



REVIEW ARTICLE

Smoking in inflammatory bowel disease: Impact on disease course and insights into the aetiology of its effect



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Abstract

The chronic intestinal inflammation that characterises Crohn's disease and ulcerative colitis arises from a complex interplay between host genotype, the immune system, and the intestinal microbiota. In addition, environmental factors such as smoking impact on disease onset and progression. Individuals who smoke are more likely to develop Crohn's disease, and smoking is associated with recurrence after surgery and a poor response to medical therapy. Conversely, smoking appears protective against ulcerative colitis and smokers are less likely to require colectomy. The mechanism by which smoking exerts its impact on disease and the rationale for the dichotomous effect in patients with Crohn's disease and ulcerative colitis is not clear. Recent evidence suggests that smoking induces alterations to both the innate and acquired immune system. In addition, smoking is associated with a distinct alteration in the intestinal microbiota both in patients with active Crohn's disease and healthy subjects.

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1. Introduction

Inflammatory bowel disease (IBD) occurs when there is an abnormal immune response to the host microbiota in genetically susceptible individuals.¹ Genome wide association studies (GWAS) have enhanced our understanding of the genetic susceptibility to IBD and highlighted the role of specific pathways such as the IL-23/bacterial sensing and autophagy to disease pathogenesis.² Many of the risk alleles for Crohn's disease (CD) appear to be involved in bacterial sensing at a mucosal level such as CARD15 gene which codes for the pathogen recognition receptor NOD2.^{3,4} However, the currently identified susceptibility genes only account for a fraction of disease risk which highlights the importance of environmental factors in the onset and progression of IBD.⁵ Epidemiological studies have suggested a role for an urban environment,⁶ the oral contraceptive pill,⁷ appendectomy⁸ and in particular tobacco smoke which has a protective effect in ulcerative colitis (UC) and yet exacerbates CD.

Despite recent advances in our understanding of the aetiology of IBD in areas such as autophagy,² the gastrointestinal (GI) microbiota,⁹ the innate immune system¹⁰ and T-cell regulation,¹¹ the impact of environmental factors such as smoking on these remains opaque. The aim of this article is to review the evidence that smoking alters inflammatory bowel disease severity and also to examine recent data on the effect of smoking on the host immune system and microbiota in an attempt to better understand its pathological role.

2. Smoking and ulcerative colitis

Smoking has been shown to protect against the development of UC and, in those with established disease, smoking results in a less severe course. The evidence for a protective effect of smoking in patients with UC is well established. A 1981 questionnaire survey of 230 patients with UC, 192 with CD and 230 age and gender matched controls found that whereas 42% of patients with CD and 44% of controls smoked, only 8% of patients with UC were current smokers ($P < 0.001$).¹² A higher proportion of UC patients were ex-smokers than patients with CD or controls (44% vs. 27%

vs. 20% $P < 0.001$) and the majority (87%) of those who had given up, did so prior to the onset of their GI symptoms. A recent cohort study from Hungary examined 1420 patients with IBD including 914 patients with UC and 506 with CD and found the prevalence of smoking to be 14.9% and 47.0% respectively compared to a prevalence of 36% in the general adult population.¹³ Meta-analysis has confirmed that current smoking has a protective effect in UC, the most recent of which has demonstrated that smokers have an odds ratio (OR) of developing UC of 0.58; (95% confidence interval (CI), 0.45–0.75) compared to non-smokers.^{14,15}

A ten-year cohort study of 556 patients with UC analysed differences in disease course between smokers and non-smokers.¹⁶ The study found a reduction in both oral corticosteroid use (52% vs. 63% $P = 0.05$) and actuarial colectomy rates (32% vs. 42% $P = 0.04$) in the smokers with UC compared to non-smokers with UC. It also found that in those patients with limited disease at entry to the cohort, progression to pancolitis was reduced in the smoking vs. non-smoking populations (14% vs. 26% respectively; $P = 0.04$).

In contrast, smoking did not impact upon response to thiopurine or disease progression in the 60 patients with steroid dependant UC included in a recent Spanish study.¹⁷ Interestingly the same study used multivariate analysis to examine tolerance to thiopurines in all patients and found that smoking significantly increased the risk of thiopurine discontinuation because of side effects (OR 0.36, 95% CI 0.14–0.93, $P = 0.036$). There is scarce data demonstrating the effects of smoking status on response to biological therapy in UC. In one small study of 47 patients treated with open label infliximab for UC, multivariate analysis did not demonstrate that smoking status affected the outcome.¹⁸

2.1. Smoking cessation in ulcerative colitis

Several studies have addressed whether smoking cessation has a negative impact on UC disease course. Analysis from the Nurses Health Study, a cohort of greater than 200,000 women over a 30 year period found that the hazard ratio (HR) for developing UC in the 2–5 year period following smoking cessation was 3.06 (95% CI 2.00–4.67).¹⁹ A cohort study of 32 patients with UC who quit smoking, compared them to age and gender matched smokers and non smokers

with UC with a mean follow-up of 9 years prior and 7 years post cessation of smoking.²⁰ When comparing the time periods before and after smoking cessation, patients who smoked had fewer years with active disease ($P < 0.01$), hospitalizations ($P < 0.05$), and medical therapy (steroids; $P < 0.05$, immunomodulatory therapy; $P < 0.05$). Use of immunomodulators was greater in the non-smoking cohort and those who had quit compared to those who continued to smoke ($P < 0.01$), however there were no differences in the colectomy rates between the three groups.

2.2. Nicotine replacement in UC

There have been a number of studies examining the role of nicotine replacement in the induction of remission in patients (both ex-smokers and non-smokers) with UC.^{21–24} A meta-analysis of these trials demonstrated that transdermal nicotine replacement was superior to placebo in the induction of remission (OR = 2.56, 95% CI 1.05–5.10).²⁵ However, when compared to standard therapy (either prednisolone or oral 5-aminosalicylic acid (5-ASA)) there was no significant benefit (OR = 0.77, 95% CI 0.37–1.60). In addition, transdermal nicotine was associated with an increased risk of withdrawal from the trial due to side effects (OR = 5.82, 95% CI 1.66–20.47) and adverse events (OR = 3.54, 95% CI 2.07–6.08).

There has been a single open label trial of resumption of low dose smoking in 17 patients with medically refractory UC who declined colectomy.²⁶ The majority of these patients were steroid dependant, and all had failed or were intolerant of 5-ASA's, immunomodulators and anti-TNF- α agents. Out of the 15 patients that recommenced smoking (mean cigarette dose 8.6/d), 14 were able to maintain steroid free clinical remission during the unspecified follow-up period. Three of these patients were then able to switch from tobacco cigarettes to a nicotine compound whilst maintaining clinical remission. Clearly a randomised controlled trial would be required to substantiate this data and there are a number of ethical issues with such a therapeutic strategy. The authors stress that careful consideration of, and monitoring for, adverse events is required prior to advising patients to recommence smoking. It is also unclear where liability for such events would lie.

3. Smoking and Crohn's disease

In contrast to UC, smoking has been shown to be an independent risk factor for the development of CD and is associated with more severe, refractory disease. The first data examining the role of smoking and CD was based on a UK questionnaire study involving 82 patients with CD and 82 matched controls.²⁷ The study found that patients with CD were more likely to smoke (Relative Risk (RR), 3.5, 95% CI 1.8–6.6) compared to controls and that this association was even stronger within three months of disease diagnosis (RR = 4.8, 95% CI 2.4–9.7). Interestingly the association between CD and smoking at the time of diagnosis was stronger in women (RR = 8.2, 95% CI 2.8–24.0) than men (RR = 2.4, 95% CI 0.96–7.1). A study of 339 sibling pairs examined 89 pairs who were dichotomous for smoking status, 23 of whom were also dichotomous for diagnosis. Of these 23 pairs the smoker had CD in 91% of cases with an OR = 10.5 (95% CI 2.6–92, $P < 0.001$).²⁸ A meta-analysis of nine studies has shown that

smoking results in an odds ratio of 1.76 (95% CI 1.40–2.22) for the development of CD.¹⁴

A French study of almost 3000 patients with CD divided into non-smokers, light smokers (1–10 cigarettes per day) and heavy smokers (>10/day) examined the percentage of time patients experienced active disease and their requirement for immunosuppression.²⁹ Multivariate analysis revealed that non-smokers spent less time with active disease than light smokers and heavy smokers (33% vs. 38% vs. 41% years with active disease, respectively; $P < 0.0001$ for non-smokers compared to light or heavy smokers and $P < 0.01$ for light-smokers compared to heavy smokers). The number of years exposure to immunosuppressants was lower in non-smokers than light smokers and heavy smokers (32% vs. 34% vs. 36% respectively; $P < 0.001$ heavy-smokers compared to non-smokers and $P = 0.04$ heavy-smokers compared with light smokers).

In addition to increasing the risk of developing CD, smoking appears to alter the natural history of the disease. A recent cohort study of 3224 patients with CD on the Spanish national IBD database (ENEIDA) found that current smokers were less likely to have colonic disease than non-smokers (7.9% vs. 10.9% $P < 0.05$) and more likely to have perianal disease (29.5% vs. 26.2% $P < 0.05$).³⁰ This study also found that stricturing disease was more common in smokers than non smokers (22.5% vs 19.3% $P < 0.05$). Two further studies have demonstrated that continued smoking is a risk factor for disease progression from simple 'inflammatory' disease (Montreal classification B1) to stricturing or penetrating disease (B2/B3 respectively).^{13,31} One study retrospectively examined case notes of a cohort of 506 patients with CD and found that in those patients who had B1 disease at diagnosis the odds ratio of developing B2/B3 disease was 2.02 in smokers vs non smokers (95% CI 1.30–3.16).¹³ There is marked heterogeneity in studies that have examined smoking status and disease location in CD with several studies suggesting a positive correlation with ileal disease,^{32,33} some showing a negative correlation with smoking and colonic disease^{33–35} and several showing no relationship at all.^{36–38} A systematic review examining this topic suggested that one possible explanation is the lack of uniformity in the definition of smoking status.³⁹ The authors suggested using the following terms of 'current', 'former' and 'never' smokers in order to minimise heterogeneity in the future.

Several studies have demonstrated the detrimental effects of smoking on the likelihood of surgical intervention in patients with CD. A cohort of 174 patients with CD followed up for 10 years found that smokers had a 29% increased risk of surgery compared to non-smokers. Again this effect was more pronounced in women (OR = 4.2, 95% CI 2.0–4.2) than men (OR = 1.5, 95% CI 0.8–6.0).⁴⁰ A second cohort study followed 182 patients who had undergone surgery for CD and used multivariate analysis to determine risk factors for clinical, endoscopic and surgical recurrence.⁴¹ The presence of extra-intestinal manifestations, extensive pre-operative disease and smoking was associated with clinical recurrence; in addition, smoking was associated with post-surgical recurrence HR 2.0 (95% CI 1.2–2.3). Finally a retrospective analysis of endoscopic balloon dilatation of intestinal strictures in Crohn's disease found that smokers were more likely to require further dilatation

or surgery following an index dilatation than non-smokers HR 2.50 (95% CI 1.14–5.50).⁴²

In addition to its impact on CD onset and progression, smoking effects response to medical therapy. In one study, analysis of clinical outcome revealed that 73% of non-smokers experienced response to the episodic use of infliximab compared to only 22% of smokers ($P < 0.001$).⁴³ However, smoking did not alter the clinical outcome in patients with fistulating disease. A second study prospectively assessed 74 patients with CD treated with a single dose of infliximab at four weeks and reported that smokers were significantly less likely to respond than non-smokers (OR = 0.22, 95% CI 0.08–0.41). In addition, the duration of response was significantly longer in non-smokers than smokers ($P = 0.003$).⁴⁴ A more recent survey of 1170 patients with CD in Spain found that smoking was an independent predictor of the need for immunosuppressant and biologic therapy to maintain remission.³⁵

3.1. Smoking cessation in Crohn's disease

In keeping with the detrimental effects of smoking on disease development, progression and both surgical and medical therapy, smoking cessation appears to be beneficial for patients with CD. One study investigated 474 patients with CD who smoked more than two cigarettes a day and invited them to quit with support in the form of counselling and nicotine replacement therapy.⁴⁵ The 59 patients (12%) who abstained from smoking for at least one year (self reported abstinence confirmed by urinary cotinine analysis) were compared with the same number of matched non-smoking and smoking patients with CD over a two-year follow-up. The risk of disease flare, steroid and immunosuppression use in those that quit smoking was lower than those who continued to smoke ($P < 0.001$ for all three groups) there was no difference between ex-smokers and non-smokers. Encouraging patients to quit smoking is difficult and time consuming, a recent study of 408 smokers with CD given professional cessation advice and support, demonstrated abstinence rates of 31% albeit this fell to 23% at the end of the one year follow-up period.⁴⁶ However a further study examining the effect of communicating a DNA based risk assessment to unaffected siblings of patients with CD who smoke found that not only was the use of DNA information ineffective at improving cessation but that the overall success rate was around 5% at six months.⁴⁷ Smoking cessation is clearly difficult, a Cochrane systematic review on the role of physician advice in smoking cessation amongst the general population demonstrated that a brief medical intervention only improved the chance of cessation by 1–3% beyond an unassisted success rate of 2–3%.⁴⁸ However the studies from Cosnes⁴⁵ and Nunes⁴⁶ demonstrate that higher cessation rates are possible in patients with Crohn's. A multidisciplinary approach utilizing the whole of the IBD team should be used, as well as access to expert cessation advice and nicotine replacement.

4. Passive smoking and IBD

Passive smoking at birth (although interestingly not at the time of symptom onset) has been shown in two studies to be a risk factor for the development of IBD in children with an OR 3.02, (95% CI 1.28–7.06) and an OR 2.04 (95%

CI 1.06–3.92) respectively.^{49–50} However a meta-analysis of epidemiological studies, failed to find that childhood passive smoking alters the incidence of UC or CD in adults.⁵¹

5. Gender, IBD and smoking

A number of published studies report an interaction between gender and the effect of smoking on IBD. The data suggests that women are more likely to be smoking at the time of CD diagnosis than men²⁷ and that female smokers are more likely to require surgery for their CD than male smokers.⁴⁰ Analysis of 688 patients with Crohn's colitis revealed that female smokers are likely to present at a younger age than female non-smokers (29 years vs. 35 years $P < 0.001$) and require immunomodulators (10 year cumulative risk $58\% \pm 4\%$ in female smokers vs. $48\% \pm 5\%$ in female non-smokers $P < 0.001$); neither of these effects were seen in men.⁵² The same study found that the protective effect of smoking in patients with UC (978 patients) and indeterminate colitis (118 patients) was more marked in men. Thus, whereas the age of UC onset was significantly increased in male smokers compared to non-smokers (41 years vs. 32 years $P < 0.001$), this effect was not seen in women (33 years in both groups). Likewise, use of immunomodulators in UC was significantly reduced in male smokers compared to non-smokers ($8 \pm 4\%$ vs. $26 \pm 4\%$ $P < 0.01$), an effect not seen in women. The explanation for why the negative effects of smoking in CD are more pronounced, and the protective effects of smoking in UC are less pronounced, in females is not clear. However, a similar phenomenon is seen in other disease states such as cardiovascular disease⁵³ and essential thrombosis.⁵⁴ Smoking lowers plasma oestrogen levels possibly due to induction of oestrogen metabolising cytochrome P450 isoenzymes CYP1A1 and A2,⁵³ potentially negating the beneficial effects of oestrogen on thrombosis formation and macrophage function.

6. Putative mechanisms for the role of smoking in IBD

Despite the clear evidence for a link between smoking and IBD outlined above, the mechanisms that mediate these effects remain unclear. Cigarette smoke is highly complex and there is still uncertainty as to the role of specific components. Smoking appears to alter both the timing of onset of IBD and the course of disease itself. There are four key areas with relevance to the impact of smoking on IBD: the host GI microbiota, the integrity of the intestinal epithelium, the immune system and potentially epigenetic susceptibility.

6.1. Cigarette smoke

Cigarette smoke contains approximately 4500 components of which around 150 are thought to exert a carcinogenic or toxic effect in humans.⁵⁵ These components include: polycyclic aromatic hydrocarbons; tobacco-specific nitrosamines; phenolic compounds; alkaloids (such as nicotine); volatile aldehydes (formaldehyde); dioxins and heavy metals (cadmium and arsenic).⁵⁵ Although nicotine is the most extensively investigated, dioxins and a number of

the other compounds have immunomodulatory effects. Therefore establishing which component exerts the greatest effect is difficult.

Nicotine is an alkaloid compound found naturally in tobacco and although not toxic is highly addictive. The effects of nicotine have been widely studied in IBD both *in vivo* and *in vitro* with a particular focus on its therapeutic effect in UC as described above. Dioxins are known not only to be both carcinogenic but also exert an immunomodulatory effect *via* dioxin responsive elements (DRE) found in the promoter regions of many genes.⁵⁶ Cadmium and arsenic known carcinogens and have both been shown to be involved in the development of gastric ulceration.⁵⁷ Arsenic compounds have been shown to be effective in the treatment of refractory proctitis.^{58,59} Many *in vitro* studies use tobacco smoke rather than individual components when studying the effects on cell lines or animal models,^{57,60,61} which makes isolation of the active component of the smoke extremely difficult.

6.2. Smoking and the gastrointestinal microbiota

Recent advances in molecular microbiology allow detailed assessment of the microbiota of patients with IBD and have demonstrated a clear dysbiosis in both UC and CD.⁶² In patients with active CD, adherent invasive *Escherichia coli* have been demonstrated within the lamina propria and have been found to survive within macrophages leading to subsequent activation of dendritic cells and migration of T-cells.⁶³ *Faecalibacterium prausnitzii* a major representative of the Clostridium leptum group with known anti-inflammatory properties is reduced in both CD and in UC.^{64,65} Although environmental factors such as diet can alter the GI microbiota, until recently no-one had examined the influence of smoking.⁶⁶

A recent study used fluorescent *in situ* hybridisation to examine the luminal microbiota of 101 patients with active CD.⁶⁶ Multivariate analysis, which adjusted for disease severity, revealed that smokers had increased proportions of *Bacteroides-Prevotella* than non-smokers (mean 38.8% SD 13.7 vs. mean 28.3%, SD 12.6; $P < 0.001$). In order to exclude the possibility that the impact of smoking on the microbiota was mediated by its documented effect on disease severity, faecal samples from 66 healthy controls were subsequently analysed to see if this effect was specific to CD. Once again multivariate analysis demonstrated that healthy control smokers had higher percentages of *Bacteroides-Prevotella* than non-smokers (mean 34.8%, SD 4.8 vs. mean 24.1% SD 2.1). The relevance of this alteration is unknown. Some studies have shown that strains of *Bacteroides* induce CD4 T-cell mediated colitis in animal models⁶⁷ whilst in humans, IL-12 positive intestinal dendritic cells more frequently coexist in Crohn's patients who have higher *Bacteroides*.⁶⁸ In a further study, inflamed mucosal tissue was harvested from 15 patients during surgical resection for active CD and analysed for mucosal-associated microbiota using fluorescent *in situ* hybridisation. Interestingly, the numbers of *F. prausnitzii* were lower in smokers compared with non-smokers ($P = 0.036$).⁶⁹ This is of clinical importance because lower ileal mucosal *F. prausnitzii* is associated with greater risk of endoscopic recurrence following surgical

Resection.⁶⁴ This may relate to the immunoregulatory characteristics of this strain, including *in vitro* evidence for a reduction of peripheral blood mononuclear cell IL-12 and an increase in IL-10 release.⁶⁴

The mechanisms through which smoking is associated with alterations in microbiota are unclear. Smokers may have behavioural characteristics, such as diet, that predispose to a luminal and mucosal dysbiosis, including higher energy/fat and lower fibre consumption than non-smokers.⁷⁰ However, it is also possible that smoking has a direct influence on the microbiota.

6.3. Smoking and intestinal permeability

There is relatively little mechanistic data to explain the protective effect of smoking in patients with UC. However, it has been reported that exposure to nicotine increased the thickness of the colonic mucous layer in cell culture and in histologically normal biopsies obtained from patients with UC.⁷¹ However, a second study reported no difference in mucin gene transcription in UC patients being treated with trans-dermal nicotine compared to placebo. This latter study reported that nicotine treated UC patients had a reduction in pro-inflammatory chemokine IL-8 transcription.⁷² *In vitro* studies measuring the effects of nicotine on the trans-epithelial resistance (TER) of Caco-2 cells found that nicotine and to a lesser extent its metabolites increased TER indicating reduced permeability.⁷³ This effect was likely to be due to up-regulation of tight junction proteins occludin and claudin-1. An *in vivo* study using 51Cr-EDTA urinary excretion to assess small intestinal permeability in healthy controls reported similar intestinal permeability between smokers and non-smokers (median 1.22% IQR 1.00–1.58 vs. 1.24, IQR 0.94–1.66; $P = \text{ns}$).⁶⁰ However, smokers were protected against the increased permeability resulting from an indomethacin challenge compared to non-smokers (110%, IQR 71–141% vs. 156% IQR 78–220% $P = 0.04$). In contrast, a second study of the effects of smoking on intestinal permeability that included 32 patients with UC and 50 controls, reported that patients with UC that smoked had the highest levels of permeability of any of the subjects studied.⁷⁴ Thus, the role of permeability as the basis of the protective effect of smoking in UC remains unclear.

6.4. Smoking and gastrointestinal immune system

The relationship between the effects of smoking and the immune system is complex and it would seem likely that the dichotomy in the impact of smoking on UC and CD may be explained in part by this complexity. Passive smoke exposure in mice leads to increased epithelial cell apoptosis and an increase in dendritic cell numbers, chemokine expression and subsequent T lymphocyte recruitment.⁶¹ Oral nicotine ingestion aggravates small intestinal inflammation and ameliorates colonic inflammation in the IL-10 knockout mouse model of CD.⁷⁵ Studies on the innate immune system have demonstrated that nicotine can directly inhibit TNF- α from stimulated macrophages⁷⁶ and in the lung nicotine interferes with toll like receptor signalling in alveolar macrophages again

reducing inflammatory cytokine release.⁷⁷ Studies using human peripheral blood mononuclear cells (PBMCs) from controls, CD and UC patients, demonstrated that although smoking did not significantly alter PBMC IL-8 release in response to stimulation with lipopolysaccharide (LPS) in controls and UC patients it significantly reduced IL-8 release in CD patients.⁷⁸ The same group studied the release of the anti-inflammatory cytokine IL-10 and the pro-inflammatory cytokine IL-12 from stimulated and unstimulated PBMCs. Whereas IL-10 release was significantly impaired in smokers with CD smokers, IL-12 release was not. This data would suggest that smokers with CD have a significant reduction in the IL-10/IL-12 ratio compared with non-smokers. Given the evidence for an impaired innate immune response in CD and an exaggerated macrophage response to bacterial products in UC¹⁰ this data goes some way to explain the difference seen in the two diseases.

Tobacco smoke also contains high levels of dioxins, a by-product of combustion, which can have immunomodulatory effects in humans. The aryl hydrocarbon receptor (AhR) is a ligand-inducible transcription factor ubiquitously expressed in vertebrate cells and is the only known dioxin receptor.⁷⁹ AhR has been recently postulated to link environmental factors (both inhaled and ingested) to the host immune system in IBD.⁷⁹ Dioxins are a diverse group of halogenated aromatic hydrocarbons and include toxic compounds such as the high affinity prototypical AhR agonist 2,3,7,8-tetrachlorodibenzodioxin (TCDD). Other AhR ligands include 6-formylindolo (3,2b) carbazole (Ficz) and non-toxic ligands such as the naturally occurring chemicals indole-3-carbinol (I3C) found in cruciferous vegetables (cabbage, broccoli, cauliflower). In murine models of colitis administration of Ficz ameliorated inflammation via an IL-22 dependant pathway and subsequent blockade of the AhR pathway exacerbated the colitis.⁸⁰ The same group examined levels of AhR RNA expression in inflamed and uninfamed colonic mucosa in CD, UC and in healthy controls and found that AhR expression was down regulated in inflamed CD tissue compared to uninfamed tissue in the same patients as well as inflamed tissue in UC and controls. In further work, the effects of AhR knockout (AhR $-/-$) in murine models of colitis were assessed. Although AhR $-/-$ mice died rapidly with severe inflammation in response to dextran sodium sulphate (DSS), AhR $+/-$ mice had an attenuated reaction to both DSS induced colitis and to exposure to cigarette smoke than wild type littermates.⁸¹ The authors suggest that low/normal stimulation of the AhR pathway is overall anti-inflammatory and protective. It is worth noting that AhR ligands are diverse and found in a number of foodstuffs as well as environmental contaminants. Different ligands may well have different effects on the host immune system^{81,82} and although TCDD and Ficz are used as experimental ligands some authors have questioned whether these are of relevance in human exposure to dioxins.⁸² Further work is required before the exact role of AhR in IBD is understood.

It is likely that smoking, like other environmental factors, exerts its greatest influence in IBD via the host immune system. With greater understanding of the pathogenesis of CD and UC and how the two disease processes differ it is possible to better understand the way in which environmental factors can affect them. Nicotine appears to directly inhibit the innate

immune system and yet ameliorate colitis at least in animal and cell culture models as well as potentially *in vivo*. Given the recent focus on impaired bacterial handling by the innate immune system in CD the detrimental role of tobacco would fit this hypothesis. It is interesting that smoking is associated with early disease recurrence in post-surgical CD patients who have at least for a time had the inflammatory component of their disease 'cured'. What re-starts the cycle of inflammation is unclear, however further inhibition of the innate immune system by cigarette smoke is likely to be involved. The role of AhR and other xenobiotic receptors offers a bridge between environmental compounds and the host immune system. Exactly how the effects of dioxins on AhR would create the inflammatory dichotomy seen in IBD is not completely understood but it does appear that AhR stimulation ameliorates inflammation and that the receptor expression is down regulated in CD.

6.5. Smoking and epigenetics

Clearly smoking cannot change an individual's genotype, however, it might alter epigenetic events. Epigenetics describes the post-translational methylation or histone modification of the genome.⁸³ Smoking has been shown to influence the development of a number of chronic diseases such as macular degeneration via epigenetic pathways.⁸⁴ Epigenetics has been shown to play a role in UC associated colorectal cancer and potentially altered immune regulation in CD.^{83,85}

AhR activation has been demonstrated to influence T cell differentiation into the pro-inflammatory Th-17 subset in autoimmune diseases both *in vitro* and in murine models of encephalitis.⁸² A group examining the effects of AhR on regulatory T-lymphocytes (T-reg) found that this immune regulation appears to be an epigenetic phenomenon.⁸⁶ AhR stimulation with one component of cigarette smoke (TCDD) leads to demethylation of promoter regions of the Foxp3 gene leading to increased numbers of T-reg's and hyper-methylation of the IL-17 promoter gene thereby decreasing expression of the cytokine which is critical in the differentiation of Th-17 cells. Thus smoking and other environmental factors in addition to their direct interaction with the immune system may alter the expression of proteins critical to the balance of inflammation within the GI mucosa.

Epigenetics also encompasses the role of micro RNA (miRNA) which are non-coding short segments of RNA that bind to cellular RNA and alter protein translation. There is evidence in bronchial epithelium that smoking can substantially alter miRNA profiles and in turn lead to altered gene expression.⁸⁷ There is a growing body of evidence demonstrating the importance of miRNA in IBD both as regulators of inflammation and carcinogenesis.^{88–90} Although to date there are no studies examining the role of smoking on miRNA expression in IBD this is likely to be an area of interest.

Finally, although there appears to be a robust epidemiological relationship between smoking and IBD the majority of reported studies were conducted in Caucasian populations. Studies from Israel failed to find a significant relationship between smoking and CD incidence or severity^{91,92} indicating that differing genotypes may actually respond differently to tobacco smoking. Most xenobiotic compounds such as those

found in tobacco smoke are metabolised by enzymes such as CYP1A1 (part of the cytochrome P450 family), and the breakdown products cleared by a further set of phase II enzymes such as GSTM1 (a glutathione S-transferase enzyme). Polymorphisms of these enzymes can greatly alter the effects of smoking, for example in their carcinogenic properties.⁹³ Given that the chief downstream target of AhR is CYP1A1,⁸² polymorphisms of these enzymes could influence patient response to cigarette smoke.

7. Conclusion

Smoking is the most clearly defined environmental risk factor for the development and progression of IBD and yet, as a result of the chemical complexity of tobacco smoke, one of the most poorly understood. Thus it is not certain why it affects patients with UC and CD in different ways. From a clinical perspective smoking cessation is of demonstrable benefit in patients with CD and yet is underutilised and should be set as an important treatment goal with dedicated resources. In UC a component or components of cigarette smoke offer the potential for therapeutic targets reinforced by the pilot study in recommencing smoking in refractory UC. The rather modest benefits of trans-dermal nicotine replacement suggest that further research in this area is required.

However advances in our understanding about the aetiopathogenesis of the impact of smoking in IBD are being made. Recently published research offers insights into how xenobiotic agents interact with the host immune system, GI microbiome, epigenetic machinery as well as the host response to pharmaceutical agents. Further exploration of these interactions offers not only a better understanding of the aetiopathology of IBD but may reveal novel therapeutic pathways.

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