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Crohn's disease and smoking: a review of the effects of the latter on inflammatory markers and gene expression

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ABSTRACT

Crohn's disease (CD), a chronic form of inflammatory bowel disease, affects the gastrointestinal tract and is characterized by a multifactorial aetiology involving both genetic predisposition and environmental influences. Among environmental modifiers, cigarette smoking plays a pivotal role in exacerbating the progression and severity of CD. Individuals with CD who smoke exhibit a heightened risk of disease flare-ups, increased surgical intervention rates, and diminished responsiveness to pharmacological therapies. Smoking intensifies intestinal inflammation by elevating key biomarkers, including C-reactive protein, erythrocyte sedimentation rate, and faecal calprotectin, while simultaneously dysregulating pro-inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-6, interleukin-1 beta, and interleukin-17. Furthermore, smoking alters gene expression by upregulating cytokine and matrix metalloproteinase pathways, and downregulating tight junction proteins essential for maintaining intestinal epithelial barrier integrity. These molecular disruptions compromise epithelial cohesion, exacerbate mucosal injury, and sustain chronic inflammation. Epigenetic modifications – most notably DNA methylation – further contribute to immune dysregulation in smokers with CD. Notably, smoking cessation has been associated with downregulation of pro-inflammatory gene expression and attenuation of disease activity, underscoring its therapeutic relevance in CD management. A deeper understanding of the mechanisms by which smoking modulates inflammatory biomarkers and gene expression may inform the development of targeted interventions aimed at improving clinical outcomes in patients with CD.

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1. Introduction

Crohn's disease (CD) is a chronic, idiopathic form of inflammatory bowel disease that can affect any segment of the gastrointestinal (GI) tract, from the oral cavity to the anus. The etiopathogenesis of CD is multifactorial, involving both genetic predisposition and environmental influences. The management of CD typically requires long-term pharmacological treatment, which may be associated with adverse effects, and in some cases necessitates surgical intervention and recurrent hospital admissions. These burdens significantly impact patients' social, professional, and psychological well-being. CD affects males and females equally and is most commonly diagnosed in young, active adults, thereby imposing a substantial societal and economic burden[1].

Cigarette smoking is a well-established environmental risk factor for CD. The prevalence of current smokers is significantly higher among individuals with CD compared to control populations. A systematic review and meta-analysis of 33 studies has demonstrated that smokers with CD are at increased risk of spontaneous disease exacerbation, postoperative recurrence, and a higher likelihood of requiring both initial and repeat surgical procedures[2]. Tobacco smoking is the most extensively studied environmental modifier in CD and has been shown to increase the need for additional immunosuppressive agents while reducing both the efficacy and durability of pharmacological treatments. In CD, smoking elevates the risk of disease flares, increases reliance on glucocorticoids and immunosuppressants, and diminishes therapeutic response to agents such as infliximab. Smokers also exhibit altered T cell profiles, with heavy smoking associated with elevated levels of suppressor CD8+ cells, suggesting a link between smoking and immune suppression.

Cigarette smoke may influence the gut microbiota by upregulating oxidative stress-related enzymes in intestinal immune tissues, disrupting the mucin layer, altering the expression of tight junction proteins, and inducing acid–base imbalance in the colon. These effects may result from direct toxicity of tobacco constituents or from bacterial transmission *via* cigarette exposure[3]. The present review aims to summarize how smoking modulates inflammatory markers and gene expression in patients with CD, thereby contributing to disease severity (Table 1).

2. Impact of smoking on inflammatory markers in CD

C-reactive protein (CRP) is a non-specific biomarker of systemic inflammation and is frequently elevated in individuals with CD. Smoking has been shown to further increase CRP levels, thereby amplifying systemic inflammatory responses and potentially worsening clinical outcomes. The erythrocyte sedimentation rate (ESR), another non-specific marker of inflammation, is commonly elevated in CD and correlates with disease activity. Smoking exacerbates ESR elevation, reinforcing its role in intensifying systemic inflammation in CD[4].

Faecal calprotectin (FC) is a specific marker of intestinal inflammation and is widely used in order to monitor disease progression in CD. Elevated FC levels reflect active mucosal inflammation, and smoking has been shown to significantly increase FC concentrations, indicating a worsening of localized GI inflammation. Additionally, pro-inflammatory cytokines – including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and interleukin-17 (IL-17) – are frequently dysregulated in CD. These cytokines drive the inflammatory cascade characteristic of the disease, and smoking further disrupts their regulation, thereby intensifying the inflammatory milieu and contributing to disease severity.

Finally, adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) facilitate leukocyte migration to inflamed tissues. Elevated ICAM-1 levels in CD enhance leukocyte adhesion and promote tissue inflammation. Smoking has been associated with increased activity of adhesion molecules, thereby aggravating mucosal damage and perpetuating inflammation[5].

3. Impact of smoking on gene regulation in CD

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Table 1. Major studies exploring the association of smoking with gene expression with Crohn's disease.

Study	Methodology	Main findings
Boronat-Toscano *et al.*[10]	genome-wide epigenetic analysis; quantitative gene expression evaluated by qPCR	smoking alters adipose stem cells' immune regulatory properties; ex-smokers retain pro-inflammatory epigenetic changes in stem cells
Wang *et al.*[6]	sure independence screening (SIS) for mediator CpGs selection; LASSO regression for variable selection in mediation analysis	smoking is significantly associated with Crohn's disease; changes in DNA methylation mediate the effect of smoking on Crohn's disease
Papoutsopoulou *et al.*[3]	Medline search for relevant smoking and intestinal inflammation terms; assessment of epidemiological, experimental, and clinical evidence	smoking causes oxidative damage and impairs intestinal barrier function; it alters immune cell function and microbiota composition
Allais *et al.*[8]	examined cytokine profiles in human subjects and mouse models; investigated TRPV1 expression and cytokine production effects	cigarette smoke increases IL-8 in healthy ileum; TRPV1 levels decrease in Crohn's disease patients and smoking controls
Yan Ang *et al.*[9]	prospective cohort study in UK Biobank participants; two-sample Mendelian randomization and genome-wide methylation analysis	current smoking is associated with higher risk of Crohn's disease; epigenetic alterations in DNMT3A, TNF/LTA, and AHRR genes are linked to inflammatory bowel disease risk
Nicolaides *et al.*[4]	comprehensive review of English literature from 1946 to April 2019; search conducted using Medline, Embase, and Cochrane central library	smoking affects treatment choice and efficacy in inflammatory bowel disease; impact of smoking on disease pathways and therapy efficacy
Lee *et al.*[5]	systematic review and meta-analysis conducted; searched databases for smoking effect on anti-TNF therapy in Crohn's disease	smoking reduces effectiveness of anti-TNF therapies in Crohn's disease; current smokers less likely to achieve clinical response and remission

Smoking influences the expression of multiple gene families that govern inflammation and immune responses in CD. It upregulates genes encoding pro-inflammatory cytokines, thereby exacerbating inflammatory signalling. TNF-α is a central mediator of inflammation and contributes to CD progression, IL-6 is associated with systemic inflammation and adverse clinical outcomes, and IL-1β plays a key role in tissue injury and inflammatory amplification[5].

The expression of genes involved in innate immunity, such as that of nucleotide-binding oligomerization domain-containing 2 (*NOD2*), may also be altered by smoking. The dysregulation of *NOD2* increases the susceptibility to intestinal inflammation and is implicated in CD pathogenesis[3]. Smoking further affects the expression of microRNAs (small non-coding RNAs that regulate gene expression related to immune function and inflammation): altered microRNA profiles disrupt intestinal homeostasis and contribute to inflammatory dysregulation[6].

Moreover, smoking elevates the expression of matrix metalloproteinases (MMPs), enzymes responsible for extracellular matrix remodelling. Increased MMP activity leads to mucosal degradation and sustained inflammation, thereby exacerbating tissue injury in CD[7]. Smoking also downregulates genes encoding tight junction proteins such as occludin and claudins, which are essential for maintaining epithelial barrier integrity. This downregulation results in increased intestinal permeability ("leaky gut"), further fuelling inflammation[8].

Finally, smoking induces the expression of genes associated with oxidative stress, activating pro-inflammatory pathways. Elevated oxidative stress contributes to mucosal injury and accelerates disease progression in CD[9]. The regulation of apopto-

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sis-related genes is also affected by smoking, potentially prolonging the survival of inflammatory cells within the intestinal mucosa; this dysregulation sustains chronic inflammation and worsens CD symptoms[10].

4. Conclusion

Smoking alters the expression of the NOD2 gene, and individuals with such dysregulation exhibit more severe disease progression compared to non-smokers. Moreover, smoking increases the levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-17, and induces epigenetic modifications (including DNA methylation) that contribute to immune dysregulation in CD. Smoking also significantly elevates inflammatory markers such as CRP. Conversely, smoking cessation has been associated with a downregulation of pro-inflammatory gene expression and an attenuation of disease activity, underscoring its therapeutic importance in CD management.

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Conflicts of interest

None exist.

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