Microscopic Colitis: What Do We Know About Pathogenesis?

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Abstract: Microscopic colitis (MC) is a common cause of chronic diarrhea. The 2 most frequent forms of MC are collagenous colitis and lymphocytic colitis. Over the past years, the incidence and prevalence of microscopic colitis are rising and this is largely attributed to a greater awareness, and concomitantly an increasing number of diagnoses. Patients with microscopic colitis report watery, nonbloody diarrhea of chronic course, abdominal pain, weight loss, and fatigue that may impair patient's health-related quality of life. The underlying mechanisms involved in the pathogenesis of microscopic colitis remain unspecified but is probably multifactorial. Collagenous colitis and lymphocytic colitis may represent specific mucosal responses to different luminal agents in predisposed individuals, resulting in an uncontrolled immune response. Genetic predisposition, altered modulation of cytokines and miRNAs, and aberrant response to drugs seem to be involved in the development of MC. Despite the progress of knowledge, still many questions remain unsolved regarding the etiology, pathophysiology, and optimal management of MC. This review gives an update on the immunological aspects of collagenous colitis and lymphocytic colitis.

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Microscopic colitis (MC) is regarded as one of the most common causes of chronic watery diarrhea in developed countries. Two main histologic forms of microscopic colitis have been characterized, lymphocytic colitis (LC) and collagenous colitis (CC).[1] Lymphocytic and CC present with very similar symptoms such as chronic or intermittent relapsing watery, nonbloody diarrhea. Less frequent are cramping abdominal pain, fecal incontinence, and weight loss.[2,3] Thus, from a clinical point of view, there are no specific clinical features allowing to discriminate between the 2 conditions. Accordingly, the diagnostic differentiation relies on specific histological changes.[4]

Most patients with MC have essentially normal endoscopic appearance, with occasional erythema and/or edema.[3] In particular, an abnormal vascular pattern may also be observed in LC[5,6] and, occasionally, there may be ulcerations in CC.[6,7]

Colonoscopy with multiple biopsies is pivotal to obtain the diagnosis. The histopathological hallmark of all MC is an abundant infiltration of inflammatory cells in colonic mucosa with a normal appearance and architecture of the crypts.[4] Inflammatory cells are increased both in the surface epithelium and in the lamina propria. In LC, the intraepithelial lymphocytes (IELs) are more than 20 per 100 surface epithelial cells, whereas CC is defined by the presence of a thickened subepithelial collagen band (>10 μm) in addition to the lymphocytic infiltrate.[4]

The true incidence of MC is not known. The disease has been increasingly diagnosed over the past 20 years but is still uncommon.[3] A recently published population-based study found the incidence of microscopic colitis to be strikingly increased from 1.1 per 100,000 persons in the late 1980s to 19.6 per 100,000 persons by the end of 2001.[2] Epidemiological studies confirmed these high prevalence numbers, showing that current incidence and prevalence are higher than initially thought and still increasing, although the rise seems to be less pronounced than before.[2] Most recent North American studies show incidence rates of 7.1 per 100,000 person-years for CC and 12.6 per 100,000 person-years for LC.[8]

LC affects similarly men and women, whereas CC can be found more frequently in women than in men.[9,10] Both conditions are commonly observed in people older than 40 years, with peak incidence in the 60s to 70s and their incidence increases with age. Nonetheless, isolated cases have been observed in younger populations and children.[9,11]

PATHOGENESIS

The underlying mechanism(s) involved in the pathogenesis of microscopic colitis remain(s) unspecified, but it is probably multifactorial. CC and LC are considered to represent specific mucosal responses to different luminal agents in predisposed individuals, resulting in an uncontrolled immune response.[12] As

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CC and LC have similar clinical presentations and histopathological features, except for the collagen band in CC, it has been discussed whether the 2 diseases could be a single entity, seen in different phases of development.[13] Unfortunately, the study of the events leading to the development of MC is particularly challenging; in fact, no established animal model recapitulating these diseases is available and current data on pathogenesis were mostly obtained from descriptive studies on patients; thus, we are still far from a mechanistic dissection of the molecular pathways driving MC onset and chronicization. Nonetheless, a substantial and increasing amount of evidence allows researchers to propose a few key pathogenic mechanisms, as discussed below and summarized in Figure 1.

Genetics

Current studies suggest that patients with MC might be genetically predisposed to the disease. The interleukin (IL)-6-174 gene polymorphism has a possible association with MC, as the IL-6 GG genotype is more frequent in patients either with LC or with CC.[14] As this polymorphism may be linked with an enhanced IL-6 production, this genotype could influence the pathogenesis of MC by evoking a proinflammatory bias in the mucosal cytokines milieus. IL-6 is a potent proinflammatory molecule, capable of promoting T- and B-lymphocyte maturation; it contributes to macrophage recruitment to the site of inflammation, skewing from acute to chronic immune responses[15] and to Th2 and Th17 lymphocyte polarization.[16,17] Moreover, IL-6 is a profibrogenic cytokine; it promotes a robust T-cell–mediated response that disrupts the normal turnover of extracellular matrix through enhanced STAT1 signaling within the stromal compartment, which in turn promotes fibrosis.[18] In addition, IL-6 increases fibroblast proliferation, collagen, and glycosaminoglycan production and deposition and inhibits tissue metalloproteinases.[19] Given these activities of IL-6, its enhanced concentration observed in CC compared

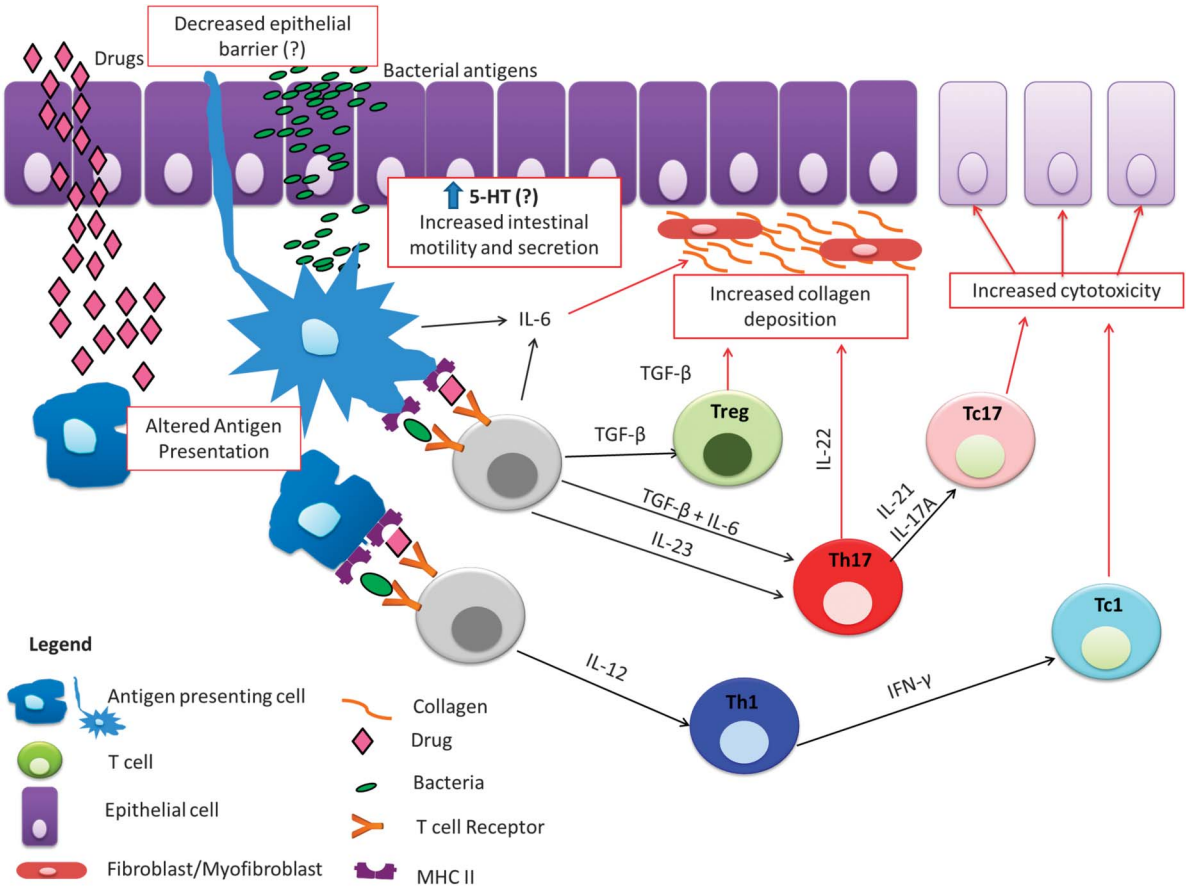

FIGURE 1. Key events in microscopic colitis pathogenesis. Exposure to specific drugs and bacterial antigens is thought to inappropriately trigger the inflammatory cascade. Although not universally accepted, it has been suggested that the influx of luminal antigen through gut mucosa is enhanced by a constitutively decrease in epithelial barrier function, leading to increased epithelial permeability and bacterial penetration. HLA genetic overlap with coeliac disease suggests an altered antigen presentation occurring within the lamina propria. This results in an overactivation of Th1- and Th17-immune responses and ultimately to increased Tc1- and Tc17-mediated cytotoxicity. Genetic data also suggest that microscopic colitis is characterized by altered serotonin (5-HT) reuptake; this may lead to increased levels of 5-HT, contributing to the augmented intestinal motility and secretion. Increased mucosal levels of profibrogenic cytokines, such as TGF-β, IL-6, and IL-22, seem to be more specific for CC, likely concurring to the subepithelial deposition of collagen, a hallmark histologic feature of this type of microscopic colitis.

with LC may suggest the presence of slightly different pathogenetic mechanisms between the 2 subgroups of MC.[14]

Previous studies have assessed the correlation between MC and HLA-DQ haplotypes similar to those found in coeliac disease as DQ2 and DQ1,3.[20] In this field, Fernandez-Banares et al[21] showed a positive correlation between either the DQ2 heterodimer or the DQ2/DQ8 alleles and the diagnosis of LC. The odds of having LC were almost 3 times higher in the DQ2-positive group than in the DQ2-negative group. Based on this observation, the authors suggested that HLA-DQ2 genes are involved in the pathogenesis of MC.[21] The major known function of HLA class II molecules is binding antigenic peptides to be presented to T cells as a signal to initiate the immune response. Thus, it can be speculated that there are abnormalities in the HLA binding to peptide antigens in microscopic colitis, and that a colonic luminal antigen (perhaps a bacterial antigen) might trigger an HLA-immunoregulated inflammatory reaction.[21] Both CC and LC are associated with the HLA-DR3-DQ2 haplotype and with TNF2 allele carriage. These associations are also present in MC patients without coeliac disease. The shared predisposing HLA-DR3-DQ2 haplotype and the high prevalence of coeliac disease in patients with MC suggest an epidemiological overlap, and probably some similarities in the pathogenesis of coeliac disease and MC.[21]

Differential expression of matrix metalloproteinases (MMPs) has been implicated in the pathogenesis of CC. MMPs are predominantly expressed in various inflammatory conditions such as inflammatory bowel disease (IBD) or gastrointestinal ulcers.[22] MMPs play an important role in tissue remodeling during active IBD.[23,24] Recently, Madisch et al[25] have assessed the genetic polymorphisms of MMPs loci −1, −7, and −9 in a case–control setting for susceptibility to CC. The genotypization for single nucleotide polymorphisms revealed that the carriage of the allele GG in the MMP-9 gene significantly increased the risk for CC. The functional role of this gene polymorphism is not yet established. Nonetheless, a possible defect in activation of MMP9 might cause an abnormal collagen degradation.[26]

Serotonin (5-HT) release and serotonin reuptake transporter (5-HTT) expression has been reported to be decreased in experimental colitides, such as in interleukin-10 knockout-associated colitis, and in patients with ulcerative colitis (UC). Serotonin plays an important role in the pathogenesis of colitis, but individual genetic variants of 5-HTT gene in MC and UC are not known. A significant association was observed between LL genotype of 5-HTTLPR polymorphism and MC, suggesting that 5-HTTLPR is a potential candidate gene involved in the pathogenesis of MC, also considered the importance 5-HT physiologically possesses in regulating intestinal motility and secretion. As a matter of fact, in patients with MC and UC, serotonin levels were significantly higher compared with those of healthy controls.[27]

Taken together, these initial pieces of evidence clearly support the correlation between MC and peculiar genetic fingerprints, thereby confirming the putative role played by the immune system. However, the meaning of all the presently reported genetic associations is poorly understood, and we are still far from being able to outline a possibly complex genetic risk profile for the diagnosis and the differential diagnosis of MC.

Features of Microscopic Colitis Immune Response

Few studies have characterized the inflammatory mechanisms sustaining MC pathology. Until now, it is indeed clear that MC is an immune-mediated disorder, with a prominent contribution from the adaptive immune system and cytotoxic responses. The minor involvement of innate immunity is testified by some histopathologic features, such as the lack of granulocyte infiltration, and by the weak correlation between MC activity and the levels of available fecal biomarkers of inflammation that mostly reflect granulocytes activity and trafficking (e.g., fecal calprotectin).

Adaptive Immune Response

Similarly to other idiopathic chronic inflammatory disorders of the gut, such as Crohn's disease and UC, it is postulated that MC is caused by a dysregulated immune responses to luminal antigens in predisposed individuals.[28] In fact, several alterations in the balance of different lymphocyte populations and cytokine profiles have been described in MC. The cytokines potentially involved in pathogenesis of MC are summarized in Table 1.

Both LC and CC patients express increased mucosal mRNA levels for TNF-α, IFN-γ, and IL-15, but not IL-2 or IL-4.[29] Immunohistochemical analysis revealed that most lamina propria $CD4^+$ T cells expressed the Th2 transcription factor GATA-3, whereas lamina propria $CD8^+$ T cells expressed both GATA-3 and the Th1 transcription factor T-bet at similar levels.[31] In contrast, most $CD8^+$ IELs expressed T-bet, whereas <20% expressed GATA-3.[31] Flow cytometry analyses and immunohistochemistry studies have shown heavy infiltration of $CD8^+$ T cells in the mucosa of patients with CC and LC.[32,33] An increased activation of $CD4^+$ and $CD8^+$ T cells both in the lamina propria and in the intraepithelial compartment has been also demonstrated by the elevated expression of CD45RO and Ki67.[33]

Th1/Tc1 stimulates cell-mediated immunity, including activation of macrophages and cytotoxic T lymphocytes, thereby sustaining chronic inflammation. Th17/Tc17 cells serve an important function in antimicrobial immunity at mucosal barriers by stimulating production of antimicrobial proteins by epithelial cells and recruitment of neutrophils.[34] As a matter of fact, IL-17A exerts protective functions in the gut also strengthening tight junctions by inducing claudin expression in intestinal epithelial cells and inducing mucin production.[35] However, inappropriate Th17 responses are involved in the pathogenesis of several immune and inflammatory diseases, such as rheumatoid arthritis, psoriasis, Sjögren syndrome, IBD, multiple sclerosis, and systemic lupus erythemathosus.[36,37] Given the double role of IL-17, this cytokine is a god candidate to be involved in the immunopathogenesis of CC and LC.

TABLE 1. Cytokines Expression in Microscopic Colitis

Study	Cytokine	LC or CC	Effects
Tagkalidis et al[29]	TNF-α	Increased	Enhances innate immune response
	IFN-γ	Increased	Enhances lymphocyte infiltration in the gut; reduces barrier function; activates macrophages
	IL-15	Increased	Induces proliferation and activation of intraepithelial lymphocytes
Kumawat et al. 2013[38]	IL-6	Increased	Neutrophils recruitment; induces nitric oxide synthase
	IL-1β	Increased in CC only	Neutrophils recruitment; induces nitric oxide synthase
	IL-21	Increased	Pleiotropic and proinflammatory effects; correlates with disease activity
	IL-22	Increased	Induces IL-8 and TNF-α; induces myofibroblasts to produce collagen; correlates with disease activity
	IL-12	Increased	Enhances IFN-γ production by lamina propria mononuclear cells
	IL-23	Increased	Releases TNF-α, IL-1, and IL-6; neutrophils recruitment; induces nitric oxide synthase
	IL-17A	Increased	Releases TNF-α, IL-1, and IL-6; neutrophils recruitment; induces nitric oxide synthase; strengthens tight junction; induces antimicrobial peptides
Günaltay et al[30]	IL-37	Decreased	Sustains chronicity of inflammation

Indeed, a mixed Th1/Tc1 and Th17/Tc17 mucosal cytokine profile was demonstrated in both CC and LC patients compared with either controls or patients with UC.[38]

Interestingly, gene expression levels of the prototypic Th1 cytokine, IFN-γ, were higher in both LC and CC patients than those in patients with UC. However, IFN-γ protein levels were not altered in any of the colitis groups.[29,38] It is possible that the IFN-γ protein is consumed by $CD8^+$ T lymphocytes during and after their differentiation into active cytotoxic T lymphocytes, corroborating the finding that there are significantly higher proportions of both total $CD8^+$ IELs and increased proportions of them expressing an activated CD45RO+ Ki67+ phenotype in both CC and LC patients.[33] Certainly, IFN-γ plays a vital role in lymphocyte infiltration in the gut, as it regulates the production of IEL-attracting chemokines such as IP-10 (CXCL10) and MIG (CXCL9) by intestinal epithelial cells.[39] IFN-γ also reversibly reduces the barrier function in intestinal epithelial cell monolayers[40] and activates macrophages to release proinflammatory cytokines such as TNF-α, IL-1, and IL-6, which in turn sustain and increase local inflammatory responses. Consistently, TNF-α, IL-1, and IL-6, either at mRNA or at protein levels, are overexpressed in patients with CC and LC.[29,38] Taken together, this evidence suggests that IFN-γ is a pivotal driver of MC pathogenesis.

IL-12, the most potent Th1-polarizing cytokine, significantly increases IFN-γ production by lamina propria mononuclear cells during intestinal inflammation.[41] IL-12 alone or together with IFN-γ can convert Th17 and Tc17 cells into Th1/Tc1 like cells or Th17/Th1 and Tc17/Tc1-like cells, and induces upregulation of T-bet.[42,43] The enhanced transcription levels of IFN-γ and IL-12 found in patients with CC or LC but not with UC suggest that Th17/Tc17 and Th1/Tc1 responses predominate in the inflamed mucosa of patients with MC, with no difference between CC and LC.

IL-23, TGF-β, IL-6, and IL-1 are essential in driving and regulating the differentiation and function of Th17/Tc17 cells.[44,45] Both IL-23 and IL-17A mRNA but not protein levels were found to be increased in both CC and LC patients.[38] These cytokines can trigger the release of TNF-α, IL-1, and IL-6, as well as chemokines involved in neutrophil recruitment and inducible nitric oxide synthase,[35] thereby leading to chronic inflammation. IL-23 plays a primary role in inducing $CD4^+$ T cells to produce IL-17.[46] In a recent case report, IL-23 was shown to be increased in active CC and its levels seemed to be dependent on bacterial load. After fecal stream diversion due to temporary ileostomy in a severe and intractable CC, IL-23 and other overexpressed proinflammatory cytokines, such as IL-1β, IL-6, IL-12, IL-17A, TNF-α, INF-γ, IL-4, IL-5, and IL-13, significantly decreased. Interestingly, the subsequent restoration of intestinal continuity leads to a clinical relapse with a concomitant upregulation of IL-23, IL-2, and IL-21.[47]

IL-21 is a cytokine secreted by Th17 and Tc17 cells; its mRNA and protein levels are upregulated in both CC and LC patients.[38] In addition, the transcript levels of IL-21, IL-22, and IFN-γ were significantly correlated with clinical activity in patients with MC.[38] IL-21 has pleiotropic effects on immune cells, enhancing IFN-γ production by mucosal T cells and NK cells and promoting the lytic activity of $CD8^+$ CTLs.[48] Moreover, IL-21 induces secretion of IL-17 by lymphocytes[49] and can stimulate nonimmune cells to synthesize various inflammatory molecules. Excessive production of IL-21 has been described in many human chronic inflammatory disorders, and there is evidence that blockade of IL-21 helps attenuate detrimental responses in mouse models of immune-mediated diseases.[50] Interestingly, IL-21–deficient mice produced less Th1 and Th17 cytokines.[49] These observations suggest a possible pathogenic role of IL-21 during the onset of MC.

IL-22 is another Th17 cytokine, which is overexpressed in both CC and LC.[38] In addition to Th17 cells, it is also expressed by Th1 lymphocytes, $CD8^+$ Tc17 cells and NK cells as well as $CD11^+$ DCs and innate lymphoid cells.[51] IL-22 induces the production of IL-8 and TNF-α by epithelial cells and colonic myofibroblasts, and induces proliferative and antiapoptotic pathways, as well as the production of antimicrobial peptides, which help prevent tissue destruction and assist in its repair and restoration.[51,52] IL-22 also stimulates the production of mucins and antimicrobial peptides, factors that are important in maintaining tissue integrity.[51] However, IL-22 activates colonic myofibroblasts, which might result in excessive production and deposition of collagen in the basement membrane. Thus, although IL-22 may exert protective effects in MC enhancing epithelial repairing and barrier function, it may also promote the synthesis of several extracellular matrix components of the collagen band.[53]

Although Th1 and Th17 cytokines seem to be the prominent players in MC pathogenesis, Th2 immune responses seem to be suppressed. In fact, expression levels of mRNA encoding the Th2 signature cytokine IL-4 were very low and only detected in some patients with MC. In addition, neither mRNA nor protein levels of IL-5 or IL-10 were altered in patients with MC.[29,38]

Overall, anti-inflammatory cytokine production seems to be dampened in MC. Gunaltay et al[30] have recently shown that IL-37, a newly described member of the IL-1 family, is downregulated in MC. Endogenous IL-37 exerts anti-inflammatory effects by suppressing innate immune responses through attenuating the production of inflammatory cytokines induced by TLR agonists, as well as those induced by IL-1 and TNF-α.[54] Consistently, IL-37 mRNA levels are increased in patients with UC during remission and not in those with active disease.[30] Further studies will confirm whether the low expression of IL-37 may sustain chronic inflammation in patients with MC as well.

As aforementioned, cytotoxic T cells mediate a substantial part of MC immunopathogenesis.[55] However, it was also shown that the ratio of T lymphocytes CD8+/Foxp3 (CTLs) is lower in LC and CC than in controls, with the ratio being lowest in CC.[55] CTLs have been reported to secrete IL-2, which stimulates proliferation of Tregs, and Tregs in turn inhibit CTL-induced cytotoxic tissue damage. Foxp3 in Tregs regulates T-cell–related immune responses.[56] This result, along with progression of the disease, indicates that the increased numbers of Foxp3 cells in LC and CC seem to inhibit the "deteriorating" effect of $CD8^+$ T cells. This action may be modulated by the functions of secreted cytokines including TGF-β and IL-10. TGF-β is secreted by Foxp3+ cells and acts as a suppressive factor for inflammatory cell proliferation and function. TGF-β has the capacity to cause accumulation of collagen in tissues, such as that seen in CC.[55] As previously discussed, IL-2 was shown to be increased during active CC and its levels were dependent on gut bacterial burden.[47] IL-2 is vital for determining the magnitude and duration of immune responses. In fact, this cytokine is an important expansion factor for most or all types of activated T cells, plays a central role in downregulating immune responses, and its absence result in severe autoimmunity due to a failure to eliminate activated T cells.[56]

Innate Immune Response

As far as innate immunity is concerned, very scarce data are available and mainly describing alterations of intestinal barrier mechanisms. As an example, it has been shown that the mucosal expression of the antibacterial protein lysozyme is constitutively upregulated in CC colonic crypts and in LC lamina propria macrophages, again providing insights on the relevance of the interactions between intestinal mucosa and gut microflora in MC and on the slight molecular differences characterizing CC or LC.[57] Markedly augmented iNOS and nitric oxide levels have also been reported in the mucosa of both CC and LC patients.[58,59] In addition to its potent effects on endothelial cells, nitric oxide affects the functions of intestinal epithelial cell tight junctions leading to increased paracellular permeability.[60] The increase of intestinal epithelial paracellular permeability is a pathogenic event shared by several inflammatory disorders of the gut. In fact, the intestinal epithelium constitutes an impermeable layer that has the ability to selectively absorb what is necessary to sustain the organism, while denying passage of other pathogenic and noxious molecules. Disruption of this selective physical barrier may result in uncontrolled or dysregulated gut epithelial permeability and induce chronic intestinal inflammation.[61] Some reports describe alterations of intestinal paracellular permeability and barrier functions in MC[62,63]; however, whether intestinal barrier defects are primary, pathogenic features of MC or, simply, epiphenomena secondary to inflammatory activation need to be further investigated.

MicroRNAs

MicroRNAs represent a class of regulatory RNAs that suppress gene expression at a posttranscriptional level. Differential miRNA expression pattern has been reported in IBD.[64,65] The miRNAs potentially involved in the pathogenesis of MC are summarized in Table 2. Among them, miR-31 is differentially expressed in colonic mucosa of IBD in both frozen and formalin-fixed, paraffin-embedded tissue.[64] miR-31 is a pleiotropically acting microRNA that is preserved in vertebrates and *Drosophila*[67,68] and expressed in a variety of tissues and cell types.[69,70] Upregulation of miR-31 expression was reported in IBD and proved to be a relatively sensitive and specific biomarker for both UC and Crohn's disease.[64] Zhang et al[66] demonstrated distinct miR-31 expression pattern between IBD and MC, expanding the knowledge that miR-31 is a universally expressed specific biomarker for IBD. Another interesting finding in this study was the increased miR-31 levels in patients with CC compared with that of patients with LC.

Other studies have reported a modulation of miRNAs whose expressions depend on NF-kB activity, identified as posttrascriptional regulators of multiple Toll-like receptor (TLR)-signaling components. miR-146a has an important regulatory role in TLR signaling through inhibition of IRAKs and THF

TABLE 2. MicroRNA Expression in Microscopic Colitis

Study	miRNA	LC or CC	Effects
Günaltay et al[30]	miR-146a	Increased in quiescent LC patients	Inhibits production of proinflammatory cytokines; negative feedback on NF-kB signaling
	miR-155	Increased in LC and CC	Enhances TLR inflammatory pathway; promotes expansion and activation of Th1 and Th17 cells
	miR-21	Increased in LC and CC	Anti-inflammatory miRNA that decreases miR-155 expression; drives the Th1 differentiation by modulation of IL-12
Zhang et al[66]	miR-31	Significantly increased in CC	Promotes chronic inflammatory response

receptor–associated factor 6 (TRAF6) at the mRNA level[71] and has a negative feedback loop that controls the intensity and duration of NF-kB signaling.[72] By negatively regulating TLR signaling, miR-146a inhibits production of proinflammatory mediators and induces endotoxin tolerance.[73,74] Notably, Gunaltay et al[30] have reported an increased expression of miR-146a in patients with LC in remission versus those with active LC, but no differences were reported among patients with CC.

miR-155 is a proinflammatory miRNA that enhances the TLR signaling pathway by repressing the TLR signaling inhibitors SHIP1 and SOCS1.[75,76] Its expression is increased in both CC and LC.[30] miR-155 enhances both Th1 and Th17 cell-dependent tissue inflammation and promotes activation and expansion of T cells.[72] An anti-inflammatory mechanism is usually initiated to decrease a proinflammatory response; therefore, the anti-inflammatory miR-21 is upregulated to decrease miR-155 expression.[30,77] miR-21 can also influence Th1-cell differentiation by modulating IL-12 production by dentritic cells (DCs), which induces T-bet and IFN-γ expression[72]

Overall, the increased expression of miR-146a, miR-155, and miR-21 in quiescent but not in active LC patients indicates their possible role in maintaining mucosal integrity.[30] Conversely, no differences were observed between active and quiescent patients affected by CC.

Drug-Induced Microscopic Colitis

In the past decade, the role of several drugs in inducing microscopic colitis has been suggested. This hypothesis relies on either strong clinical and/or histologic evidence after drug rechallenge or isolated chronological and/or frequency arguments.[78]

Noxious luminal substances such as drugs and smoking may trigger the chronic inflammation seen in MC and 1 postulated hypothesis points to increased colonic permeability in patients with MC, thereby allowing luminal antigens to enter the lamina propria and elicit an immune and inflammatory reaction.[61] A variety of drugs have been associated with MC and are supposed to induce MC. The increased use of medications, especially in older people, might explain the reported increased incidence of MC.[1] Of all drug groups suggested to play an etiological role in MC, the most convincing evidence exists for nonsteroidal anti-inflammatory drugs (NSAIDs). Intestinal side effects of NSAID have been documented extensively, as they can induce small intestinal and/or colonic injury and inflammation and possibly exacerbate IBD.[79] Furthermore, 60% to 70% of patients on long-term NSAIDs intake may have asymptomatic enteropathy.[79] NSAIDs intake has in fact been associated with increased risk of acute diarrhea.[80]

Therefore, the ability of NSAIDs to cause or at least exacerbate MC is not unexpected. NSAID-related erosions and ulcers are most commonly seen in the distal ileum and rectum. In the small intestine, NSAIDs uncouple mitochondrial oxidative phosphorylation leading to reduced intracellular ATP levels. This, in turn, leads to loss of cytoskeletal control over tight junctions and increased paracellular permeability.[81] This increased permeability may allow passage of luminal antigens, possibly eliciting a detrimental immune response, which may potentially result in clinically manifest MC.

Recent studies have emphasized the association between exposure to proton pump inhibitors (PPIs) and development of MC. PPIs are one of the most frequently prescribed classes of medications worldwide because they combine a high level of efficacy with low toxicity.[82] The potential pathophysiological mechanisms underlying PPI-related induction of MC are poorly understood, but it is important to recognize that PPIs are interacting at multiple targets. Proton pumps as H^+/K^+ ATPases are present not only on gastric epithelium but also on colonic epithelium where they contribute to whole-body potassium homeostasis.[83] Inhibition of the colonic proton pumps may therefore affect local electrolyte balance and compromise fluid acidification, which can possibly affect immune reactions in the colonic mucosa. Moreover, recent case reports have correlated the occurrence of severe hypomagnesemia with long-time PPI exposure caused by a defect in the active absorption of magnesium in the intestine.[84] This may result from an effect of PPIs on the tight junction proteins or on the TRPM6 and TRPM7 channels (transient receptor potential melastin 6 and 7), which are key molecules involved in active magnesium absorption. Also changes in intestinal pH induced by PPIs may affect channel and tight junction functions.[84] Although these mechanisms fit well with the chronic watery diarrhea complained by patients with MC, it does not explain the presence of the inflammatory infiltrate.

PPIs have been observed to induce smooth muscle relaxation and to inhibit contractile activity.[83] This effect on contractile systems may also affect tight junction functionality as tight junction proteins are directly linked to the actinomyosin cytoskeleton. Therefore, conformational changes in the cytoskeleton of intestinal epithelial cells may result in alterations in the tight junction function, increased paracellular permeability and, consequently, intestinal inflammation.

In addition, it is well known that PPI therapy affects intestinal microbial profiles.[85] PPIs can directly influence microbial growth by inhibition of the H^+/K^+ ATPase that are highly homologous to their human counterparts.[86] In contrast, increase of intestinal pH can result in a diminished host defense against certain bacteria. As such, profound acid suppression not only increases the risk of enteric infections in susceptible individuals[86] but may also lead to microflora imbalance/bacterial overgrowth.[87] Definitely, PPI-induced dysbiosis may contribute to MC chronic intestinal inflammation.

A number of other drugs have been associated with MC, including antiplatelet drugs,[88] acarbose,[89] β-blockers,[78] venotonic drugs,[90] and statins.[91] However, the molecular events linking these medications to the onset of MC have yet to be elucidated.

COLORECTAL CARCINOGENESIS AND MICROSCOPIC COLITIS

The influence of the immune system on tumor development is most pronounced when cancer develops in the context of chronic inflammation, such as in hepatitis-associated hepatocellular carcinoma, *Helicobacter pylori*–related gastric carcinoma or in colitis-associated intestinal cancer.[92] Nevertheless, some evidence does not fit into this general pattern. In certain circumstances, the presence of inflammatory cells is associated to better prognosis, as they can destroy tumor cells, in addition to normal tissue cells.[93,94] Moreover, diseases characterized by a marked chronic inflammatory condition, such as psoriasis, are not associated with an increased risk of developing skin cancer.[95] This might be the case for MC, as well. In a recently published pilot study, our group found a lower risk of colorectal neoplastic lesions in patients diagnosed with MC compared with negative subjects presenting with chronic nonbloody diarrhea (4.6% versus 17.9%; $P = 0.035$).[10] If further confirmed, these evidences suggest that the inflammatory pathways underling MC may result in a protective effect against colorectal carcinogenesis. As a matter of fact, during tumorigenesis, the immune system has a paradoxical role.[96] The adaptive immune system mainly functions as a tumor surveillance machinery, protecting tissues from malignantly transformed cells. On the contrary, the innate immune system can play a tumorigenic role being activated by a variety of microbe-derived substances, or by factors that are released from damaged cells. Engagement of innate immunity receptors often lead to the activation of NF-kB, a key transcription factor involved in both inflammatory responses and cellular proliferation,[97] which also affects the balance between the tumor promoting M2 and the tumor inhibiting M1 macrophages.[94] Accordingly, in patients with IBD with a long history of colitis, the innate immune pathways are constantly overactivated and the risk of colitis-associated cancer is increased.[98,99] On the contrary, in MC, the predominant involvement of the adaptive immunity and cytotoxic responses may account for the reduced incidence of colonic tumors, despite chronic inflammation. It is interesting to point out that NF-kB seems to be overactivated in the colonic mucosa of both CC and UC. However, significant differences in the pattern of NF-kB localization were noted: in UC NF-kB localized to both epithelial cells and lamina propria macrophages, whereas in CC, it was segregated only in epithelial cells and not associated to mucosal damage.[100] Taken together, those data suggest a prominent role of innate activation and specific differentiation of macrophages in the onset of colitis-associated cancer. Moreover, they further confirm the T-lymphocyte–driven nature of MC.

CONCLUSIONS

Microscopic colitis is an umbrella term, which describes immune-mediated disorders affecting the large bowel mucosa of adult and especially elderly patients presenting with chronic nonbloody diarrhea. The 2 main forms of MC, CC, and LC share the clinical presentation and have most histopathological hallmarks in common. Nonetheless, whether LC and CC are 2 separate entities rather than different stages or phenotypes of the same disease is still unclear.

Very recently, converging lines of evidence have shed new light on the pathogenesis of MC. Collected data have shown a genetic predisposition in patients with either CC or LC and a key role in the dysregulation of adaptive immune responses. More specifically, MC seems to be mediated by Th1/Th17-polarized responses and by cytotoxic T lymphocytes. Unfortunately, most of the studies regarding MC pathogenesis are descriptive because of the lack of appropriate animal models closely resembling human disease. Furthermore, the bulk of mechanistic data is derived from studies on human IBD and animal models of IBD, which represent a very different paradigm of inflammatory disorder.

In conclusion, although the pathogenesis of LC and CC is not clearly defined, several pieces of data are being collected, that delineate specific immune profiles and disease features. The establishment of adequate models to mechanistically dissect the molecular pathways involved in MC will greatly help to understand, recognize, and treat these diseases more efficiently.

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