Received: 7 March 2020 | First decision: 13 April 2020 | Accepted: 16 April 2020

DOI: 10.1111/apt.15774

AP&T Alimentary Pharmacology & Therapeutics WILEY

Review article: impact of cigarette smoking on intestinal inflammation—direct and indirect mechanisms

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Funding information
No funding was received to support writing of this paper. SP was a past employee at University of Manchester, funded by the European Union Seventh Framework Programme (SysMedIBD FP7/2007-2013) under grant agreement number 305564. BJC and CSP were work package partners (at University of Liverpool) on the same EU FP7 project.

Summary

Background: The inflammatory bowel diseases, Crohn's disease and ulcerative colitis are related multifactorial diseases. Their pathogenesis is influenced by each individual's immune system, the environmental factors within exposome and genetic predisposition. Smoking habit is the single best-established environmental factor that influences disease phenotype, behaviour and response to therapy.

Aim: To assess current epidemiological, experimental and clinical evidence that may explain how smoking impacts on the pathogenesis of inflammatory bowel disease.

Methods: A Medline search for 'cigarette smoking', in combination with terms including 'passive', 'second-hand', 'intestinal inflammation', 'Crohn's disease', 'ulcerative colitis', 'colitis'; 'intestinal epithelium', 'immune system', 'intestinal microbiota', 'tight junctions', 'mucus', 'goblet cells', 'Paneth cells', 'autophagy'; 'epigenetics', 'genes', 'DNA methylation', 'histones', 'short noncoding/long noncoding RNAs'; 'carbon monoxide/CO' and 'nitric oxide/NO' was performed.

Results: Studies found evidence of direct and indirect effects of smoking on various parameters, including oxidative damage, impairment of intestinal barrier and immune cell function, epigenetic and microbiota composition changes, that contribute to the pathogenesis of inflammatory bowel disease.

Conclusions: Cigarette smoking promotes intestinal inflammation by affecting the function and interactions among intestinal epithelium, immune system and microbiota/microbiome.

The Handling Editor for this article was Professor Richard Gearry, and this uncommissioned review was accepted for publication after full peer-review.

1 | INTRODUCTION

The detrimental effect of cigarette smoking on cardiovascular and pulmonary disease has long been recognised: the first review describing the effects of cigarette smoking on physiological parameters, such as peripheral blood flow, heart rate and body temperature was published in 1946.[1] Despite legislation prohibiting cigarette smoking in the workplace and public buildings in most western countries, it remains a major risk factor for numerous life-threatening, noncommunicable diseases, such as coronary heart disease[2,3] and many cancers[4,5] and for inflammatory disorders, such as asthma,[6] chronic obstructive pulmonary disease,[7,8] idiopathic pulmonary fibrosis,[9,10] multiple sclerosis[11] and psoriasis.[12]

Smoking has been also correlated with inflammatory bowel disease.[13-15] Inflammatory bowel disease is a chronic inflammatory disorder of the gut which encompasses Crohn's disease and ulcerative colitis.[16,17] Crohn's disease was first described in the early 19th century since when, its global prevalence has steadily risen, in line with industrialisation and urbanisation (for a recent review see 18). Inflammatory bowel disease is a multifactorial disease, influenced by each individual's characteristics, such as the immune system, their microbiome and genetic predispositions and their 'exposome', ie the environmental factors that an individual has been exposed to. The strongest environmental risk factor for the development and progression of Crohn's disease is cigarette smoking.[19] Conversely, it is perceived that smoking exerts protective effects on the development and progression of ulcerative colitis.[20,21] Understanding the effect of smoking is complex because inhaled smoke contains over 5000 ingredients and amongst these, ~100 compounds are known to have toxic or carcinogenic effects.[22] Cigarette smoking affects the integrity of the gut epithelium, the immune responses, the diversity and composition of the gut microbiota and causes epigenetic modifications influencing gene expression.[23-25]

This review discusses the wealth of emerging evidence characterising the effects of smoking on various cell types and physiological processes within the intestinal epithelium, and how these mechanistic actions play an important role in determining susceptibility to, and disease course of, inflammatory bowel disease. We also define a research agenda for the next decade to address the key unresolved issues, for both Crohn's disease and ulcerative colitis.

1.1 | Smoking and inflammatory bowel disease—clinical epidemiology

The incidence and prevalence of inflammatory bowel disease are increasing globally, with the highest relative increase observed in developing and recently developed nations.[26] Studies of immigrants moving from a country with low incidence of inflammatory bowel disease to one with higher incidence of inflammatory bowel disease, have suggested higher risk of developing inflammatory bowel disease, particularly for second-generation immigrants and younger individuals.[27] This phenomenon is attributed mainly to 'westernisation' of lifestyle and key environmental drivers, such as diet (ie lower intake of fresh fruits/vegetables and higher intake of ultra-processed foods rich in animal protein and fat, additives and emulsifiers), medication/surgery (eg early life course exposure to antibiotics, appendectomy/tonsillectomy), and perhaps increased sanitation and hygiene resulting in loss of immune tolerance. Cigarette smoking was the first environmental risk factor for Crohn's disease.[23] Crohn's disease is associated with smoking[14] but nonsmoking is associated with ulcerative colitis.[13,14] Notably, the first presentation of ulcerative colitis is associated with smoking cessation, implying that early smoking suppressed the colitis.[21] Some studies have reported a gender association, where smoking delayed the onset of the disease only in men or having more protection in females at diagnosis.[21] In patients with ulcerative colitis, smoking has been shown to reduce relapses, hospitalisations, the need for oral corticosteroids and immunosuppressants, also the risk of colectomy and, in some studies, proximal disease extension.[21,28] The effect of smoking on relapse in ulcerative colitis is best illustrated in the prospective, population-based inception cohort study of patients from seven European countries and Israel who were followed up for 10 years.[29] The mechanism of protection is not clear and studies of nicotine in the treatment of ulcerative colitis were limited and the adverse effects were common.[20] It is important though to mention that some studies failed to identify beneficial effect of smoking on the course of ulcerative colitis.[30,31] A recent study on extraintestinal manifestations (EIM) in inflammatory bowel disease patients revealed an association between smoking and EIMs in a dose-response relationship, in both ulcerative colitis and Crohn's disease patients.[32] Moreover, a very recent study on clinical data covering a 12-year period, revealed that smoking cessation was not associated with worse disease course in ulcerative colitis patients.[33]

Smoking is known to increase the incidence of Crohn's disease by a factor of 1.8[34] to 4.6[35] and has negative impact on quality of life of Crohn's disease patients.[36,37] The age of onset of Crohn's disease is bimodal: the first and largest peak occurs at young adulthood, the second smaller peak appears in people between 50 and 70 years of age.[38] It has been suggested that smoking increases the risk of Crohn's disease onset in older group.[31,39,40] It is clear that Crohn's disease patients who are active or ex-smokers have frequent relapses, more severe pain, higher rate of hospitalisation, worse response to treatment, greater need for surgery and greater risk of post- operative relapse.[20,23,41-44] Interestingly, some studies have correlated smoking to ileal involvement and a lower prevalence of colonic Crohn's disease in active smokers.[45-48] This raises the possibility that smoking might have a protective effect in colonic inflammation in both ulcerative colitis and Crohn's disease.[20] Smoking cessation has shown to improve the course of Crohn's disease and therefore it has been recommended as a primary therapeutic approach.[19,49] Vavricka and colleagues have shown recently that high altitude flights are a risk factor for relapse of both ulcerative colitis and Crohn's disease, with exposure to a hypoxic environment likely the key driver or modifying factor of inflammation[50,51]: Links to hypoxia may also explain the association between smoking and inflammatory bowel disease,

as smoking and hypoxic environments may synergistically act as potent environmental risk factors for inflammatory.[52,53]

1.2 | Passive smoking and inflammatory bowel disease

Passive smoking or 'second-hand' smoking is the involuntary inhalation of tobacco smoke (as from another's cigarette) especially by a nonsmoker, with children especially vulnerable. According to World Health Organisation, there is no safe level of exposure to second-hand tobacco smoke.[54] Second-hand smoke causes serious cardiovascular and respiratory diseases, including coronary heart disease[55] and lung cancer[56] and it causes complications during pregnancy such as low birth weight and premature deaths.[57-59] The development of inflammatory bowel disease has been studied in relation to prenatal smoke exposure and passive smoke exposure during childhood.[21] A limited meta-analysis of key observational studies published 12 years ago, suggested that there was no strong association between prenatal exposure to maternal smoke nor childhood passive smoke exposure and the development of Crohn's disease, nor was there any evidence that passive smoke exposure exerted a protective effect against ulcerative colitis.[60] The authors expressed caution about the degree of heterogeneity between the studies used in the meta-analysis. Supporting these conclusions, Rigas and colleagues also showed no association between maternal smoking and inflammatory bowel disease.[61] In contrast, there are other studies that show childhood exposure to smoke and/or maternal smoking increasing risk of developing Crohn's disease,[62-65] or offering protection against ulcerative colitis.[66] Maternal smoking, amongst other early life environmental factors, has been highlighted as a key influencing factor of disease course in Crohn's disease.[67] Overall, this remains a very important issue for further research—at present, it is difficult to make definitive conclusions because there are very few studies performed to date.

1.3 | Smoking effects on the intestinal epithelium

The intestinal epithelium consists of multiple cell types (ie enterocytes, goblet cells, neuroendocrine cells, tuft cells, Paneth cells and M cells), and these can develop further into specialised subsets.[68,69] Its functions are absorption of nutrients and prevention of inflammatory conditions induced by exogenous factors, such as the commensal bacteria and foreign antigens.[70] This is achieved by maintaining physical barrier (eg presence of intact tight junctions), synthesis of a mucus layer, secretion of antimicrobial peptides and immunoglobulin A, and by actively involved in immune cell regulation, capable of internalising, processing, and efficiently presenting foreign antigens.[71] The function of the intestinal epithelium in health and inflammatory conditions, such as inflammatory bowel disease, has been studied.[70-73] During inflammatory bowel disease the barrier integrity is compromised, there is an increasing tissue destruction and dysregulated mucosal inflammation.

1.3.1 | Tight junctions and epithelial barrier integrity

Epithelial cells of the intestine are sealed together with tight junctions, which are positioned at the boundary of the apical and lateral membrane surfaces. They maintain cell polarity, regulate flux of ions and solutes and provide epithelial barrier integrity, preventing bacteria/bacterial product translocation to underlying tissues.[74] It is well-established that the dysfunction of the tight junction barrier system under inflammatory stress play a key role in the pathogenesis of Crohn's disease. Compromised tight junctions increase epithelial paracellular permeability and trigger an array of events including cellular apoptosis, mucosal erosion and ulcers that contribute to intestinal epithelium damage.[75-77] Studies on airway epithelial barrier have shown that smoking can downregulate apical tight junction protein genes, impacting on epithelial barrier function and inducing permeability of the airway mucosa.[78] There are few studies relating to intestinal epithelium,[79,80] which they mainly focus on nicotine effect.[81] An in vivo study on mice showed that cigarette smoke exposure was associated with intestinal barrier dysfunction such as increased permeability, bacterial translocation, intestinal villi atrophy and damaged tight junctions, in the small intestine but not in the large.[82]

1.3.2 | Goblet cells and the mucus barrier

Goblet cells are epithelial secretory cells that secret mucins, a family of glycoproteins that are the main component of mucus layers.[83] Mucus and other epithelial-derived factors play a critical role in host defence against invading bacterial pathogens,[84,85] with mouse models of inflammatory bowel disease, whether chemically induced colitis (eg using dextran sodium sulphate [DSS], 2,4,6-trinitrobenzenesulfonic acid [TNBS] etc) or genetic mutations (eg *Muc2*, *Tlr5* or *Il10* knock-out transgenic strains), showing defective mucus barrier structure and function.[86] In human ulcerative colitis, the layer is significantly thinner or absent, whereas in Crohn's disease the colonic mucus layer is significantly thicker, as it was shown by measurement of mucus thickness in freshly resected colonic biopsies.[87] Nicotine can induce mucus synthesis in explant culture of normal colonic tissue.[88] However, in a similar *in vitro* study, smoking habit had no effect on mucus synthesis in explants from healthy donors, suggesting that smoking could not explain differences in inflammatory bowel disease.[89] The data showed though that mucus glycoprotein synthesis is reduced in inactive ulcerative colitis, rising to normal levels in active disease and that synthesis is increased in Crohn's disease.[89]

1.3.3 | Paneth cells and antimicrobial activity

Paneth cells are highly secretory cells, lying at the bottom of intestinal crypts, that produce antimicrobials to control gut microbial communities.[90] The role of Paneth cells in inflammatory bowel disease has recently been discussed in depth in a recent review, focusing on defective autophagy, reduced level of α-defensins in Paneth

cells and the resultant decreased levels antimicrobial activity.[91] The effect of smoking on Paneth cell function has not been studied in depth. A key study in mice, has shown that intragastric exposure to smoking causes significant reduction in antimicrobial production by Paneth cells.[92] In humans, tobacco consumption appears to cause defective Paneth cell function only in combination with genetic defects, specifically with Autophagy related 16 like 1 gene T300A variant (*ATG16L1*^{T300A}) associated with a high risk for Crohn's disease.[93] Crohn's disease patients of *ATG16L1*^{T300A} genotype who are smokers have reduced number of Paneth cells and higher degree of apoptosis at the base of the crypts when compared to the wild type allele, whether they were smokers or nonsmokers.

1.3.4 | Intestinal transient receptor potential channels

The gut is extensively innervated, and its function is controlled by both the autonomous nervous system and its own enteric or intrinsic nervous system.[94] Intestinal epithelial cells and neurons of the intrinsic nervous system have similar expression patterns of specific sensory transient receptor potential channels; including TRPA1, TRPV1 and TRPV4. These channels are tetramers, functioning to detect noxious chemicals, toxins or irritants that might be present in the gut lumen, contribute to Ca^{2+} and Mg^{2+} absorption, induce the release of neuropeptides by afferent sensory neurons, as well as regulate innate immune responses and the production of tumour necrosis factor from mucosal macrophages and dendritic cells.[94] TRP channels show increased expression in the colon of inflammatory bowel disease patients.[95] As discussed by Allais and colleagues, similarities between inflammatory conditions in the lung and the intestine suggests that smoking may affect transient receptor potential channels in the gut in a similar manner to its actions on transient receptor potential channels in the lung epithelium—namely infiltration of immune cells, changes in the microbiome and induction of oxidative stress, but more work needs to be done to confirm this hypothesis.[94]

1.3.5 | Autophagy

One of the intestinal epithelium self-protective intracellular mechanisms is autophagy, an evolutionary conserved catabolic process.[96,97] The role of autophagy in the pathogenesis and progression of inflammatory bowel disease has been reported extensively, with strong association between variants of the autophagy-related gene *ATG16L1* and another key autophagy gene *IRGM* (encoding immunity-related GTPase family M protein), and susceptibility to Crohn's disease, and inability to function normally in recognition, handling and clearance of invading pathogens.[97-99] Cigarette smoke exposure can induce autophagy in murine follicle-associated epithelium and in immune cells of the lymphoid follicle underlying Peyer's patches, suggesting that smoke exposure might increase risk for Crohn's disease by causing epithelial oxidative damage, which needs to be repaired by autophagy.[100,101] This could correlate with observations, using confocal laser endomicroscopy, of the earliest lesions of Crohn's disease in the Peyer's patches and therefore defective clearance of bacteria and increased inflammation.[102,103] The effect of smoking and contribution of specific mutations in autophagy-related genes, *ATG16L1*, *IRGM and NOD2/CARD15* (an intracellular pathogen recognition receptor[104]) will be discussed further in a following section.

1.4 | Influence of smoking on the gut microbiota

Microbial colonisation of the gut begins immediately following birth and co-evolves with the host having a lifetime effect on an individuals' health.[105] The intestinal microbial communities (microbiota) of healthy donors, as assessed by metagenomic sequencing, is consistently dominated by bacteria of two phyla, Bacteroidetes and Firmicutes.[106] The composition of gut microbiota shows dynamic changes responding to various environmental factors, such as pH, oxygen levels/redox state, availability of nutrients, temperature, enabling various populations to thrive and exert different activities while interacting with their environment, including the host.[107-109] There have been numerous studies of the gut commensal bacteria and their role in health and disease.[110-112] Inflammatory bowel disease has been associated with decrease in gut microbial diversity, an imbalance in the composition of host-associated microbiota (reduction in beneficial bacteria within the phyla Firmicutes and Bacteroidetes) and an increase shift towards potentially pathogenic microorganisms (especially mucosa-associated *Enterobacteriaceae* within the phylum Proteobacteria), a phenomenon often described, albeit controversially, as a 'dysbiosis'.[113-117] Imbalance in the composition of host-associated microbiota can lead to impaired epithelial barrier function, defective bacterial recognition, antigen presentation and autophagy, dysregulated T cell responses leading to aberrant innate immune responses.[118-121] Smoking may modify the microbiome of the oral, lung and gut, leading to disease including periodontitis, asthma, chronic obstructive pulmonary disease, Crohn's disease, ulcerative colitis and cancer.[122-125] Huang et al, highlight that changes in the microbiota can be linked to the disease progression in the lung.[122] The most important effect of cigarette smoking on the colon is a prominent shift in microbiome composition and activity.[126] A population-based cross-sectional study in Korean smokers showed altered faecal microbiota composition in current smokers compared to those who had never smoked, with a lower observed Firmicutes:Bacteroidetes ratio and lower relative abundance of Proteobacteria.[127] Dysbiosis was also observed in the duodenal mucosa-associated microbiota of patients undergoing endoscopy for upper GI symptoms, iron deficiency or Crohn's disease, with increased Firmicutes and lower relative abundance of Bacteroidetes and Actinobacteria in current smokers vs never smokers,[128] as shown in Figure 1. Moreover, study of faecal samples from Crohn's patients with active disease, analysed using fluorescent in situ hybridisation targeting bacterial 16S ribosomal RNA, showed that smokers had luminal microbiota of significantly higher ratio *Bacteroides*:*Provetella*

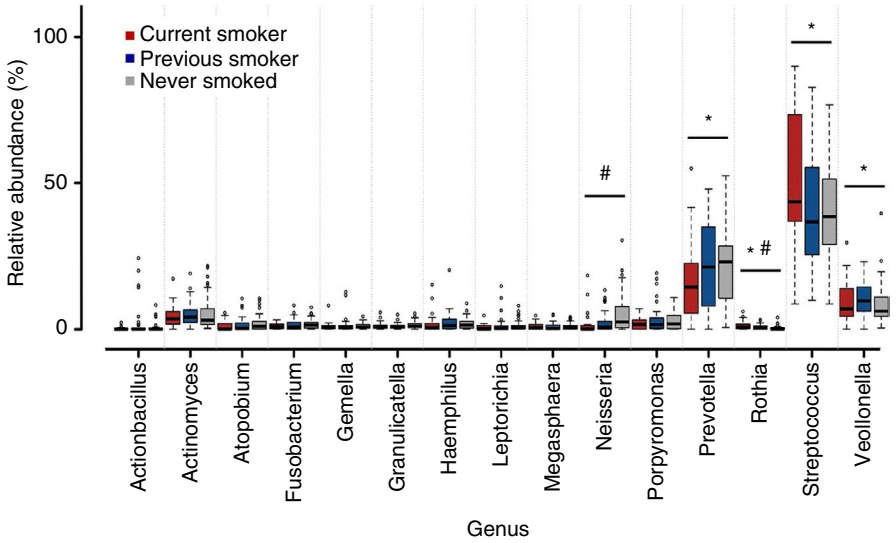

FIGURE 1 Relative abundances of bacterial genera present in the duodenal (2nd part) mucosa-associated microbiota of patients with documented iron deficiency (ID, with and without anaemia), functional dyspepsia (FD) or FD with additional irritable bowel syndrome-like symptoms or Crohn's disease. Patients were grouped based on smoking status. Data were normalised via total sum scaling and is expressed as relative abundance. The 15 most abundant genera are displayed. Error bars represent standard deviation. * $P < 0.005$, FDR $q < 0.05$, Kruskal-Wallis with false discovery rate (FDR); # $P < 0.05$ ALDEx2 Wilcoxon rank test with Benjamini-Hochberg (BH) correction. o—order. The image was taken from ER Shanahan, A. Shah, N. Koloski, MM Walker, NJ Talley, M. Morrison and GJ Holtmann (2018) Microbiome; 6:150, which is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/). No changes were made in this figure

genera than those patients who were nonsmokers; and similarly for healthy controls that smoked.[129] Smoking cessation studies in healthy smokers followed over a 9-week period showed increases in phyla Firmicutes and Actinobacteria, and decreased Bacteroidetes and Proteobacteria.[130,131] However, there are still several limitations in studying the gut microbiome, like difficulties to culture in vitro several bacterial species, differences of bacterial proportions in different parts of gastrointestinal tract and environmental influences. As a consequence, the exact relationship between smoking and microbiome alteration remains to be further explored. Nevertheless, the microbiota has been recognised as an important target for therapeutic interventions, such as the use of antibiotics, prebiotics, probiotics and faecal microbiota transplantation.[118]

1.5 | Inflammatory bowel disease, the immune system and the influence of smoking

An impaired immune response in inflammatory bowel disease patients is essential to perpetuate intestinal inflammation.[132] Smoking affects both adaptive and innate immunity and plays dual roles in regulating immunity by either exacerbation of pathogenic immune responses or attenuation of defensive immunity.[133-135]

1.5.1 | Adaptive immunity

A dysregulated intestinal T cell response is observed in inflammatory bowel disease patients. T cell profiling studies on biopsies taken at time of diagnosis have revealed that inflammatory bowel disease patients have higher percentage of CD4+ T cells, T regulatory cells (Tregs) and central memory T cells (TCM), and a lower percentage of $CD8^+$ T cells.[136] Crohn's disease and ulcerative colitis though have different adaptive immune responses. Crohn's disease patients show a Th1/Th17 response with increased pro-inflammatory cytokines, such as tumour necrosis factor, interferon-gamma and interleukin-17A.[16] In contrast, ulcerative colitis patients show a Th2 adaptive immune response, with high levels of interleukin-4, interleukin-13 and interleukin-14.[17] Smoking induces the inflammatory phenotype of inflammatory bowel disease towards a Th-1 response.[137] Experiments in rodents have shown that cigarette smoke exposure can cause colitis, mainly mediated by Th-1 response, with interferon-gamma $CD4^+$ T cells having detrimental role.[137] Nicotine modulates the response of mucosal T cells towards a Th-1 phenotype via nicotinic acetylcholine receptors, which might explain the beneficial effect of smoking seen for ulcerative colitis patients.[138] It has also been suggested that nicotine has a protective role, ameliorating DSS-induced colitis through blockade of signal transducer and activator of transcription 3 (STAT3) activation, and consequent proliferation of T-lymphocytes.[139] T cell receptor sequencing on isolated mucosal T cells has shown that Crohn's disease patients have variable clonal expansion of lamina propria $CD8^+$ cells.[140] Active smoking at the time of the surgery correlated with a high percentage of $CD8^+$ clonal expansion, and persistence of similar T cell receptor repertoire at postoperative endoscopy was associated with both smoking and disease recurrence.[140] Whether in vitro or in vivo, exposure of human peripheral blood mononuclear cells to

cigarette smoke showed that only peripheral blood mononuclear cells from Crohn's disease donors, and not from patients with ulcerative colitis, were functionally impaired, releasing lower levels of cytokines (eg interleukin-8, interleukin-12) and prostaglandin E2 and showing defective sensitivity to antioxidants, by releasing lower levels of heat shock protein 70.[141] Another key study, has demonstrated that smoking may alter the composition of murine gut-associated lymphoid tissue, leading to a dramatic increase of $CD4^+$,$CD8^+$ T cells, and dendritic cells within Peyer's patches of the terminal ileum.[142] This observation could explain why Crohn's ileitis is negatively affected by smoking. Analysis of small intestinal immune cell populations in a mouse model of short-term cigarette smoke exposure followed by DSS-induced colitis, identified that smoking induces intestinal inflammation via increase in Th17 cells, which further promote the recruitment of neutrophils by secreting Interleukin-17A.[143] The combination of use of Interleukin-17 knockout and blocking anti-interleukin-17 antibodies revealed that the Th17 cells precede and are responsible for recruitment of neutrophils to the intestine.

1.5.2 | Innate immunity

Our innate immune system comprises of macrophages, dendritic cells, neutrophils and natural killer T lymphocytes, as well as type 1-3 innate lymphoid cells that express the interleukin-23 receptor (IL-23R), all major players in the pathogenesis of inflammatory bowel disease.[144] These cells can sense and respond to conserved structural motifs on microorganisms, known as pathogen-associated molecular patterns, and act as antigen-presenting cells (APCs), presenting antigen to T and B cells promoting adaptive immunity. They are phagocytotic and produce chemo-attractants and cytokines to regulate the immune response.[134]

Natural killer T lymphocytes secrete interleukin-13, a cytokine which causes damage to the epithelium, and that has an autocrine action, stimulating further natural killer T cell function.[145] However, Montbarbon and colleagues have shown clearly that smoking can improve DSS-induced colonic inflammation, partially by causing a marked recruitment of invariant natural killer T lymphocytes (iNKT), possibly the iNKT2 subpopulation based on the cytokines detected.[146] Invariant Natural Killer T lymphocytes are differentiated in the thymus, and they appear to be four subtypes based on their cytokine expression; iNKT1 (tumour necrosis factor, interferon-γ, interleukin-4), iNKT2 (interleukin-4, nterleukin-5, interleukin-13), iNKT17 (interleukin-17, interleukin-22, tumour necrosis factor, granulocyte-macrophage colony-stimulating factor) and iNKT10 lymphocytes (interleukin-10).[147] Different invariant natural killer T cell subsets are enriched in distinct tissues, for example iNKT2 cells populate several sites including the lung and spleen, but they are uniquely more abundant in mesenteric lymph nodes.[148]

Dendritic cells are found throughout the gut, including in the lamina propria, within isolated lymphoid follicles and the lymphoid tissue underlying Peyer's patches, and in mesenteric lymph nodes.[149] As it has been discussed recently, intestinal dendritic cells are important for maintenance of immune tolerance to the commensal microbes and dietary antigens.[132] In patients with inflammatory bowel disease, dendritic cells are attracted and accumulate at the inflammatory sites. Dendritic cells from mesenteric lymph nodes of patients with Crohn's disease preferentially induce the Th1 response.[67] And the myeloid dendritic cells from mesenteric lymph nodes of patients with Crohn's disease produce high levels of interleukin-23 and low levels of interleukin-10.[150] In vitro exposure of dendritic cells to crude cigarette smoke extract had a differential effect on phenotype and function of dendritic cells derived from both Crohn's disease and ulcerative colitis patients, with increasing T cell proliferation and Th1 polarisation seen in Crohn's disease, and increased levels of forkhead box P3-positive ($Foxp3^+$) T cells and decreases in the Th1 subset observed in ulcerative colitis samples.[151]

Intestinal macrophages are the most abundant mononuclear phagocytes within the intestine, especially in the colon, where they represent approximately 20% of all leucocytes.[152,153] These resident intestinal macrophages are not typical antigen presenting cells, in that they do not secrete proinflammatory cytokines.[141] In inflammatory bowel disease, the dynamics of blood monocyte differentiation into resident intestinal macrophages is likely altered.[154] Animal models of colitis show increased infiltration of monocytes and immature macrophages into the gut mucosa, which during inflammation subsequently differentiate into mature, proinflammatory macrophages and where they produce a large amount of proinflammatory mediators, such as tumour necrosis factor, interleukin-6 and nitric oxide.[155] A study on myeloid cell populations isolated from either human colonic inflammatory bowel disease biopsy specimens or murine DSS- induced colitis tissue samples has identified that the macrophage-monocyte balance within the colon is also altered during colitis, with pro-inflammatory blood monocytes increasingly recruited to the lamina propria.[156] Moreover, in vitro infection of monocyte-derived macrophages with various strains of *Escherichia coli* showed that the Crohn's disease-derived macrophages were dysfunctional, allowing intramacrophage persistence/ survival of all *Escherichia coli* strains tested, including the non-invasive K-12 strain.[157,158] However, other studies contradict these data, by showing that Crohn's disease-derived macrophages are not defective at killing unless they have a genetic polymorphism. It is rather the innate ability of the Crohn's disease associated *Escherichia coli* to survive and replicate whereas the non-invasive K-12 strain is killed or mildly persistent.[159] The effect of smoking on macrophages has been studied mainly in the context of the lung and smoking-related lung disease. *Listeria* infection experiments on alveolar macrophages showed that those macrophages derived from smokers had no bactericidal or bacteriostatic activity.[160] Also, alveolar macrophages from smokers showed defective autophagy and therefore aberrant clearance of internalised pathogens.[161] Work from our lab has recently shown that peripheral blood monocyte-derived macrophages from active smokers (mainly Crohn's disease patients) show hyperactivation of the transcription factor Nuclear factor kappa B (NF-κB),

releasing higher amounts of proinflammatory cytokines upon stimulation with bacterial lipopolysaccharide in vitro, compared to macrophages of nonsmokers.[162] Multivariate analysis demonstrated that this phenotype did not correlate with disease severity, activity or disease status, nor type of medication, but it was only correlated with smoking status of Crohn's disease patients.

1.5.3 | Interaction between the immune system and intestinal microbiota

Physically, the epithelial barrier and the mucus layer(s), along with secretory IgA and anti-microbial peptides (eg defensins/cryptdins, lysozyme, cathelecidin etc), limit contact of bacteria to underlying immune cells.[163-165] A major shift in the composition of the commensal community can result in overgrowth of invasive pathogenic microbes, as discussed in detail by Littman and Palmer.[163] The concept that *Escherichia coli* are involved in the pathogenesis of inflammatory bowel disease is supported by multiple studies demonstrating intramucosal or mucosa-associated *Escherichia coli* in patients with Crohn's disease[166-169] and in ulcerative colitis,[170,171] and defective processing of intracellular bacteria by the innate immune cells. The gut microbes also indirectly, via intestinal mononuclear phagocytes, regulate the function of innate lymphoid cells (ILCs) which by producing interleukin-22 regulate the function of Paneth cells, enhance the proliferation of $Lgr5^+$ stem cells and influence the adaptive immune responses.[172] There is also literature on how specific components of gut microbiota and their metabolites shape the balance of Th17 cells and Tregs.[173] As an example, gut microbiota-derived metabolites adenosine-triphosphate and short-chain fatty acids were shown to stimulate the differentiation and development of Th17 and Tregs, respectively.[174,175] Based on what we know so far about the effects of smoking on either the immune system or the intestinal microbiota, we could hypothesise that it could impact on their mutual interactions and consequently on the pathogenesis of inflammatory bowel disease.

1.6 | Cigarette smoke constituents and mucosal cell responses

Cigarette smoke is composed of gas and tar (or particulate) phases and contains >5000 chemical constituents[22] Substances in the gas phase, such as carbon monoxide and light aldehydes, can pass through the airway epithelial barrier, enter the systemic circulation via the pulmonary circulation, increasing systemic oxidative damage and leading to the development of cigarette smoking-related diseases.[23,176-178] On the other hand, compounds such as nicotine, polycyclic aromatic compounds, nitrosamines and heavy metals are predominantly found in the tar phase, being absorbed by mucous membranes, skin, alveoli and the gastrointestinal system.[42] A summary of smoke constituents that have been studied in relation to gastrointestinal inflammatory disease, as well as their major cellular targets/interactions/actions are presented in Table 1. Among all the constituents described, nicotine and carbon monoxide have gained greatest interest due to their beneficial effects as highlighted in a number of studies.[23,179-181] Nevertheless, the overall results are controversial and clinical trials do not support a positive role for nicotine-based treatment approaches

TABLE 1 Summary of cigarette smoke constituents and their effects on the intestinal mucosa

Constituent	Cell type affected	Action	Ref
Nicotine	Macrophage, dendritic cells	Activation of nicotinic receptors α7 leads to decreased production of pro-inflammatory cytokines, both in vitro and in vivo	249,250
	Endothelium of colonic microvessels	Inhibits MAdCAM-1 expression and leucocyte recruitment	251
	Intestinal epithelium	Mucus (mucin) synthesis and secretion	70
Acrolein	Goblet cells	Hyperplasia	252
	Intestinal epithelium	Disrupts tight junctions, causes cell death	253
	Gut microbiota	Increased Firmicutes and decreased Bacteroidetes	254
	Human BEAS-2B and A549 cell lines	ACR-histone adduct formation and inhibition of histone acetylation	255
Polycyclic aromatic hydrocarbons	Colonocytes	Oxidative DNA damage, activation of AHR transcription factor, carcinogenesis	256
Carbon monoxide	Macrophages, Dendritic cells	Increased bacterial clearance.	23,178,257-259
	Colonic myofibroblasts	Alters interferon-γ signalling. Inhibits nitric oxide production via IRF-8. Induction of FGF15 and intestinal epithelial restitution	183
Reactive oxygen species	Intestinal epithelium	Induce proinflammatory cytokine production. Cause lipid peroxidation and other cell membrane constituents.	260

Abbreviations: MAdCAM-1, mucosal addressin cell adhesion molecule-1; ACR-histone, acrolein-histone; AHR, aryl hydrocarbon receptor; IRF-8, interferon regulatory factor 8; FGF15, fibroblast growth factor 15.

for ulcerative colitis.[20,182] Carbon monoxide has been shown to enhance intestinal epithelial restitution, having anti-inflammatory effects and modulating T-cell differentiation and activation, including inhibiting Th-17 cell formation.[183] More recently, heme-oxygenase 1 (HMOX1), the enzyme that metabolises heme to ferrous iron (Fe^{2+}), biliverdin and carbon monoxide, has been suggested as key modulator of inflammation in the intestine.[184] One major issue in developing carbon monoxide based therapeutics, is its delivery in a pharmaceutically acceptable form, although there are a number of carbon monoxide pro-drugs in development.[185]

1.6.1 | Hypoxia

Chronic cigarette smoke exposure has shown to cause systemic hypoxia that affects the function of the, driving increased colonic tissue hypoxia and altered mucosal microvasculature, both common features of inflammatory bowel disease.[186] An in vivo mouse model of chronic cigarette smoke exposure demonstrated induced histological and inflammatory changes in the colon.[186] In the same study, smoke exposure predisposed to more severe TNBS-induced colitis, higher severity of pathology and increased levels of pro-inflammatory cytokines. Another study examining levels of angiotensinogen in human ileal biopsy tissue, at both the messenger RNA and protein level, revealed reduced angiotensinogen levels in ileal Crohn's disease patients who were smokers implicating the mesenteric vasculature and mucosal hypoxia as co-factors in ileal Crohn's disease pathogenesis.[52]

1.6.2 | Nitric oxide

Nitric oxide is synthesised by nitric oxide synthase and is an unstable molecule.[187] In physiological conditions, nitric oxide is produced by constitutively expressed nitric oxide synthase (cNOS) in the endothelium or within the enteric nervous system of the gastrointestinal tract. The low levels of nitric oxide protect against intestinal mucosal damage, promoting repair of epithelial erosions and ulcer healing. In pathological situations though, there is activation of inducible nitric oxide synthase (iNOS) which produces nitric oxide for long periods of time (hours to days), having detrimental effects via potentiation of the adverse actions of other reactive oxygen species.[187,188]

1.6.3 | Reactive oxygen species

Reactive oxygen species are chemically unstable reactive free radicals that contain oxygen, including peroxides (such as hydrogen peroxide (H_2O_2)), the superoxide anion ($O_2^{\bullet -}$) and hydroxyl radicals ($OH^{\bullet}$), that cause oxidative damage to cellular membrane lipids, proteins, enzymes and nucleic acids such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).[177] Most cell types, during a variety of biochemical processes, are capable of generating reactive oxygen species, but the major sources are from phagocytic cells (via action of phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, that upon stimulation generates superoxide anions) and various epithelial cell types, including intestinal cells.[189] Reactive oxygen species, and consequent oxidative stress, are major characteristics of inflammatory bowel disease development and progression and have been discussed extensively in previous reviews.[190-193] Cigarette smoke is known to contain stable gaseous free radicals, reactive oxygen species and tar semi-quinone radicals, that either directly affect living cells, or indirectly by dysregulation of cascades such autophagy that lead to further production of reactive oxygen species.[177,194]

1.7 | Gene polymorphisms determining inflammatory bowel disease susceptibility and influence of smoking

Genetic predisposition in inflammatory bowel disease patients, observed almost 30 years ago by identifying familial risks, is still an exciting area of clinical and basic research.[195-198] In this section, we will discuss the genetic defects that are linked to inflammatory bowel disease and the differential gene expression observed in cell types that are major players, such as immune and intestinal epithelial cells.

1.7.1 | Genetic polymorphisms

There are numerous genome-wide association studies (GWAS) and large meta-analyses that have identified susceptibility risk polymorphisms of genes strongly associated with inflammatory bowel disease. Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation. Single nucleotide polymorphisms are of great importance because they may influence gene expression, messenger RNA stability, and subcellular localisation of messenger RNAs and/or proteins and hence may produce disease.[199] More than 200 genes have been identified by these approaches and most of them are linked to Crohn's disease.[200-204] These include genes that encode, cytokines, cytokine receptors, autophagy-related proteins, signalling molecules and other proteins with enzymatic or not activities. Extensively studied examples are the genes *NOD2/CARD15*, encoding the nucleotide-binding oligomerisation domain-containing protein 2/caspase recruitment domain-containing protein 15, two autophagy-related genes *ATG16L1* and *IRGM* and the *IL23R*, encoding the receptor for the interleukin-23 cytokine. Smoking has been associated with genetic polymorphisms and higher risk for surgery.[205] Six single nucleotide polymorphisms associated with smoking quantity and behaviour were analysed in a Swiss cohort and were combined to form a risk score. Further analysis revealed that in Crohn's disease patients who smoke, the number of surgeries was associated with the genetic risk score.[205] Crohn's disease smokers who were of the $ATG16L1^{T300A}$ genotype, showed significantly shorter time to recurrence after surgery.[93] The strongest

genetic defects were associated with smoking quantity and nicotine dependence and genome-wide association studies have discovered high-risk single nucleotide polymorphisms close to nicotinic acetylcholine receptor subunits.[205,206] The number of inflammatory bowel disease-associated genes that have been studied and found to be affected by smoking is presented in Table 2. It seems that there is no defined group of genes or cellular pathway, nor process correlating with smoking status. Instead, there is a wide spectrum of genes including major histocompatibility complex proteins, cytokines, cytokine receptors, neurotransmitters, and metabolic enzymes.

1.7.2 | Dysregulation of gene expression

Gene expression is not only affected by the presence of single nucleotide polymorphisms, but also by mutations, such as deletions or duplications, as well as by dysregulation of upstream pathways and exogenous factors. Transgenic animal models, eg gene knockouts, have been extensively used to study the effect of gene expression on health and disease. Well-known examples in the field of intestinal inflammatory diseases are the *NOD2*$^{-/-}$,[207] *Il10* $^{-/-}$,[208] *Il10R*$^{-/-}$,[209] *ITGA4*[210] and many more. Deficiencies of human *IL10* and *IL10R* genes are also well-established defects linked to inflammatory bowel disease.[211,212] Smoking has been shown to interfere with gene expression in studies on genetically modified mice, as well as on human population studies focused on inflammatory bowel disease cohorts. In vitro experiments in intestinal epithelial cell-lines showed that cigarette smoke extract delayed TNF-induced *NOD2* mRNA expression and that this resulted in abnormal NF-κB regulation and cytokine production.[213] Chronic cigarette exposure of mice induced mRNA expression of *Muc2* and *Muc3* in the ileum, whereas *Muc4* increased in the distal colon. Furthermore, increased chemokine (C-X-C motif) ligand 2, *Cxcl2*, and decreased interferon-γ, *Ifng*, in the ileum were observed.[126] Microarray analysis of colonic biopsies identified dysregulation of the β-defensin-2 gene, *HBD2*, whose expression was augmented in consequent in vitro cultures by the addition of nicotine.[214] Quantitative real-time polymerase chain reaction performed on inflamed vs non-inflamed biopsies from ileal Crohn's disease patients showed that active smokers had down-regulated angiotensinogen mRNA levels.[52] In a recent cross-sectional study, the mRNA levels of various cytokines were measured in mucosa biopsies from inflamed and no-inflamed areas in inflammatory bowel disease patients.[215] They found that smokers with Crohn's disease

TABLE 2 Genetic risk alleles and smoking correlation in inflammatory bowel disease

Gene	Observation	Reference
Ulcerative colitis and smoking - associated genes		
HSPA6	Induced by smoking and shown to stabilise the anti-apoptotic protein B-cell lymphoma extra-large (Bcl-XL)	261
HLA	HLA-DRB1*15:02 was associated with ulcerative colitis in never smokers and HLA-DQB1*06 was associated with ulcerative colitis in active smokers	262
GSTP1	Former smokers who were heterozygous or homozygous for polymorphisms near the glutathione S-transferase P1 gene had increased risk of ulcerative colitis	263
TRIM39, *HLA*, *GRB10*, *PTPLA*, *ADAM1*, *SMAD3*	An analysis of 55 immunochip-wide data sets identified SNPs whose association with risk for inflammatory bowel disease is modified by tobacco smoking	264
Crohn's disease and smoking - associated genes		
CYP2A6	Current smoking was associated with Crohn's disease only in individuals with AG/GG genotype	263
TNFR2	In Crohn's disease, the *TNFR2* polymorphisms were negatively associated with smoking at diagnosis.	265
TUCAN (CARD8) *NOD1*, *IBD5* *TNFSF15*	Highly significant association between Crohn's disease and a diagnostic panel of smoking status that includes *TUCAN*, *NOD2*, *IBD5*, *NOD1 and TNFSF15*	266
PLAG2, *POMC*, *LYG2*	An analysis of 55 immunochip-wide data sets identified single nucleotide polymorphisms whose association with risk for inflammatory bowel disease is modified by tobacco smoking	262,264
NOD2/CARD15	DSS-induced colitis in *Nod2*$^{-/-}$ mice showed strong protective role of interleukin-10 on intestinal homeostasis in response to tobacco smoking. High absolute risks of Crohn's disease can be obtained by incorporating information on smoking, family history and *NOD2/CARD15* mutations	264,267,268
IL10	DSS-induced colitis in *Il10*$^{-/-}$ mice showed strong protective role of interleukin-10 on intestinal homeostasis in response to tobacco smoking	198,264
SP	Smoking habit was significantly associated with substance P levels in Crohn's disease	269
IL23R	A strong additive interaction exists between *IL23R* single nucleotide polymorphisms and smoking behaviour resulting in a dramatic increase in Crohn's disease risk	270

Abbreviations: HLA-DRB1, HLA class II histocompatibility antigen, DRB1 beta chain; HLA-DQB1*06, HLA class II histocompatibility antigen, DQ beta 1 chain.

had significantly higher *TNF* mRNA levels in inflamed mucosa compared with nonsmokers. Also, in smokers with ulcerative colitis, they observed significantly higher *IL10* mRNA levels in non-inflamed mucosa.[215] Another study, on expression on colonic detoxification genes, showed that of the 244 detoxification genes investigated, 65 were dysregulated in ulcerative colitis patients in comparison to healthy controls or Crohn's disease patients.[216] Of the 65 genes dysregulated, 43 were brought back to normal levels in biopsies of ulcerative colitis current smokers in remission and in colonic explants of ulcerative colitis patients exposed to cigarette smoke extract, supporting the protective role of smoking in ulcerative colitis.[216]

1.8 | Smoking and epigenetic modifications in inflammatory bowel disease

Epigenetic modifications are heritable changes that affect gene expression or cellular characteristics and processes. Smoking is an environmental factor that can cause epigenetic modifications and this effect has been studied extensively in many inflammatory diseases as discussed previously.[25] Three major types of epigenetic modifications; (a) methylation, (b) histone modifications and (c) noncoding RNA, and current knowledge in relation to intestinal inflammation and smoking will be discussed in the following sections.

1.8.1 | DNA methylation

DNA methylation is a physiological mechanism of gene suppression that maintains pluripotency, X-chromosome inactivation and genomic imprinting.[217] The methylation patterns are controlled by DNA methyltransferases (DNMTs) as well as CpG methyl binding proteins (MBD).[218] DNA methyltransferases comprise a family of tightly regulated enzymes that are responsible for the transfer of methyl group on the fifth carbon of cytosine residues in DNA within CG dinucleotides, the so called methylation process.[219] Among the epigenetic mechanisms, DNA methylation has been widely studied with respect to smoking because it causes dysregulated global and gene-specific DNA methylation. One of the first studies on ulcerative colitis patients performed methylation analysis on mucosal biopsies and identified increased methylation of promoter regions.[220] More recently, a study on methylation pattern on blood samples from paediatric inflammatory bowel disease donors indicated that Crohn's disease-associated patterns of DNA methylation observed are a result of the inflammatory features of the disease and are less likely to contribute to disease development or progression.[221] Comments on that study highlighted the positive points, especially the identification of a target gene *RPS6KA2* (encoding the enzyme ribosomal protein S6 kinase alpha-2), that has been shown in previous study to be significantly hypomethylated in inflammatory bowel disease across several independent paediatric and adult cohorts.[222] There are numerous publications linking DNA methylation to inflammatory bowel disease, identifying epigenetic methylation signatures on genes such as tumour necrosis factor, *TNF* and human alpha defensin 5, *DEFA5*,[223] or tyrosine-protein kinase TXK,*TXK*,[224] Interestingly, all the studies in the field of intestinal inflammation that focus on smoking and DNA methylation are linked to colorectal cancer. Both inflammatory bowel disease and CpG island methylation confer high risk for malignancies, as it has been discussed in several reviews over the last two decades.[225-232]

1.8.2 | Histone modifications

Histones are basic proteins that interact with negatively charged DNA to form the compact nucleosomes, the basic unit of the chromosomes. There are several histone modifications which affect chromatin structure and gene expression. These modifications include methylation, acetylation, phosphorylation, ubiquitination, sumoylation, crotonylation, ADP-ribosylation and deamination.[233,234] The role of histone modifications in inflammatory bowel disease is very limited. A recent review by Ray and Longworth discusses the most updated information about histone modifications and their role in intestinal epithelium and T cells.[235] Moreover, the microbiome and some of its metabolites, eg short-chain fatty acids, polyamines, polyphenols and vitamins, have been shown to affect the genome via histone modification,[236,237] a function which is modulated further by dysbiosis that takes place during intestinal inflammatory conditions.[238]

1.8.3 | Noncoding RNAs

The microRNAs (miRNAs) are short noncoding RNAs that affect gene expression post-transcriptionally.[239] They function via base-pairing with complementary sequences within mRNA molecules and as a result, these mRNA molecules are silenced.[240] Under physiological conditions, microRNAs contribute to intestinal homeostasis by regulating intestinal epithelial differentiation, architecture and barrier function.[241] There is extended literature though about the role of various microRNAs in intestinal inflammation and the risk of cancer development. One study showed that nicotine increased the levels of miR-124 in epithelial cells and infiltrated T cells of mice during DSS-induced colitis.[139] Another category of noncoding RNAs are the long noncoding RNAs (lncRNAs).[242] They have been shown to affect the intestinal epithelial barrier by modulating the translation of the tight junction mRNAs.[243] Long noncoding RNAs are also involved in pathogenesis of inflammatory bowel disease and this topic is discussed by Yarani and colleagues in a recent review.[244]

Smoking has been shown to affect all three types of epigenetic modifications.[24,245-247] In a systematic review that analysed 14 epigenome-wide association studies of smoking exposure it was shown that DNA methylation is a reversible modification and after smoking cessation, most of the genes returned to physiological levels within 5 years.[248] More recently, another systematic review summarised a

10-year literature, including all types of studies in the field of smoking and chronic obstructive pulmonary disease, identifying differentially expressed genes and microRNAs in smokers and their potential to be biomarkers, highlighting the transgenerational effects of maternal and paternal smoking on offspring.[25]

1.9 | Implications for pathogenesis—definition research agenda

As it is discussed above, cigarette smoking affects inflammatory bowel disease pathogenesis at various levels. It targets the genetic information (DNA and RNA), modifies structures and protein functions, alters pathways and processes, effects that are amplified at the tissue and organ levels. The effects of smoking, summarised in Figure 2, are caused by a variety of chemicals existing in the gas and tar phase, they are systemic and local, and they can be direct or indirect. The oxidative damage of lipids, proteins and DNA, the activation of the nicotinic acetylcholine receptor and the transient receptor potential channels on intestinal epithelium or on neurons are few of the direct effects. Examples of indirect effects are the major changes in the microbiome constitution and the epigenetic modifications on immune cells and intestinal epithelium. It is still unknown whether cigarette smoke causes specific epigenetic alterations in the intestinal commensal bacteria. This area needs to be explored further because the intestinal microbes and their products are in a constant interaction with the host tissues and have the potential to modify their functions. The research interest has started to focus on epigenetic changes that could explain the phenotypic differences within inflammatory bowel disease. Evolution of sequencing approaches and their analyses will help identify cell-specific epigenetic changes and how these affect cellular functions and interactions within tissues and with other organ systems or organisms.

ACKNOWLEDGEMENTS

Conception of this review followed original research by the European Union Seventh Framework Programme (SysMedIBD FP7/2007-2013) under grant agreement number 305564.

Declaration of personal interests: SP, BJC and CP are employees of the University of Liverpool. JS is an employee of the University of Oxford. BJC has served as a consultant for Symprove; Farnham, UK and is an advisory board member for Anatara Lifesciences Ltd, Melbourne, Australia.

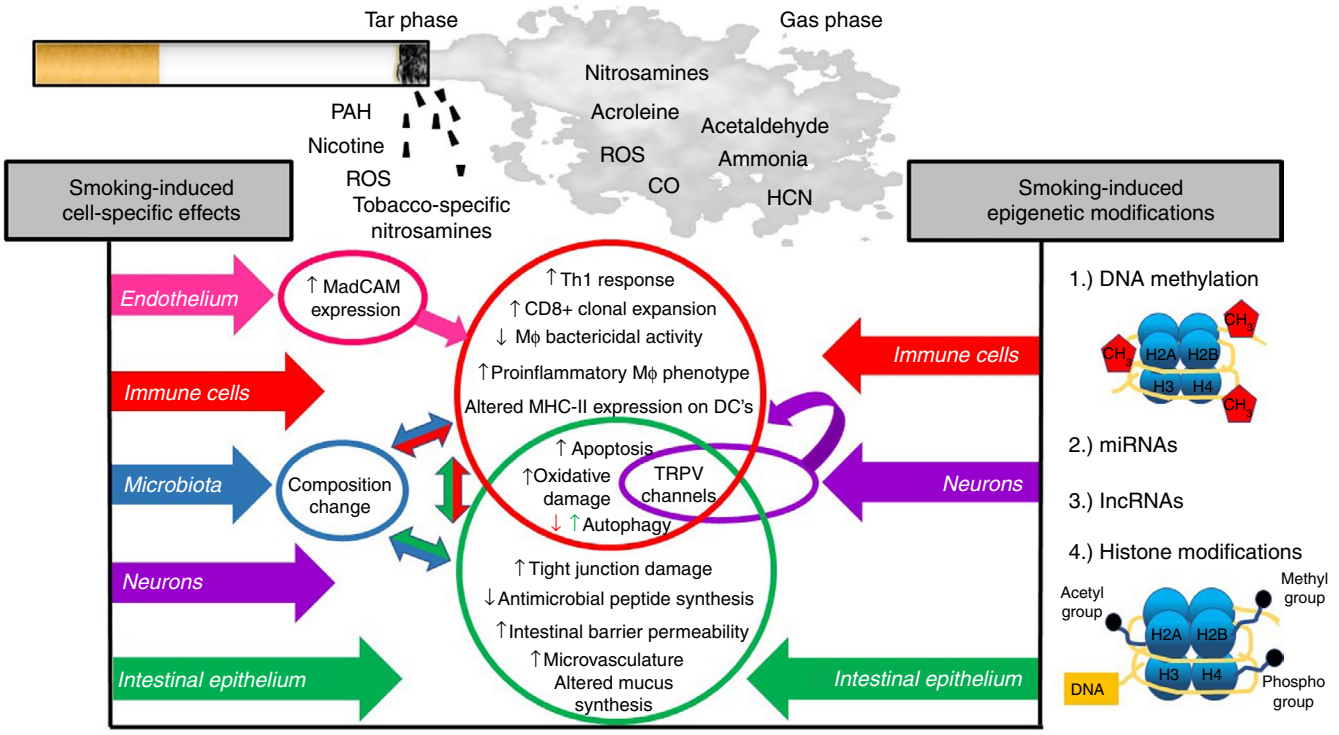

FIGURE 2 Composite effects of cigarette smoking on cells that contribute to the pathogenesis of inflammatory bowel disease. The mostly studied constituents of cigarette smoke (gas and tar phase) appear at the top of the figure. Coloured diagrams represent different cell types: immune cells (red), endothelium (pink), neurons (purple), intestinal epithelium (green) and microbiota (blue). Smoking-induced cell specific effects appear within the diagrams and common processes appear in the overlapping areas of the coloured diagrams. Single and double-coloured arrows represent the effects of one cell type to another, or mutual interactions, respectively. ROS, reactive oxygen species; HCN, hydrogen cyanate; CO, carbon monoxide; PAH, polycyclic aromatic hydrocarbons; miRNAs, micro RNAs; lncRNAs, long noncoding RNA; CH_3, methyl group; MAdCAM-1, Mucosal addressin cell adhesion molecule-1; Mϕ, macrophage; DC, dendritic cells; MHC-II, major histocompatibility complex II; TRPV, transient receptor potential cation channel subfamily V

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Guarantor of the article: Stamatia Papoutsopoulou.

Author contributions: SP performed the research and wrote the paper, JS, BJC and CP contributed to, and edited, the draft manuscript.

All authors approved the final version of the manuscript.

Declaration of personal interests: SP, BJC and CSP are employees of the University of Liverpool. JS is an employee of the University of Oxford. BJC has served as a consultant for Symprove; Farnham, UK and is an advisory board member for Anatara Lifesciences Ltd, Melbourne, Australia.

Declaration of funding interests: No funding was received to support writing of this paper. SP was a past employee at University of Manchester, funded by the European Union Seventh Framework Programme (SysMedIBD FP7/2007-2013) under grant agreement number 305564. BJC and CSP were work package partners (at University of Liverpool) on the same EU FP7 project.

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How to cite this article: Papoutsopoulou S, Satsangi J, Campbell BJ, Probert CS. Review article: impact of cigarette smoking on intestinal inflammation—direct and indirect mechanisms. *Aliment Pharmacol Ther*. 2020;51:1268–1285. https://doi.org/10.1111/apt.15774