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Review

Pathogenesis of Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD) is a multifactorial condition characterized by chronic inflammation of the gastrointestinal mucosa. Despite extensive research, its precise etiology remains unknown. However, significant progress has been made in understanding its complex pathogenesis, which involves a combination of genetic predisposition, environmental influences, microbial dysbiosis, and immune dysregulation. Numerous genetic loci are associated with Crohn's disease. Environmental factors such as smoking, dietary habits, physical activity, antibiotic exposure, and early-life influences play crucial roles in disease initiation and progression. Dysbiosis disrupts intestinal homeostasis and exacerbates inflammation. Immune dysregulation, particularly involving the Th1, Th2, and Th17 pathways, results in an imbalance between proinflammatory and regulatory responses, perpetuating chronic inflammation.
Keywords: Crohn's disease, microbiota, ulcerative colitis

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, relapsing inflammatory disorder of the gastrointestinal tract that primarily includes Crohn's disease (CD) and ulcerative colitis (UC). The pathogenesis of IBD is multifactorial, involving a complex interplay of genetic predisposition, immune dysregulation, environmental factors, and gut microbiota. Although the precise etiology remains unclear, it is well established that multiple contributing factors collectively influence disease onset, progression, and severity (Figure 1).

Genetic susceptibility plays a crucial role in IBD pathogenesis, as evidenced by the identification of multiple risk loci associated with immune response regulation, epithelial barrier function, and microbial interactions. Genome-wide association studies have highlighted key genetic variations, such as mutations in *NOD2*, *ATG16L1*, and *IL23R*, which significantly contribute to disease susceptibility, particularly in Crohn's disease. However, genetic predisposition alone is insufficient to trigger IBD, indicating the necessity of additional environmental and immunological factors.

Environmental factors, including diet, smoking, antibiotic exposure, and alterations in the gut microbiome, have been implicated in disease pathogenesis. Smoking has been found to exert differential effects on IBD subtypes, exacerbating Crohn's disease while providing a protective effect against ulcerative colitis. Emerging evidence suggests that early-life antibiotic exposure and altered gut microbial composition may disrupt intestinal immune homeostasis, further contributing to IBD development.

Immune dysregulation is a hallmark of IBD, characterized by an imbalance between proinflammatory and anti-inflammatory responses. In patients with IBD, an exaggerated immune reaction to commensal gut microbiota leads to persistent intestinal inflammation. Dysregulation of key immune pathways, including the Th1/Th17 axis in Crohn's disease and the Th2/Th9 response in ulcerative colitis, plays a central role in disease pathogenesis. Additionally, cytokine networks, such as tumor necrosis factor-alpha (TNF-α), interleukin-12 (IL-12), and interleukin-23 (IL-23), have been identified as pivotal mediators of inflammation, paving the way for the development of targeted biological therapies.

Given the complexity of IBD pathogenesis, ongoing research continues to explore novel mechanisms underlying disease development. Understanding the intricate interactions among genetic, environmental, and immune-related factors is essential for identifying new therapeutic targets and improving disease management. This review aims to provide an updated overview of the key pathogenic mechanisms driving IBD, with a focus on emerging insights that may shape future treatment strategies.

GENETIC FACTORS

Recent advancements in genetic research, driven by initiatives such as the *Human Genome Project* and the advent of genome-wide association studies (GWAS), have uncovered various genetic risk factors for IBD. These breakthroughs have significantly enhanced our understanding of the hereditary aspects of this disease and its molecular foundations.[1,2]

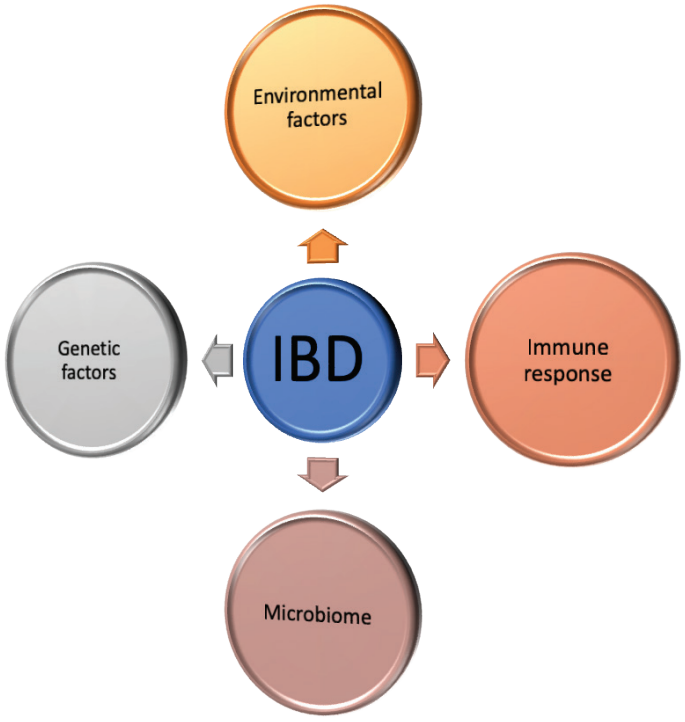

Figure 1. Factors affecting IBD pathogenesis.

Family studies have reported a family history in 1.5%–28% of CD cases and 1.5%–24% of UC cases.[3–5] In CD, the risk is approximately eightfold higher, whereas in UC, the risk is fourfold higher.[6] However, the incomplete concordance rates among twins suggest that genetic factors alone are insufficient to explain disease occurrence, highlighting the role of environmental influences.[7,8]

To date, over 240 genetic loci have been implicated in IBD susceptibility, with at least 30 loci shared between CD and UC. *NOD2* is a key player in CD, as variants of *NOD2* are frequently observed in affected patients. Studies have reported a mutation prevalence of up to one-third in certain populations.[9,10] For example, a 2006 study conducted in Turkey found a mutation frequency of 10.7% among patients with CD.[11]

ENVIRONMENTAL FACTORS

Environmental factors play a significant role in the progression of IBD by interacting with an individual's genetic predisposition, ultimately influencing both disease susceptibility and clinical presentation.

Smoking

Smoking has a paradoxical effect on IBD. While it worsens Crohn's disease, it appears to protect against ulcerative colitis. The mechanisms underlying these effects include alterations in immune responses, increased mucus production, and inhibition of autophagy, a process critical for maintaining cellular homeostasis.[9,12–14]

Physical Activity

Regular physical activity is associated with a reduced incidence of Crohn's disease. In patients with established Crohn's disease, physical activity has been linked to decreased disease activity and improved overall well-being. However, the relationship between physical activity and ulcerative colitis remains less clear.[15]

Dietary Factors

Studies suggest that a diet rich in fiber and fruits is associated with a lower risk of Crohn's disease, while high vegetable consumption appears to have a protective effect against ulcerative colitis. In contrast, diets high in animal fat, polyunsaturated fatty acids, and refined carbohydrates have been linked to an increased risk of IBD. Although elimination diets and specific dietary interventions, such as the Mediterranean and specific carbohydrate diets, may help alleviate symptoms, their impact on objective inflammatory markers remains uncertain due to methodological limitations in current research.[16,17]

Antibiotic Use

Antibiotic use has been associated with an increased risk of IBD. A large case-control study involving 24,000 patients demonstrated a correlation between the frequency of antibiotic use and an increased risk of developing ulcerative colitis and Crohn's disease. Antibiotics are thought to disrupt gut microbiota composition, contributing to dysbiosis and intestinal inflammation.[18]

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are known to have adverse effects on the gastrointestinal system. Regular use of high-dose NSAIDs has been associated with an increased risk of IBD.[19]

Hormonal Factors

Oral contraceptives and hormone replacement therapies have been linked to an increased risk of IBD in women, highlighting the potential influence of hormonal modulation on disease onset and progression. This association suggests that exogenous hormonal factors may contribute to alterations in immune responses, gut microbiota composition, and intestinal barrier function, all of which play critical roles in IBD pathogenesis.[20,21]

Appendectomy

Appendectomy has been recognized as a risk factor for Crohn's disease, potentially due to immune system alterations. However, it appears to have a protective effect against ulcerative colitis, suggesting a complex relationship between the appendix, gut immunity, and IBD pathogenesis.[22]

Psychological Factors

A study suggested that individuals experiencing lower levels of stress had a decreased likelihood of developing IBD, indicating a potential link between psychological well-being and disease risk.[23]

MAIN POINTS

- **Complex Pathogenesis:** IBD arises from genetic predisposition, environmental factors, microbial dysbiosis, and immune dysregulation.
- **Genetic and Environmental Influences:** Key mutations (*NOD2, ATG16L1, IL23R*) increase susceptibility, while smoking, diet, and antibiotics affect disease risk.
- **Gut Microbiota Imbalance:** IBD is linked to reduced beneficial bacteria (*Faecalibacterium, Roseburia*) and increased proinflammatory taxa (*Enterobacteriaceae, Fusobacterium*).
- **Immune Dysregulation:** Crohn's disease is driven by Th1/Th17 pathways, ulcerative colitis by a Th2 response, leading to chronic inflammation.
- **Targeted Therapies:** Anti-TNF agents and IL-23 inhibitors help modulate immune pathways and improve patient outcomes.

Exposures During Infancy
Early postnatal factors, such as breastfeeding, mode of delivery (vaginal vs. cesarean), and antibiotic exposure, influence gut microbiota development and immune system maturation. These factors have been associated with an altered risk of developing IBD later in life. Breastfeeding, in particular, promotes intestinal barrier integrity and immune tolerance.[24–27]

Other Factors
The rising prevalence of IBD in developing countries correlates with increasing industrialization and urbanization.[19] Air pollution, dietary changes, and environmental toxins are believed to contribute to this trend.

MICROBIOME
Over the past two decades, the microbiome has become a central focus of research on IBD.[28] The gut microbiota plays a crucial role in maintaining the balance between T helper cells (Th cells) and regulatory T cells (Tregs), ensuring equilibrium between proinflammatory and anti-inflammatory responses. This highlights the essential role of gut microbiota in preserving host health and metabolic balance. Disruptions in the composition or function of these microorganisms disturb microbial homeostasis, leading to intestinal inflammation. This imbalance is further exacerbated in IBD, promoting dysbiosis and altering the regulation of key metabolic pathways.[29]

Dysbiosis is characterized by a reduction in the number, diversity, and stability of bacterial populations within the microbiome, and these imbalances are closely linked to the onset and progression of IBD. In individuals with IBD, a notable depletion of beneficial commensal bacteria and essential microbial metabolites is frequently observed, further contributing to disease pathogenesis and intestinal inflammation.[30]

Healthy gut microbiota is predominantly composed of *Firmicutes* and *Bacteroidetes*, which together constitute approximately 90% of the bacterial population. In patients with IBD, there is a marked reduction in beneficial bacteria such as *Faecalibacterium* and *Roseburia*, alongside an increase in proinflammatory taxa such as *Enterobacteriaceae* and *Fusobacterium*. Dysbiosis is also characterized by a decline in microbial diversity and stability, leading to impaired production of short-chain fatty acids and other essential metabolites that play crucial roles in maintaining intestinal health and immune regulation.[28,31–36]

Numerous studies have investigated changes in the microbiome and/or metabolome in IBD. However, environmental factors such as nutrition, medications, ethnicity, and geographic location can influence the gut microbiome. It remains uncertain whether these microbial alterations are a driving factor in the development of inflammation or a consequence of the inflammatory process itself. Therefore, the association between the microbiome and IBD is not yet fully understood.

IMMUNE SYSTEM
Dysregulation of the immune system plays a pivotal role in the pathogenesis of IBD, involving complex interactions between innate and adaptive immune responses. The intestinal immune system is finely tuned to maintain a balance between tolerating commensal microbiota and mounting an effective defense against harmful pathogens. Disruptions in this equilibrium can lead to excessive immune activation, chronic inflammation, and the development of IBD. This persistent immune imbalance contributes to ongoing inflammation in affected individuals.

The key immune changes observed in patients with IBD include:
- Dysregulation of the Epithelial Barrier
- Dysregulation of Immune Cells
- Dysregulation of Secreted Mediators

Innate Immune System
The innate immune system serves as the body's first line of defense against microbial invaders, with Toll-like receptors (TLRs) and NOD-like receptors (NLRs) playing essential roles in detecting microbial components and initiating immune responses. In IBD, dysregulated expression and function of these receptors contribute to an impaired innate immune response, leading to excessive inflammation, disrupted microbial tolerance, and increased intestinal barrier dysfunction.[19]

Adaptive Immune System
The adaptive immune system, primarily mediated by T and B cells, is highly specific but requires more time to become fully activated. In Crohn's disease, a Th1-dominant immune response drives inflammation through excessive production of proinflammatory cytokines such as interferon-gamma (IFN-γ) and TNF-α. In contrast, ulcerative colitis is characterized by a Th2-skewed response, marked by elevated levels of interleukin-4 (IL-4) and IL-13, which contribute to mucosal inflammation. Additionally, Th17 cells, known to produce IL-17, IL-22, and other proinflammatory cytokines, are increased in both conditions, playing a crucial role in maintaining chronic inflammation and mucosal damage.[9,19]

Cytokine-targeted therapies, such as anti-TNF agents and IL-23 inhibitors, have demonstrated efficacy in modulating immune pathways and improving clinical outcomes.

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