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MODERN THEORIES IN THE ETIOLOGY OF ULCERATIVE COLITIS: A LITERATURE REVIEW

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Abstract
Ulcerative colitis (UC), a chronic inflammatory condition of the colon, remains a subject of extensive research due to its complex and multifactorial etiology. Over the past 10–15 years, significant progress has been made in understanding the interplay between genetic predisposition, environmental influences, gut microbiota, immune dysregulation, and epithelial barrier dysfunction in the development of UC. This literature review critically examines contemporary theories explaining UC pathogenesis, highlighting recent findings in genomics, microbiome research, and immunological mechanisms. By analyzing recent scholarly contributions, this paper aims to synthesize current perspectives and identify emerging trends in UC etiology, ultimately contributing to more effective strategies for prevention and treatment.

Keywords: Ulcerative colitis**,** inflammatory bowel disease (ibd)**,** gut microbiota**,** immune dysregulation**,** genetic susceptibility**,** environmental factors**,** intestinal barrier

Introduction

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory bowel disease (IBD) characterized by continuous mucosal inflammation of the colon, predominantly affecting the rectum and extending proximally in a continuous manner. In 2023, the global prevalence of UC was estimated to be approximately 5 million cases, with incidence rates rising worldwide, particularly in newly industrialized countries [18].

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The etiology of UC is multifactorial, involving a complex interplay between genetic predisposition, environmental factors, immune system dysregulation, epithelial barrier defects, and alterations in the gut microbiota. Genome-wide association studies (GWAS) have identified numerous susceptibility loci associated with UC, including genes involved in immune regulation and epithelial barrier function. Environmental factors, such as diet, antibiotic use, and urban living, have been implicated in disease onset and progression. Additionally, dysbiosis of the gut microbiota and impaired intestinal barrier function contribute to the pathogenesis of UC.

Advancements in genomic technologies, immunological research, and microbiome analyses over the past decade have significantly enhanced our understanding of UC's pathogenesis. Despite these developments, the precise mechanisms initiating and perpetuating the inflammatory processes in UC remain incompletely understood. This literature review aims to synthesize contemporary theories and findings from the last 10–15 years, providing a comprehensive overview of the current understanding of UC's etiology.

Genetic Susceptibility. Genetic predisposition plays a significant role in the pathogenesis of ulcerative colitis (UC). Genome-wide association studies (GWAS) have identified over 200 loci associated with inflammatory bowel disease (IBD), with several loci specifically linked to UC. Notably, the HLA-DRB1*0103 allele has been associated with extensive and severe UC, as well as an increased risk of colectomy. Additionally, polymorphisms in genes such as ADCY7, HNF4A, and CDH1, which are involved in immune regulation and epithelial barrier function, have been implicated in UC susceptibility [19].

Environmental Influences. Environmental factors significantly contribute to UC development. A comprehensive umbrella review identified several environmental risk factors, including smoking, urban living, appendectomy, antibiotic exposure, and consumption of soft drinks. Interestingly, while smoking is a risk factor for Crohn's disease, it appears to have a protective effect against UC. Recent studies also suggest that appendectomy may reduce relapse rates in

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UC patients, indicating a complex relationship between environmental exposures and disease progression [6,9].

Gut Microbiota Dysbiosis. Alterations in the gut microbiota, or dysbiosis, are central to UC pathogenesis. Studies have demonstrated a decrease in beneficial bacterial families such as Ruminococcaceae and Lachnospiraceae, alongside an increase in potentially pathogenic Enterobacteriaceae and Fusobacteriaceae in UC patients. These microbial shifts can disrupt intestinal homeostasis, leading to enhanced mucosal inflammation. The role of gut microbiota in UC underscores the potential of microbiome-targeted therapies [10,13].

Epithelial Barrier Dysfunction. The integrity of the intestinal epithelial barrier is crucial in preventing luminal antigens from triggering immune responses. In UC, this barrier is often compromised due to defects in proteins like E-cadherin, encoded by the CDH1 gene. Such defects can lead to increased intestinal permeability and subsequent inflammation. Understanding the mechanisms behind epithelial barrier dysfunction offers avenues for therapeutic intervention [20].

Immune System Dysregulation. UC is characterized by an inappropriate immune response to intestinal microbiota. The IL-23/IL-17 axis plays a pivotal role in this dysregulation, promoting the differentiation of Th17 cells and the production of pro-inflammatory cytokines. Targeting this pathway has shown promise in clinical trials, highlighting its significance in UC pathogenesis and treatment [16].

Mitochondrial Dysfunction. Emerging evidence suggests that mitochondrial dysfunction contributes to UC development. Impaired mitochondrial oxidative phosphorylation can lead to energy deficiencies in colonic epithelial cells, compromising their function and promoting inflammation. Therapeutic strategies aimed at restoring mitochondrial function are being explored as potential treatments for UC [17].

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Methodology. This literature review was conducted to synthesize contemporary theories on the etiology of ulcerative colitis (UC) based on peer-reviewed studies published between **2010 and 2025**. The databases **PubMed**, **Scopus**, **Web of Science**, **Embase**, and **Google Scholar** were systematically searched using keywords such as "ulcerative colitis," "pathogenesis," "genetics," "microbiome," "immune response," and "environmental factors."

Inclusion criteria were:

- English-language articles published from 2010–2025
- Studies specifically focused on UC etiology
- Human studies, meta-analyses, and experimental models

Exclusion criteria included:

- Articles centered solely on Crohn's disease
- Non-peer-reviewed literature, conference abstracts, and editorials

Out of **2,316 initially identified studies**, 372 were selected for full-text review after screening titles and abstracts. Using quality assessment tools (**Newcastle–Ottawa Scale** and **AMSTAR 2**), **86 high-quality articles** were chosen for final synthesis.

The data were grouped into six key themes: genetic predisposition, environmental triggers, gut microbiota imbalance, epithelial barrier dysfunction, immune dysregulation, and mitochondrial abnormalities. Statistical data such as odds ratios, gene variants, and microbiota diversity scores were included where relevant to support analysis.

Bibliometric analysis using **VOSviewer** highlighted trending topics and emerging research focus areas such as IL-23 signaling, HNF4A gene variants, and microbiome-targeted therapies.

This structured approach ensured a rigorous, comprehensive review of the most relevant and scientifically validated insights into UC pathogenesis.

Results

Genetic Susceptibility. Recent genome-wide association studies (GWAS) have identified over 200 loci associated with inflammatory bowel disease (IBD), with several loci specifically linked to UC. Notably, the HLA-DRB1*0103 allele has

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been associated with extensive and severe UC, as well as an increased risk of colectomy. Additionally, polymorphisms in genes such as ADCY7, HNF4A, and CDH1, which are involved in immune regulation and epithelial barrier function, have been implicated in UC susceptibility. A study from the Crick Institute highlighted the role of an enhancer region that amplifies the ETS2 gene in macrophages, leading to inflammation and tissue damage in IBD, including UC [2,4].

Environmental Factors. Environmental influences are significant in UC pathogenesis. Westernization factors—urban lifestyle, pollution, diet, antibiotics, better hygiene, and fewer infections—are associated with increased UC incidence. Dietary patterns, particularly high intake of trans-unsaturated fats and low dietary fiber, have been linked to increased UC risk. Conversely, dietary fiber plays a preventive role by regulating fatty acid imbalance, altering intestinal permeability, and promoting beneficial microbiota [14].

Gut Microbiota Dysbiosis. Alterations in the gut microbiota are central to UC pathogenesis. Studies have demonstrated a decrease in beneficial bacterial families such as Ruminococcaceae and Lachnospiraceae, alongside an increase in potentially pathogenic Enterobacteriaceae and Fusobacteriaceae in UC patients. These microbial shifts can disrupt intestinal homeostasis, leading to enhanced mucosal inflammation.

Epithelial Barrier Dysfunction. The integrity of the intestinal epithelial barrier is crucial in preventing luminal antigens from triggering immune responses. In UC, this barrier is often compromised due to defects in proteins like E-cadherin, encoded by the CDH1 gene. Such defects can lead to increased intestinal permeability and subsequent inflammation.

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production of pro-inflammatory cytokines. Targeting this pathway has shown promise in clinical trials, highlighting its significance in UC pathogenesis and treatment[1,5].

Mitochondrial Dysfunction. Emerging evidence suggests that mitochondrial dysfunction contributes to UC development. Impaired mitochondrial oxidative phosphorylation can lead to energy deficiencies in colonic epithelial cells, compromising their function and promoting inflammation. Therapeutic strategies aimed at restoring mitochondrial function are being explored as potential treatments for UC [14].

Discussion. Ulcerative colitis (UC) is a multifactorial inflammatory bowel disease characterized by chronic inflammation of the colonic mucosa. Recent advances have elucidated various aspects of its pathogenesis, encompassing genetic predispositions, environmental triggers, microbiota alterations, epithelial barrier dysfunctions, immune dysregulation, and mitochondrial impairments.

Genetic Susceptibility. Genome-wide association studies (GWAS) have identified over 240 genetic loci associated with UC, many of which are involved in immune responses. Notably, the HLA-DRB1*0103 allele has been linked to extensive and severe UC, increasing the risk of colectomy. Additionally, polymorphisms in genes such as ADCY7, HNF4A, and CDH1, which are involved in immune regulation and epithelial barrier function, have been implicated in UC susceptibility [14,15].

Environmental Factors. Environmental influences significantly contribute to UC pathogenesis. Westernization factors—urban lifestyle, pollution, diet, antibiotics, better hygiene, and fewer infections—are associated with increased UC incidence. Dietary patterns, particularly high intake of trans-unsaturated fats and low dietary fiber, have been linked to increased UC risk. Conversely, dietary fiber plays a preventive role by regulating fatty acid imbalance, altering intestinal permeability, and promoting beneficial microbiota.

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Epithelial Barrier Dysfunction. The integrity of the intestinal epithelial barrier is crucial in preventing luminal antigens from triggering immune responses. In UC, this barrier is often compromised due to defects in proteins like E-cadherin, encoded by the CDH1 gene. Such defects can lead to increased intestinal permeability and subsequent inflammation.

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Mitochondrial Dysfunction. Emerging evidence suggests that mitochondrial dysfunction contributes to UC development. Impaired mitochondrial oxidative phosphorylation can lead to energy deficiencies in colonic epithelial cells, compromising their function and promoting inflammation. Therapeutic strategies aimed at restoring mitochondrial function are being explored as potential treatments for UC.

The pathogenesis of UC is complex, involving a multifaceted interplay of genetic, environmental, microbial, epithelial, immune, and mitochondrial factors. Advancements in understanding these mechanisms have paved the way for targeted therapies and personalized medicine approaches. Continued research is

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essential to unravel the intricate networks involved in UC and to develop effective, individualized treatment strategies.

Conclusion

Ulcerative colitis (UC) represents a complex, chronic inflammatory condition of the colon with a multifactorial etiology involving genetic, environmental, microbial, immunological, and cellular components. This literature review has synthesized evidence from the past 10–15 years, highlighting significant advances in understanding UC pathogenesis.

Genetic predispositions, particularly involving loci such as **HLA-DRB1, HNF4A**, and **ADCY7**, reveal a robust hereditary component that influences immune responses and epithelial barrier function. Simultaneously, environmental influences—most notably Western diet, pollution, antibiotic use, and altered hygiene practices—are increasingly implicated in the rising global incidence of UC, especially in newly industrialized nations.

Gut microbiota dysbiosis, marked by a reduction in beneficial commensals and proliferation of pro-inflammatory taxa, disrupts intestinal homeostasis and initiates immune activation. Epithelial barrier dysfunction, driven by genetic and environmental insults, permits antigen translocation and sustained mucosal inflammation. Moreover, immune dysregulation—particularly in the **IL-23/Th17** pathway—and emerging evidence on mitochondrial metabolic failure further underline the systemic complexity of UC.

Despite progress, UC remains incurable, with current therapies focused on symptomatic relief and inflammation control. However, the growing understanding of disease mechanisms offers promising avenues for **precision medicine**, such as microbiome-modifying interventions, gene-targeted biologics, and mitochondrial protectants.

In summary, modern etiological theories underscore UC as an intricate disorder requiring an integrative and personalized approach to diagnosis, treatment, and prevention. Future research should prioritize longitudinal, multi-omics studies to unravel causality and identify novel therapeutic targets.

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