LITERATURE REVIEW OPEN ACCESS

# Molecular and Immune Mechanisms in Ulcerative Colitis Pathophysiology

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## Abstract

Ulcerative colitis is a chronic inflammatory bowel disease characterized by continuous, predominantly mucosal inflammation beginning in the rectum. This narrative review integrates epithelial, microbial, genetic, metabolic, and immune mechanisms that sustain colonic injury. Barrier disruption, altered mucus, and changes in sealing and pore-forming tight-junction proteins increase exposure of the lamina propria to luminal antigens. Pattern-recognition and inflammasome pathways can amplify tumour-necrosis-factor, interleukin-1, interleukin-6, and chemokine signalling, but their contribution varies by cell type, disease stage, and treatment. Adaptive immunity is heterogeneous: UC has classically been associated with an atypical Th2/IL-13 axis, while IL-23/Th17 pathways and defective regulatory networks contribute in subsets of patients. NOD2 and autophagy variants are central to Crohn disease genetics and should not be presented as defining abnormalities of UC. Dysbiosis and reduced short-chain-fatty-acid production may impair epithelial repair, although no universal microbial signature or single causal organism has been established. Neutrophil recruitment, oxidative injury, and incomplete resolution contribute to ulceration, bleeding, urgency, and diarrhoea; transmural dysfunction and toxic megacolon occur mainly in severe or fulminant disease. Persistent inflammation also increases dysplasia risk. These interacting mechanisms support phenotype-aware treatment while cautioning against universal pathway claims. Because the evidence was narratively selected, the conclusions require confirmation through a transparent and reproducible search strategy.

Keywords: ulcerative colitis; epithelial barrier; gut microbiota; NLRP3 inflammasome; Th17 cells; regulatory T cells; mucosal immunity

## 1. Introduction:

### 1.1 Background

Ulcerative colitis (UC) is a chronic inflammatory bowel disease primarily affecting the colonic mucosa. This condition induces continuous inflammation, beginning in the rectum and potentially extending throughout the colon. The inflammatory process leads to mucosal layer damage, ulceration, bleeding, and compromised colonic function (1). While the precise etiology of UC remains incompletely understood, research suggests that the disease is influenced by genetic predisposition, environmental factors, and dysregulated immune responses. The activation of both innate and adaptive immune pathways plays a central role in the pathogenesis of UC (2).

One of the primary contributors to the pathogenesis of UC is the disruption of the intestinal epithelial barrier. Normally, the mucus layer produced by goblet cells serves as a mechanical and immunological barrier against microbial pathogens in the intestinal lumen (3). However, in UC patients, this barrier becomes thinner or damaged, allowing microbes to interact directly with the colonic epithelium and trigger inflammatory responses. Genetic polymorphisms affecting mucin-encoding genes, such as **MUC2**, which is critical for mucus layer formation, further impair epithelial barrier function and exacerbate inflammation (4).

Innate and adaptive pathways both contribute to UC, but no single receptor or lymphocyte subset explains all disease. Toll-like-receptor and inflammasome signalling can activate NF-kappaB-dependent cytokine production, while IL-23/Th17 responses, atypical Th2-associated IL-13 activity, and impaired regulatory control vary across patients and disease stages (2,5,19,20). NOD2 is relevant to intestinal microbial sensing, but genetic and functional evidence is substantially stronger in Crohn disease than in UC (7,28).

Gut microbial communities are altered in many patients with active UC, including reported depletion of selected short-chain-fatty-acid-producing taxa. These observations are heterogeneous and influenced by diet, geography, disease activity, and medication. Reduced butyrate-producing

capacity may weaken epithelial energy supply and immune regulation, but dysbiosis should be interpreted as a context-dependent contributor rather than a universal initiating cause (8,13).

### 1.2 Objectives

1. To synthesize epithelial-barrier, genetic, microbial, and metabolic mechanisms implicated in ulcerative colitis.
2. To evaluate the heterogeneous contributions of innate, atypical Th2, IL-23/Th17, and regulatory immune pathways to mucosal inflammation.
3. To connect molecular mechanisms with clinical manifestations, severe complications, and translational therapeutic implications while identifying limitations in causal evidence.

### 1.3 Narrative Review Approach

This narrative review prioritizes mechanistic studies, human translational evidence, and clinically relevant reviews addressing epithelial-barrier biology, mucosal immunity, microbiota, oxidative stress, and severe UC complications. It is intended as a critical synthesis rather than a systematic estimate of effect size, and causal language is reserved for evidence supported by experimental perturbation or consistent clinical data.

[AUTHOR VERIFICATION REQUIRED: report the databases, search dates, full search terms, language restrictions, inclusion/exclusion criteria, screening process, and reviewer roles actually used. If these steps were not performed prospectively, state this explicitly as a limitation.]

## 2. Main Body:

### 2.1 Molecular Aspects of Ulcerative Colitis

Mucosal inflammation in UC arises from interacting epithelial and immune abnormalities. Microbial products and damage-associated signals can engage TLR, MyD88, NF-kappaB, and NLRP3-related pathways in epithelial and myeloid cells, promoting TNF-alpha, IL-1 beta, IL-6, and chemokine production. The magnitude and consequence of this signalling depend on cellular location, microbial context, disease activity, and treatment; pathway activation should therefore not be interpreted as uniform across all patients (5,9,20).

Adaptive immunity in UC is more accurately described as heterogeneous than as a conventional IL-4-driven Th2 disorder. Early human studies identified an atypical Th2-like response involving natural-killer T cells and IL-13, while IL-23-supported Th17 cells and tissue-resident effector populations contribute in selected phenotypes (19,20). Regulatory T cells may be numerically or functionally insufficient within an inflammatory environment, but FOXP3 promoter hypermethylation is not established as a universal mechanism. Cytokine plasticity and resistance of effector cells to suppression further complicate a binary Th2-versus-Th17 model.

Neutrophil-derived reactive oxygen species, proteases, and extracellular traps can amplify epithelial injury and release additional danger signals. Microbial depletion and loss of butyrate-synthetic capacity have been reported in active UC, yet findings vary across cohorts and may partly reflect inflammation or treatment. Short-chain fatty acids support epithelial metabolism and immunoregulation through receptor signalling and histone-deacetylase inhibition, but supplementation and microbiome manipulation require clinical validation (8,13,21).

Genetic susceptibility to UC is polygenic and overlaps partly with other inflammatory bowel diseases. NOD2 and autophagy variants are among the best-established Crohn-disease signals and should not be portrayed as defining UC mutations (7,28). Epithelial microRNAs are also context dependent: miR-31 is often increased in inflamed tissue and may support barrier repair by suppressing TNFSF15 rather than simply weakening tight junctions (27). Claudin-2 is a pore-forming tight-junction protein that is commonly increased in active intestinal inflammation, whereas sealing proteins such as claudin-5, claudin-8, and occludin may decrease (12).

### 2.2 Pathophysiology and Clinical Manifestations

UC typically begins in the rectum and extends proximally in a continuous pattern, with inflammation concentrated in the mucosa and superficial submucosa. Barrier failure, altered mucus, epithelial death, and dysregulated responses to luminal antigens promote recurrent mucosal injury. Deeper mural involvement is not a routine feature and becomes most relevant in acute severe or fulminant disease (1,2,22).

Cytokines, epithelial apoptosis, and altered tight-junction composition increase paracellular permeability. In active disease, increased pore-forming claudin-2 and reduced sealing junction proteins can permit greater ion and antigen flux, sustaining diarrhoea and immune activation (12). These changes may be consequences as well as amplifiers of inflammation.

Neutrophils recruited to colonic crypts form cryptitis and crypt abscesses, release reactive oxygen species and proteases, and can generate extracellular traps. These responses help contain microbes but also injure epithelium when excessive or poorly resolved (20-22). IL-17 and IL-22 have context-dependent protective and pathogenic effects, so their presence should not be equated automatically with tissue damage.

Mucosal ulceration exposes superficial vessels and contributes to bloody diarrhoea, while inflammatory exudate and goblet-cell dysfunction account for mucus and urgency. Fluid loss results from reduced absorptive capacity, increased permeability, and altered epithelial ion transport rather than from one cytokine pathway alone.

Toxic megacolon is a rare, life-threatening complication of severe colitis characterized by systemic toxicity and non-obstructive colonic dilatation. Its pathophysiology is multifactorial and includes intense inflammation, neuromuscular dysfunction, altered nitric-oxide signalling, electrolyte disturbance, and medication effects; nitric oxide should be considered one mediator rather than the sole cause (23).

Fever, tachycardia, anaemia, and malaise may accompany active or acute severe UC. Weight loss and nutritional deficits occur particularly with extensive, severe, or prolonged disease, but generalized malabsorption and cachexia are not typical of uncomplicated mucosal UC. Nutritional assessment should therefore be matched to disease severity and treatment exposure (24,25).

Pseudopolyps reflect cycles of ulceration and regeneration and are non-neoplastic. Long-standing, extensive, and poorly controlled inflammation can nevertheless increase dysplasia and colorectal-cancer risk through repeated epithelial injury, oxidative stress, and altered repair. Risk is modified by disease duration, extent, inflammatory burden, family history, and coexisting primary sclerosing cholangitis (1,2,22).

Microbiome changes in UC include variable reductions in diversity and in selected short-chain-fatty-acid-producing organisms. Because results depend on sampling, diet, geography, medication, and activity, a single taxon such as Faecalibacterium prausnitzii should not be treated as a universal biomarker or causal deficiency (8,13).

Rectal inflammation, altered compliance, and sensory-nerve activation contribute to urgency and tenesmus, while visceral hypersensitivity, inflammation, distension, and motility changes contribute to abdominal pain. Persistent symptoms despite endoscopic remission should prompt assessment for functional, structural, or treatment-related contributors rather than automatic escalation of immunosuppression (22).

## 3. Conclusion

Ulcerative colitis is sustained by reciprocal interactions among epithelial-barrier failure, altered mucus and junctional proteins, context-dependent dysbiosis, innate immune sensing, neutrophil injury, and heterogeneous adaptive responses. Atypical Th2/IL-13 and IL-23/Th17 pathways may both contribute, but neither is universal, and NOD2 should not be presented as a defining UC abnormality.

These mechanisms explain mucosal ulceration, bleeding, urgency, and diarrhoea, while toxic megacolon reflects acute severe, multifactorial colonic dysfunction rather than routine extension into deeper layers. Chronic inflammatory burden contributes to dysplasia risk, reinforcing the importance of sustained disease control and appropriate surveillance.

Future translation should stratify patients by validated epithelial, microbial, and immune phenotypes and test whether such markers improve treatment selection beyond established clinical measures. The present conclusions are limited by the narrative review design and should be supported by a transparent, reproducible search and critical-appraisal process.

## 4. Declarations

**Author contributions:** Abqariyatuzzahra Munasib conceptualized the review, defined its scope, performed the literature synthesis, and prepared the original draft. Devi Purnamasari Sasongko contributed to the molecular and immunological interpretation and critical revision. Putra Gelar Parlingdungan contributed to the clinical interpretation and manuscript revision. All authors read and approved the final manuscript.

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