucidate the associations and mechanisms involved. A better understanding of the nature of organ cross-talk in COPD and IBD will contribute to the elucidation of the etiologies of these conditions and may identify therapeutic strategies for mucosal inflammatory disease.

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DISCLOSURE

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