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Pathogenesis of Microscopic Colitis: Current Insights

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Abstract— Microscopic colitis (MC) is a chronic inflammatory bowel disease characterized by watery, non-bloody diarrhea and a normal endoscopic appearance, necessitating histopathological evaluation for diagnosis. Despite increasing recognition, its pathogenesis remains incompletely understood. This review synthesizes current evidence on the genetic, immunological, and luminal factors contributing to MC. Genetic susceptibility plays a crucial role, particularly the association with HLA-DQ2 haplotypes and select non-HLA polymorphisms, suggesting a distinct immune-mediated background. Immunologically, MC is marked by mucosal infiltration of $CD8^+$ T cells, Th1/Tc1 and Th17/Tc17 cytokine profiles, and enhanced local cellular proliferation, driving mucosal inflammation. Luminal influences, including altered gut microbiota composition, reduced microbial diversity, and dysregulation of bile acid signaling pathways—especially those involving farnesoid X receptor (FXR)—further compromise epithelial integrity and perpetuate immune activation. These findings underscore the multifactorial nature of MC, integrating host genetics, mucosal immunity, and environmental triggers. Understanding these mechanisms not only delineates MC as distinct from classical inflammatory bowel diseases but also provides a foundation for developing targeted therapeutic strategies. Approaches modulating the gut microbiota or bile acid pathways may represent promising directions to improve disease management and patient outcomes in microscopic colitis.

Keywords— microscopic colitis, collagenous colitis, lymphocytic colitis, pathogenesis, gut microbiota

1. INTRODUCTION

Microscopic colitis is an inflammatory bowel disease characterized by chronic, watery, non-bloody diarrhea, often accompanied by abdominal pain, nocturnal symptoms, fecal incontinence, and weight loss, which significantly impacts patients' quality of life. Many patients also experience fatigue, anxiety, and depression [1]. The disease course is chronic or relapsing, with symptoms varying from mild to severe and persisting for extended periods [2]. Unlike other inflammatory bowel diseases, microscopic colitis does not increase mortality or cancer risk and typically does not require surgery [1]. Diagnosis is challenging due to its normal or near-normal endoscopic appearance, requiring histopathological analysis of multiple colonic biopsies [1–3]. It is classified into collagenous or lymphocytic colitis, with incomplete forms also recognized [2]. The incidence and prevalence have risen, now comparable to Crohn's disease and ulcerative colitis in some populations, with an estimated incidence of 11.4 per 100,000 person-years and a prevalence of 119 per 100,000 individuals [2,4]. It most commonly affects women aged 60–65 years [4]. The pathogenesis involves an abnormal immune response to intestinal microenvironment disturbances, potentially triggered by medications like NSAIDs, SSRIs, and PPIs, or by lifestyle factors in genetically predisposed individuals [2,3]. Although the exact mechanisms remain unclear, it is understood as an immune-mediated disease with an overactive adaptive immune response to luminal and mucosal triggers in susceptible individuals [5].

The aim of this review is to synthesize current knowledge on the complex pathogenesis of microscopic colitis, emphasizing its distinct genetic, immunological, and luminal mechanisms that differentiate it from classical inflammatory bowel diseases. By examining recent findings on HLA and non-HLA genetic associations, cytokine and lymphocyte-mediated immune responses, and the role of gut microbiota and

bile acid dysregulation, this review seeks to provide an updated, integrated perspective that highlights potential diagnostic and therapeutic targets for microscopic colitis, while underlining the need for further research to clarify causal pathways and optimize treatment strategies.

2. MATERIALS AND METHODS

This review analyzed publications on the pathogenesis of microscopic colitis, focusing on genetic, immunological, and luminal factors in disease development and progression. A comprehensive literature search was conducted using PubMed and Google Scholar with keywords such as "microscopic colitis," "collagenous colitis," "lymphocytic colitis," "genetics," "immune mechanisms," "cytokines," "gut microbiota," and "bile acids." The selection emphasized studies on genetic susceptibility, cytokine profiles, immune cell dynamics, microbiome alterations, and bile acid dysregulation. Included were clinical studies, genetic association analyses, immunohistochemical investigations, and translational research on the immunopathogenesis of inflammatory bowel diseases. Comparative studies on microscopic colitis, Crohn's disease, and ulcerative colitis were also reviewed, with particular attention to HLA associations, T cell subsets, cytokine signatures, microbial shifts, and their implications for therapeutic strategies.

3. RESULTS

A. Genetic Susceptibility and HLA Associations in the Pathogenesis of Microscopic Colitis

Microscopic colitis (MC), including collagenous colitis (CC) and lymphocytic colitis (LC), demonstrates a complex genetic predisposition involving polymorphisms and HLA associations that suggest an immune-mediated etiology distinct from classical inflammatory bowel diseases (IBD) [6-12].

A polymorphism in the MMP-9 gene, specifically the GG allele of a coding Single Nucleotide Polymorphism (SNP), has been associated with an increased risk of CC, indicating that reduced matrix degradation, rather than overproduction, may contribute to collagen accumulation within the colon, aligning with prior findings of increased MMP expression in IBD and impaired epithelial healing in CC [6].

Strong associations have been identified between a PTEN SNP (rs1234224) and both CC and LC, with reduced PTEN expression observed in both subtypes, suggesting a role in regulating fibroblast activity and collagen production, while reduced MAGI1 expression, correlated with PTEN levels, suggests a shared regulatory mechanism in MC pathogenesis; additionally, a SNP in F11R, encoding JAM-A, has been linked to CC, implicating potential modulation of immune cell infiltration [7].

LC shows a unique increase in HLA-A1 and decrease in HLA-A3, a pattern not seen in other autoimmune or inflammatory diseases, supporting LC as a distinct entity despite the presence of autoantibodies and arthritis in patients [8]. A strong association between MC and the HLA-DQ2 allele has been identified, similar to celiac disease, with over 90% of MC patients carrying HLA-DQ2,x or DQ1,3 genotypes, suggesting a T-cell–mediated immune response to luminal antigens, possibly bacterial rather than gluten, and highlighting the role of environmental triggers, including NSAIDs, antibiotics, hormonal therapy, and infections, particularly in older adults [9]. The DQ2 heterodimer and DQ2/DQ8 alleles are associated with a nearly threefold increased likelihood of LC diagnosis, with the HLA-DR3-DQ2 haplotype and TNF2 allele linked to both CC and LC, reflecting the role of class II HLA molecules in antigen presentation to T lymphocytes and subsequent immune activation [10]. The association of HLA-DR3-DQ2 with MC has been consistently observed across both CC and LC, even after excluding patients with celiac disease, suggesting a shared immune-mediated pathway likely triggered by an unidentified luminal antigen, while the increased frequency of the TNF2 allele is likely due to linkage disequilibrium with HLA-DR3-DQ2 rather than being an independent risk factor [11]. Large-scale genetic association studies further confirm a strong association between CC and HLA class I/II alleles within the chromosome 6 region, particularly the ancestral 8.1 haplotype (DQ2.5) also implicated in celiac disease, reinforcing the role of immune-mediated mechanisms in CC, while the DQ8 allele, typically a celiac risk factor, appeared protective in CC, and additional suggestive signals near the NF2/CABP7 locus and PTPN2 gene, known for its association with IBD and autoimmune conditions, indicate possible non-HLA genetic contributions requiring further study [12].

Additionally, the IL-6-174 GG genotype, associated with increased IL-6 production and a pro-inflammatory cytokine profile, has been found more frequently in patients with LC and CC, indicating a potential contribution to disease pathogenesis [13]. In contrast, no association has been identified between NOD2/CARD15 polymorphisms and CC, differentiating its genetic background from Crohn's disease despite shared responses to fecal diversion, and indicating that abnormalities in collagen metabolism, including reduced MMP-1 and increased TIMP-1, may be more relevant to CC susceptibility [14].

Collectively, these findings support that MC is a distinct, HLA-regulated, immune-mediated disorder with genetic susceptibility shaped by HLA alleles, select non-HLA polymorphisms, and environmental triggers, distinguishing it from IBD while highlighting its complex pathogenesis.

B. Immunological and Cytokine Mechanisms in the Pathogenesis of Microscopic Colitis

Multiple studies have highlighted that microscopic colitis involves distinct disruptions in lymphocyte subset distributions and cytokine environments, contributing to the disease's inflammatory processes.

Under physiological conditions, CD8+ intraepithelial T lymphocytes dominate within the colonic epithelium, whereas the lamina propria is primarily populated by CD4+ T cells [15]. In patients with active lymphocytic and collagenous colitis, analyses using immunohistochemistry and flow cytometry have demonstrated an increase in CD8+ T lymphocytes in both the epithelial layer and lamina propria, alongside a reduction of CD4+ T cells in the lamina propria when compared to healthy individuals [15,16,17]. Additionally, these patients exhibit heightened activation of local CD4+ and CD8+ T cells, indicated by elevated levels of activation markers such as CD45RO and the proliferation marker Ki67 [15,16]. Studies examining circular DNA-TREC (T-cell receptor rearrangement excision circles) levels, which signify recent thymic emigrants, have shown reductions in patients with microscopic colitis [18,19], suggesting that the increased intraepithelial lymphocyte numbers in the intestinal mucosa primarily arise from local proliferation rather than thymic output [18]. Importantly, the extent of lymphocyte infiltration does not appear to correlate directly with the severity of clinical symptoms [17].

CD8+ T cells secrete interleukin 2 (IL-2), which facilitates the expansion of regulatory T cells (Tregs). These Tregs, via direct cellular interactions and the release of cytokines such as IL-10 and TGF-β, can suppress CD8+ T cell activation and proliferation, with the transcription factor Foxp3 playing a central role in Treg development [20]. Patients with microscopic colitis exhibit increased numbers of Foxp3+ Tregs in comparison to controls [15,17,20], and the CD8+ to Foxp3+ cell ratio tends to be lower in affected individuals, suggesting a potential protective mechanism against CD8+ T cell-mediated mucosal injury [20]. Treg-derived TGF-β may also contribute to tissue collagen deposition [20], with evidence indicating that eosinophils in the colonic mucosa of patients with collagenous colitis express higher levels of TGF-β mRNA compared to healthy controls [21].

The migration of CD8+ lymphocytes into the colonic mucosa appears to be guided by increased epithelial expression of chemokines, including CXCL9, CXCL10, CXCL11, CX_3CL1, and their receptor CX_3CR1, which facilitate lymphocyte recruitment. In collagenous colitis, these chemokine levels are significantly elevated during active inflammation relative to remission and healthy states, while in lymphocytic colitis, their expression remains high regardless of disease activity [22,23]. Additionally, chemokines such as CCL2, CCL3, CCL4, CCL5, CCL7, and CCL22 are upregulated in active microscopic colitis, promoting the infiltration of various immune cells including eosinophils, neutrophils, macrophages, Th1 cells, and Tregs into the lamina propria [22].

Phenotypic characterization through immunohistochemistry has revealed that lamina propria CD4+ T cells predominantly express the Th2-associated transcription factor GATA-3, while CD8+ T cells co-express GATA-3 and the Th1-associated factor T-bet. In contrast, intraepithelial CD8+ T cells largely express T-bet [24]. This distribution indicates a proinflammatory environment in which CD8+ T cells contribute to Th1-type cytokine production within the mucosa [25].

Microscopic colitis is associated with a cytokine profile reflecting a combination of Th1/Tc1 and Th17/Tc17 immune responses [25,26]. Th1/Tc1 cells enhance cellular immunity through macrophage activation and cytotoxic T cell functions, perpetuating chronic inflammation, while Th17/Tc17 cells promote antimicrobial defense mechanisms and neutrophil recruitment, facilitating acute inflammatory responses [27].

Increased expression of IFNγ mRNA, a key Th1 cytokine, has been consistently documented in patients with active forms of microscopic colitis, underscoring its pivotal role in disease pathogenesis [5,25,26]. IFNγ not only regulates the epithelial production of chemokines such as CXCL9 and CXCL10 [23] but also activates macrophages to secrete proinflammatory cytokines including TNFα, IL-1, and IL-6, thereby sustaining local inflammation [13,25,26]. Elevated mRNA and protein levels of these cytokines, along with higher levels of IL-15 and Th17-associated cytokines (IL-17a, IL-21, IL-22), have been observed in the colonic mucosa of affected patients. IL-15 and IL-21 promote intraepithelial lymphocyte proliferation and enhance IFNγ production [25,26], while increased IFNγ, IL-21, and IL-22 mRNA levels have shown associations with clinical disease activity and increased stool frequency in microscopic colitis [25]. In contrast, the detection of Th2 cytokines in microscopic colitis is limited, with IL-10 being the only cytokine consistently elevated, whereas IL-2 and IL-4 levels are often below detection thresholds [25,26]. Overall, Th2 responses and anti-inflammatory cytokines such as IL-37 appear suppressed in the disease context [25,26,28].

C. Luminal Dysregulation in Microscopic Colitis

Emerging evidence underscores a significant role for luminal factors, particularly gut microbiota alterations and bile acid receptor dysregulation, in the pathogenesis of microscopic colitis [29-33]. While overall microbial diversity in MC often remains unchanged, consistent taxonomic shifts have been observed, including an increase in pro-inflammatory *Desulfovibrio* and a decrease in protective *Akkermansia*, potentially affecting mucin integrity and the intestinal barrier, thereby promoting inflammation [29]. In collagenous colitis (CC), distinct fecal microbiome profiles are evident during active disease or corticosteroid therapy, normalizing upon remission, with a notable reduction in *Ruminococcaceae taxa* that mirrors IBD-associated dysbiosis and suggests overlapping host–microbiota interactions in pathogenesis [30]. Prospective studies further demonstrate that active MC is associated with reduced microbial diversity, particularly in CC, and that budesonide treatment can partially restore a healthier microbiome composition independent of clinical response, highlighting the dynamic responsiveness of the microbiota to therapy [31]. Additionally, successful fecal microbiota transplantation (FMT) in CC has provided clinical and immunological improvement, reducing cytotoxic CD8+ intraepithelial lymphocytes while increasing regulatory CD4+ T cells, indicating that restoring microbial balance may modulate mucosal immune responses and facilitate healing, although persistent immune activation may necessitate multiple FMTs for sustained remission [32].

Complementing these findings, reduced expression of the primary bile acid receptor FXR throughout the colon in MC, with loss of the normal proximal-distal gradient, suggests that impaired bile acid signaling may further disrupt the intestinal barrier and contribute to mucosal vulnerability, supporting a potential therapeutic role for FXR agonists in refractory MC [33].

Collectively, these data support a model in which luminal dysregulation, characterized by specific shifts in the gut microbiota and altered bile acid receptor expression, plays a central role in the pathogenesis and treatment responsiveness of MC, warranting further targeted research to clarify causal relationships and to develop microbiota- and FXR-based therapeutic strategies.

4. CONCLUSIONS

In conclusion, microscopic colitis is a distinct, immune-mediated inflammatory bowel disease with a complex pathogenesis shaped by genetic susceptibility, immune dysregulation, and luminal factors. Strong associations with specific HLA alleles, particularly HLA-DQ2, alongside select non-HLA polymorphisms, support a unique genetic background, while the mixed Th1/Tc1 and Th17/Tc17 cytokine profiles and increased mucosal CD8+ lymphocyte infiltration highlight the central role of adaptive immune responses in disease maintenance. Additionally, emerging evidence implicates gut microbiota alterations and bile acid receptor dysregulation in modulating mucosal immunity and barrier function, offering potential therapeutic avenues. Further research is essential to clarify these mechanisms, identify precise triggers, and develop targeted interventions, including microbiota-based and FXR-focused therapies, to improve disease management and patient outcomes in microscopic colitis.

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