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Review Article

Review Article

Pathogenesis of Microscopic Colitis: A Systematic Review

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Abstract

Background: Whereas the exact aetiology of microscopic colitis [MC] remains unknown, a dysregulated immune response to luminal factors or medications is the most accepted pathogenesis hypothesis.

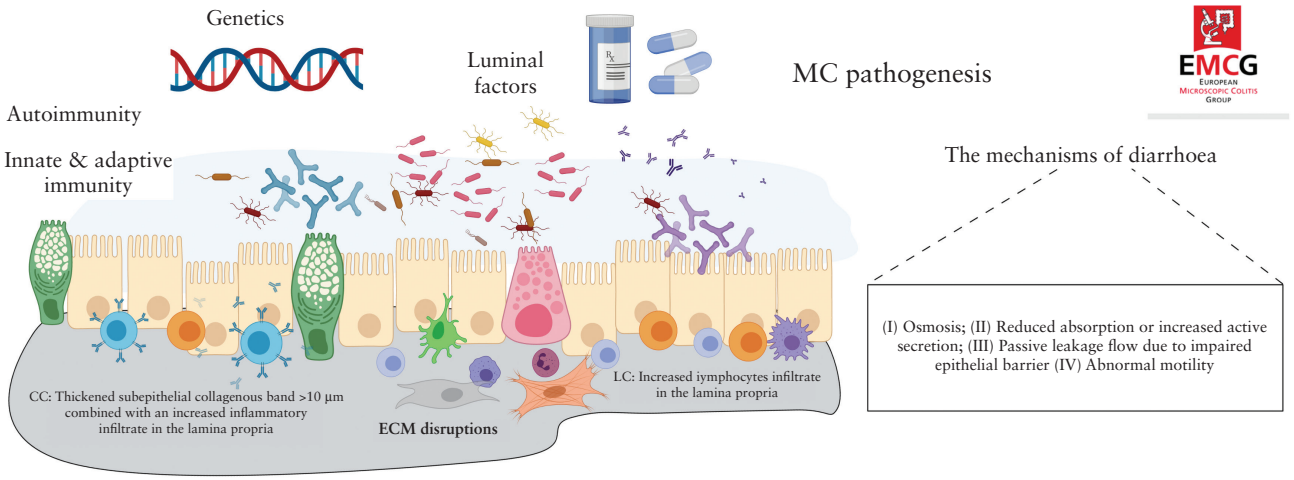
Methods: We conducted a **s**ystematic review of the pathogenesis of MC. We applied the Joanna Briggs Institute methodologies and the PRISMA statement for the reporting of systematic reviews [PROSPERO Trial Identifier: CRD42020145008]. Populations, Exposure of interest, and Outcome [PEO] questions were used to explore the following topics in MC: 1] intestinal luminal factors; 2] autoimmunity; 3] innate immunity; 4] adaptive immunity; 5] extracellular matrix; 6] genetic risk factors; and 7] mechanism of diarrhoea. A search was done in PubMed, Embase, and Web of Science up to February 2020. A narrative description was performed explaining the findings for each aspect of MC aetiopathogenesis.

Results: Thirty-eight documents provided evidence for PEO1, 100 for PEO2, 72 for PEO3 and 4, 38 for PEO5, 20 for PEO6, and 23 for PEO7. The majority of documents were cohorts, case reports, and case series, with a few case-control and some experimental studies. Consistency among data provided by different studies was considered to support pathogenetic hypotheses. MC is

a multifactorial disease believed to involve innate and adaptive immune responses to luminal factors, genetic risk, autoimmunity, and extracellular matrix alterations, all contributing by varied mechanisms to watery diarrhoea.

Conclusions: This is the first systematic review on the aetiology of MC supporting the notion that MC is a multifactorial disease. However, high-profile studies are lacking, and most evidence derives from small heterogeneous studies.

Graphical Abstract



Key Words: Microscopic colitis; collagenous colitis; lymphocytic colitis; pathogenesis; aetiology; intestinal luminal factors; autoimmunity; innate immunity; adaptive immunity; extracellular matrix remodelling; genetic risk factors; diarrhoea mechanism

1. Background

Microscopic colitis [MC] is a chronic immune-mediated disease of the colon with an overall incidence of 11.4 cases per 100 000 person-years.[1] It presents with chronic watery diarrhoea, associated with abdominal pain, urgency, nocturnal diarrhea, and faecal incontinence,[2] leading to poor quality of life and increased health care costs. MC occasionally mimics irritable bowel syndrome [IBS], but presents clear signs of inflammation upon microscopic evaluation. Therefore, diagnosis is based on histological examination on stepped colonic biopsies of a macroscopically almost normal colon. The two major subtypes of this disease are collagenous colitis [CC] and lymphocytic colitis [LC].[1,3] An incomplete MC can be also detected, sharing features of both CC and LC.

Data on the pathogenesis of MC come from small studies often providing conflicting results.[4–7] MC aetiology is unknown and probably multifactorial. The current hypothesis revolves around the interplay between luminal factors and innate and adaptive mucosal immunity, leading to gut barrier dysfunction and subtle inflammation in the colonic mucosa. Several investigators acknowledge some of these mechanisms responsible for primary MC, and drug-induced MC is considered a secondary disease.[8–11]

Several studies have addressed MC aetiology;[12–18] but no systematic review on MC pathogenesis has been performed to date. This study aims to systematically review evidences on MC pathogenesis, to provide an integrative overview on intestinal luminal factors, autoimmunity, innate and adaptive immunity, extracellular matrix remodelling, genetic risk factors, and the mechanism of diarrhoea in MC.

2. Methods

This review was performed by the European Microscopic Colitis Group [EMCG] according to the Joanna Briggs Institute methods[19] and the PRISMA statement for reporting systematic reviews.[20] The objectives, inclusion criteria, and methods of analysis for this review were specified in advance and registered in PROSPERO, the international Prospective Register of Systematic Reviews [www.crd.york.ac.uk/PROSPERO; ID: CRD42020145008]. Data sources, search strategy, inclusion and exclusion criteria, study selection, methods for data synthesis, and reporting can be consulted in the Supplementary material, available as Supplementary data at *ECCO-JCC* online. The results of this systematic review are presented as a narrative and graphical summary about the pathogenesis of MC from published literature. Consistency among data provided by different studies was considered to support pathogenetic hypotheses. Quantitative pooling of data [meta-analysis] was not performed as not enough comparable studies were found and not sufficient homogeneity arose in the data extracted.

3. Results

The systematic review flow chart is shown in Figure 1. Some documents were shared between different Population, Exposure of interest, and Outcome [PEO] questions. This is the main reason why the exact numbers of documents excluded are not provided. However, the reasons to exclude a document consisted in: no full text available, narrative review, or metanalysis; no original data provided; not related to the PEO; wrong study arm; duplicated

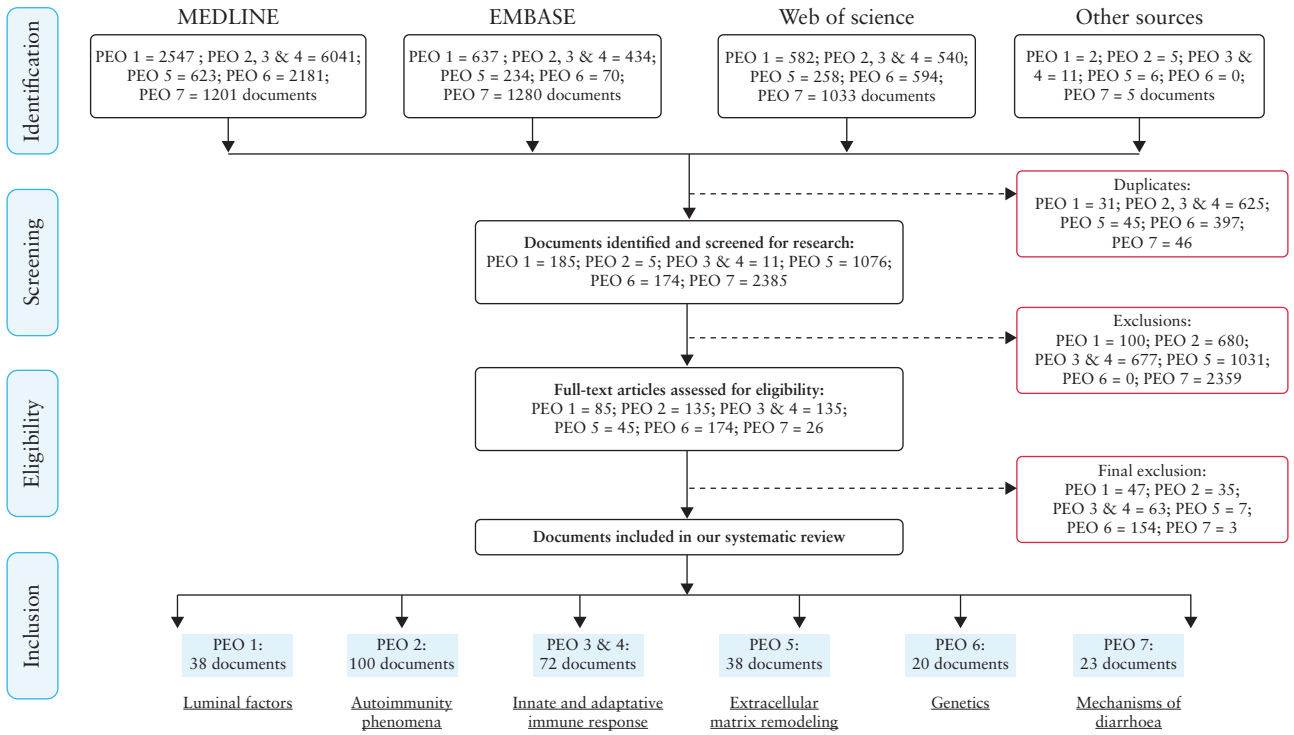


Figure 1. PRISMA diagram of microscopic colitis [MC] pathogenesis systematic review.

information; or abstract with relevant data missing. Overall, 38 studies were identified for PEO 1 [luminal factors], 100 for PEO 2 [autoimmunity phenomena], 72 for PEO 3 and 4 [innate and adaptive immune response], 38 for PEO 5 [extracellular matrix remodelling], 20 for PEO 6 [genetics], and 23 for PEO 7 [mechanism of diarrhoea]. Most studies consisted of cohorts, case reports, and case series, with some case-control and experimental studies with great heterogeneity and few individuals included.

3.1. Narrative description

3.1.1. Are intestinal luminal factors involved in the pathogenesis of MC?

Numerous preclinical and clinical studies involving molecular techniques revealed changes in the microbiome and/or specific intrinsic luminal factors in MC patients. However, the evidence is mainly based on case-control and descriptive studies and provided heterogeneous and statistically underpowered results due to low numbers of patients. Patients with active CC or ongoing corticosteroid treatment had a specific faecal microbiome similar to that described in individuals with active inflammatory bowel disease [IBD], whereas the microbiome of CC patients in remission resembled that of healthy controls, postulating that microbial alterations may trigger common mechanisms in the pathogenesis of CC and IBD.[21] A significantly higher abundance of pro-inflammatory sulphur-reducing *Desulfovibrionales* has been shown in colonic tissue samples from MC patients compared with healthy controls. *Actinomyces* and *Bacilli* abundance were associated with medications (proton pump inhibitors [PPI] and nonsteroidal anti-inflammatory drugs [NSAID]) known to increase the risk of MC.[22] Decreased levels of *Akkermansia muciniphila* were found in the faecal samples of 10 patients newly diagnosed with MC,[23] although this finding might be a consequence of diarrhoea and not specific of MC.

The faecal microbiotic profile of CC patients differed from that of healthy individuals by a lower abundance of taxa belonging to the *Ruminococcaceae* family.[24] Intriguingly, under-representation of *Ruminococcaceae* was previously associated with coeliac disease, suggesting a shared microbiome profile in these two entities. As intestinal bacteria affect mucosal immunogenicity,[25] it is tempting to speculate that additional factors [e.g., NSAID, PPIs, smoking, stress, or diet]—which are frequently associated with microbiome alterations in the gut—contribute to MC development. For example, NSAID, cyclo 3 fort, flutamide, lansoprazole, and ticlopidine were associated with LC, mediated through either cytotoxic mucosal mechanisms, antimetabolite effects, or drug allergy related to its use[26]; oral serum-derived bovine immunoglobulin/protein isolate was effective in reducing stool frequency in MC patients[27]; faecal stream diversion induced clinical and histopathological remission in patients with CC,[28] with recurrence of diarrhoea and abnormal collagen layer after closure of the ostomy. All these findings strongly indicate the pathogenetic importance of a noxious luminal factor. Also, Krogsgaard *et al*. found an altered microbiome composition in MC patients, which was driven towards the composition in healthy controls after treatment with budesonide.[29]

A refractory CC patient who remained in remission for 11 months after faecal microbiota transplantation [FMT] procedures has been reported; changes in the profile of intraepithelial and lamina propria lymphocyte subsets were documented after therapy, as a proof of the immunomodulatory effect of FMT, further supporting the involvement of colonic microbiota in the pathogenesis of CC.[30] In contrast, *de novo* onset of MC after FMT for recurrent *Clostridioides difficile* infection in previously healthy people has also been reported,[31,32] indicating that a foreign microbiome could dysregulate immune and responses, chemotaxis of lymphocytes to the affected area and increase bacterial metabolite production. In

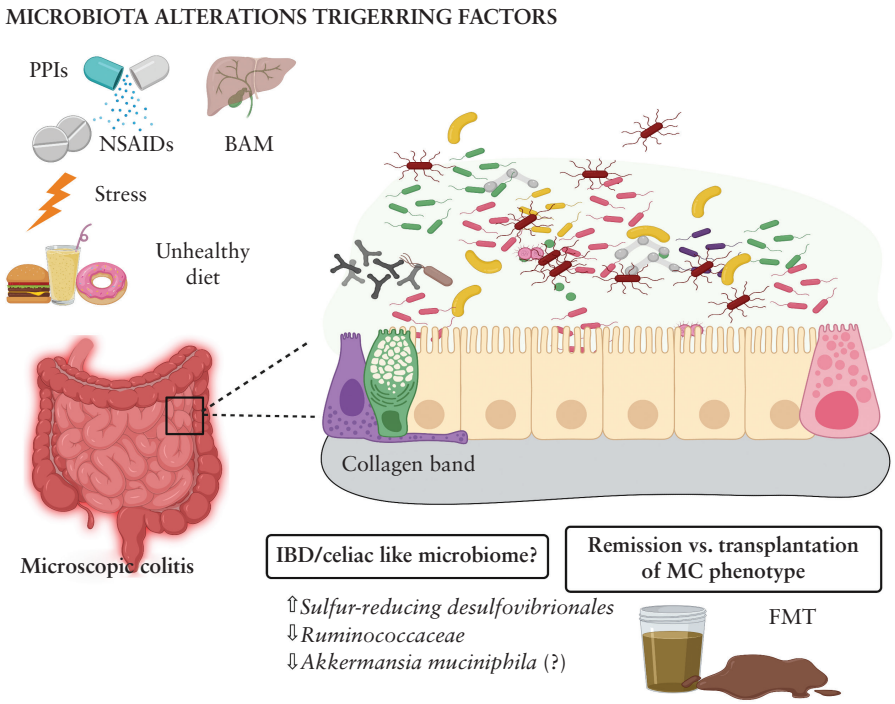


Figure 2. Luminal factors in microscopic colitis [MC].

addition, new-onset microscopic colitis in an ulcerative colitis [UC] patient after FMT transplantation has been also reported.[33]

Other luminal factors such as bile acids have been reported to trigger mucosal inflammation in people with abnormal expression of aquaporin channels and intracellular abnormalities, including altered expression of bile acid transporter and nuclear receptors.[34]

Overall, these are all small studies which only give a clue about a possible role of the microbiota and luminal factors of various sources in MC [Figure 2], and much larger studies are necessary to unravel their role in MC pathogenesis.

Importantly, as the microbiome structure in MC has been evaluated both during the acute phase of the disease and in patients under treatment, it should be borne in mind that the latter has a great impact on the intestinal ecosystem. As previously said, multiple drugs have a potential impact on both taxonomic and functional aspects.[35,36] Taking this 'pharmaco-microbiome' issue into account, studies in treatment-naïve MC patients are also needed.

3.1.1.1. Conclusion

Microbiome and specific luminal factors might play an important role in the pathogenesis of MC. An altered composition of the microbiota and/or its metabolites has been linked to mucosal inflammation in MC, but microbiome-oriented research on the MC phenotype has only recently been recognised. More research is needed to elucidate the link between the source, the type and role of luminal gastrointestinal factors, and the pathogenesis of MC.

3.1.2. Is autoimmunity a key pathogenicetic factor in MC?

An autoimmune response triggered by an unidentified luminal antigen coming from the ileal stream [from infectious agents, dietary components or additives, drugs, or of another nature] is a widely accepted hypothesis in the pathogenesis of MC. Case-control studies or case descriptions have provided evidence pointing to autoimmunity as a main characteristic in the development of MC, based on four type of findings: the association of MC with conditions which involve immune dysregulation and share common human leukocyte antigen [HLA] haplotypes; the presence of autoantibodies in some patients; the predominance of MC among elderly women; and its ability to respond to corticosteroids.[4,37–39] The presence of drug or food allergy among MC patients also suggests a hypersensitivity response.[40] Whether the association of autoimmune diseases with MC is due to an underlying autoimmune condition influencing both the gut and other organs, or whether increased bowel permeability allows antigens to cause cross-reactivity, still needs to be elucidated.[41] Illustratively, there is a case of MC debuting after a severe acute diverticulitis episode that supports the theory of enteric immunological stimulation and subsequent autoimmunity.[42]

Concomitant immune-mediated or autoimmune disorders are found in up to 50% of MC patients, including coeliac disease, autoimmune thyroid disorders, type 1 diabetes mellitus, rheumatoid arthritis, psoriasis, Takayasu's arteritis, and autoimmune hepatitis, among others.[5,39,43–48] Although reported in both CC and LC, autoimmune disorder might be more commonly associated with CC.[4] In Table 1 all immune-mediated diseases found to be associated to MC are listed, with prevalence estimated according to available evidence.

3.1.2.1. Coeliac disease

MC patients have an 50- to 70-fold increased risk for coeliac disease compared with the general population[49,50]; similar HLA variants [DQ2] and haplotypes [8.1] provide risk for coeliac disease and MC, primarily CC.[51,52] Three-quarters of MC patients who present Marsh 1 duodenal histology and express HLA DQ2 [4/23] respond to a gluten-free diet.[53] Conversely, 4.3% of coeliac patients prospectively followed over 25 years were diagnosed with MC; these tended to be older and with greater duodenal atrophy,[49] thus indicating that MC is more frequently diagnosed among coeliac patients [64%] than vice versa [25%]. The association of MC and coeliac disease suggests

Table 1. Summary of immune-mediated diseases associated with microscopic colitis[MC].

Prevalence	Disease	References
Very common [≥1/10]	None	
Common [frequent] [1/100 to 1/10]	Coeliac disease	4,6,39,45,47,49,50,53,61,195–206
	Autoimmune thyroid disease	4,5,7,8,39,45–47,59,61,198,199,205,207,208
	Type 1 diabetes mellitus	4,9,39,45,46,61,209
	Rheumatoid arthritis	4,5,9,46,59,61,205,210–217
	Ankylosing spondylitis/spondyloarthropathy	45,206,214,218–223. No association[224]:
	Seronegative polyarthritis	41,213,225
	Systemic or cutaneous lupus erythematosus	39,45,59,61,226–228
	CREST syndrome/systemic sclerosis/scleroderma	61,229–234
	Sjögren's syndrome	7,39,45,48,59,61,235,236
	Psoriasis/psoriatic arthritis	4,39,45,46,61,237–239
Uncommon [infrequent] [1/1000 to 1/100]	Pyoderma gangrenosum	210,240–243
	Temporal arteritis	4,7,206,244
	Dermatomyositis	39,61,245,246
	Recurrent idiopathic uveitis	39,205
	Polymyalgia rheumatica	4,39,61,205
	Raynaud's syndrome	39,48,61
	Autoimmune gastritis	37,208,247
	Immunoglobulin deficiencies	208,209,248–250
	Primary sclerosing cholangitis	4,205,251
	Autoimmune hepatitis	48,252
	Vitiligo	39
	Alopecia areata	39,45
	Documented allergies [drugs or food] or asthma	39,40
	Wegener's granulomatosis	61
	Myasthenia gravis	7
	Sarcoidosis	39
	Sacroileitis	253
	Takayasu's arteritis	43
	Guillain-Barre syndrome	39
	Mixed connective tissue disease	39,61
	Bechet's syndrome	61
	Multiple sclerosis	39,205
	Autoimmune polyglandular syndrome	205
Rare to very rare[a] [<1/10000 to 1/1000]	Pulmonary fibrosis	254
	SAPHO syndrome	255
	Prurigo nodularis	256
	Collagenous sprue	257
	Cutaneous polyarteritis nodosa	258

CREST, calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis.
[a]They are considered rare diseases when there is only one reported case.

similarities in the pathogenesis of both conditions, but simple epidemiological overlap cannot be excluded.[38]

3.1.2.2. Thyroid disorders

Autoimmune hypothyroidism is the most common, and also the most prevalent in women with MC. A Swedish cross-sectional study showed that symptomatic thyroid disorders were almost three times more frequent in MC (odds ratio [OR] 2.98), with no differences found for subclinical disease. Patients with MC showed lower titres of antithyroid peroxidase antibodies [10.6%] compared with controls [18.6%].[8] In addition, patients with Hashimoto's thyroiditis can present lymphocytic infiltration of the colon, concordant with LC.[54]

3.1.2.3. Articular manifestations

Joint manifestations are so common in MC patients that some authors suggest considering MC, especially CC, as one of the causes of enteropathic arthritis and taking into account MC as a cause of diarrhoea in patients with autoimmune arthropathy.[7]

3.1.2.4. Autoantibodies

An increased prevalence of serum antinuclear antibodies, IgM, antigliadin IgA, anti-endomysial, and anti-*Saccharomyces cerevisiae* [ASCA] was found in early studies on CC.[4–7] Larger studies comparing MC patients and healthy controls did not reproduce this findings, however.[8,10,55] Contrary to UC, a lower proportion of MC patients present antineutrophil cytoplasmic antibodies p [p-ANCA].[56,57] Some of them showed predominantly perinuclear immunofluorescence staining.[57] Unlike coeliac disease, the presence of antireticulin antibodies is low in MC patients.[58]

No useful clinical marker for MC has been identified so far.[59] Positive ASCA found in some MC patients is considered a non-specific epiphenomenon resulting from intestinal barrier disturbances. Autoantibodies in MC might correspond to concomitant autoimmune

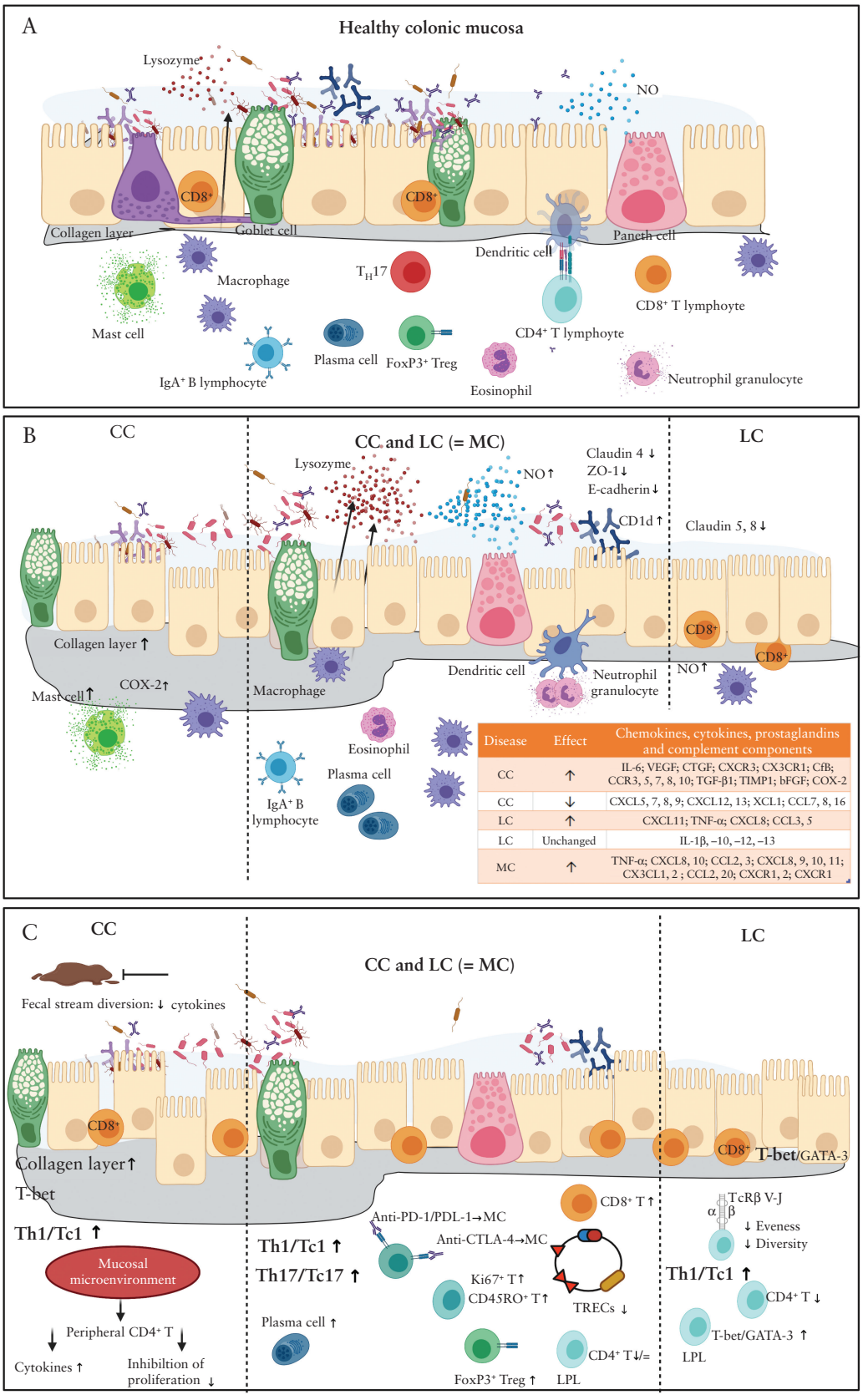


Figure 3. Innate and adaptive immunity both in healthy and microscopic colitis [MC] colonic mucosa.

disorders and are definitely not associated with symptoms.[9] Some drugs used to treat autoimmune diseases are suspected to induce MC,[60–62] as suggested in patients with MC and thyroid disorders, where introduction of levothyroxine preceded MC onset in most cases.[8]

3.1.2.5. Conclusion

There is no direct evidence to date that autoimmunity may be a key pathogenetic element in MC, although some evidence suggests it could be partially involved. No useful clinical marker for the disease has yet been identified.

3.1.3. Is innate immunity altered in MC?

The innate immune system represents the body's first line of defence. It reacts immediately to damage and generally set adaptive responses. The innate and adaptive immune systems highly interact and interdepend on each other. There is scarce knowledge about the involvement of innate immunity in MC, but some evidence is available [Figure 3].

3.1.3.1. Physiological barriers

Physiological barriers in the colon are represented by epithelial release of mucus, enzymes, and peptides with antimicrobial activity. Among the latter is nitric oxide [NO], a gaseous signalling molecule with antimicrobial properties, synthesised from L-arginine by NO synthase [NOS]. After being secreted, NO diffuses across cell membranes and causes oxidative damage to invading pathogens, thus changing microbial composition. NO also regulates multiple cell functions including vasodilation and cell migration, proliferation, differentiation, and apoptosis, and mediates inflammation. NO levels in colonic lumen and plasma are found to be increased in both CC and LC and correlate with clinical activity in both conditions.[63,64] Three major isoforms of NOS are described: the neuronal [nNOS], endothelial [eNOS], and inducible [iNOS]. Innate immune cells [neutrophils, macrophages, NK cells] and intestinal epithelial cells express iNOS and these cell types are thus known sources of NO, as already shown by Tagkalidis *et al.*[65] who found increased expression of iNOS mRNA in both CC and LC. Upregulation of iNOS mRNA in CC has recently been reproduced.[66] Colonic epithelial cells have been shown to be the main source of iNOS in CC, with inconsistent data provided in LC.[64,67] Patients with 'minimal colitis' [findings resembling incomplete microscopic colitis] had increased iNOS in basal crypt epithelial cells and in macrophages.[68] In CC, the level of iNOS mRNA was found to correlate with the degree of inflammation and clinical activity, and treatment with budesonide reduces the iNOS mRNA expression in colonic mucosa of CC patients.[69] Several cytokines induce iNOS expression and NO production. Epithelial cells in active CC show activated NFκB[68] and increased recruitment of transcriptionally active p65 to the iNOS promotor activating transcription, underlining the role of the epithelium in NO production.

Lysozyme, another antimicrobial compound, is upregulated in both CC and LC,[70] indicating a reaction to luminal agents. Lysozyme is expressed in colonic epithelial cells, metaplastic Paneth cells, and infiltrating macrophages. In particular, there seem to be more lysozyme-rich metaplastic Paneth cells in CC compared with LC. In CC the macrophages were located both above and below the thickened collagen band, whereas in LC they were located just underneath the surface epithelium. Overall, altered expression of antimicrobial compounds like NO and lysozyme may indicate that luminal microbes are involved in the pathogenesis of MC.

3.1.3.2. Anatomical barriers

Intact anatomical barriers are required to preserve the immunological balance in the gut. Detachment of surface colonic epithelium is a hallmark in patients with MC.[71] Mucosal barrier defects with increased permeability have been demonstrated in *ex vivo* models. They were restored after faecal stream diversion and decreasing mucosal inflammation, but recurred with restoration of bowel continuity.[72] Barmeyer[73] also demonstrated epithelial barrier dysfunction in LC with reduced gene expression of claudin 4, 5, and 8. Downregulated expression of the tight junction proteins, E-cadherin and zonula occludens-1 [ZO-1],[65] as well as occludin and claudin-4,[74] has been demonstrated in CC and LC patients, thus resulting in impaired barrier function and increased probability of influx of microorganisms or harmful agents into the mucosa. Single nucleotide polymorphisms [SNPs] in tight junction genes [*PTEN*, *MAGI1*, and *F11R*] were associated with MC risk,[75] and decreased expression of *PTEN* and *MGAI1* were associated with CC and LC, respectively.

3.1.3.3. Innate immune cells

Neutrophils and eosinophils inconsistently infiltrate the mucosa in both CC and LC.[71,76] Increased activities in both faecal myeloperoxidase [MPO] and eosinophil cationic protein [ECP], and also increase in MPO and eosinophil protein X [EPX], are found in rectal perfusates in CC patients and have been shown as an indirect measure of neutrophilic and eosinophilic inflammation.[75–78] Increased eosinophil infiltration and degranulation is found in CC compared with controls[79]; eosinophils show increased activity in CC samples, but not neutrophils,[80] which was restored after budesonide therapy.

Mast cells have been shown to be involved in MC, with increased cell numbers in the colonic mucosa compared with controls.[81,82] As an indirect measure of mast cell activation, metyl-histamine levels were increased in urine but, intriguingly, not in plasma of MC patients.[83]

3.1.3.4. Humoral components

Chemokines, cytokines, prostaglandins, and complement components: Several

everal innate-derived cytokines and interleukins [IL] have been studied in MC. By using nanostring techniques, Liu *et al.* performed expression profiling in a cohort of CC patients and found altered expression of inflammatory chemokines and their receptors, affecting *CCL11*, *CXCL5*, *8*, and *9*, and *CCR10*, *3*, *5*, *7*, and *8*, as well as *CXCR2*, *3*, and *6*. Chemokines *CCL7*, *8*, and *16* and *CXCL12*, *13*, and *XCL1* gene expressions were downregulated in CC compared with healthy controls.[66] Single-cell gene expression in 5 MC [not distinguishing LC and CC] patients found two cell clusters unique for MC with characteristics of epithelial cells that showed upregulated expression of the innate immunity-related genes *CXCL11*, *ISG15*, and NOS2 [coding for iNOS].[84] As for cytokines, increased mRNA expression of those characteristic of innate immune cells; tumour necrosis factor [TNF]α and IL-8 were found in LC mucosa, but IL-1β, IL-10, and IL-12/23 were not detected.[85] Increased protein levels of TNF-α were detected in all subtypes of colitis [CC, LC, UC] compared with healthy controls, whereas increase in IL-1β and IL-6 was only found in CC samples.[86] In addition, serum IL-6 concentrations were higher in patients with CC than in those with LC, thus supporting a difference in the pathogenetic mechanisms between the two subgroups of MC. An SNP in the *IL6* gene [IL-6–174 GG],

probably associated with enhanced IL-6 production, was more frequent in patients with MC compared with non-MC controls.[87]

A broad panel of chemokines were later separately screened in CC and LC mucosal biopsies: significantly enhanced gene and/or protein expression was found for CCL2, 3, 4, 5, 7, and 22, CXCL8, 9, 10, 11, and CX3CL and their receptors CCR2, 3, and 4, CXCR1 and 2, and CX3CR1. Histological remission downregulated chemokine expression to normal in CC patients, but not in LC, in which chemokine levels after treatment remained comparable to active disease.[88]

In CC, vascular endothelial growth factor [VEGF] expression was found to be increased in both colonic epithelium and lamina propria; budesonide-induced symptomatic remission reduced VEGF in lamina propria but not in the epithelium.[89] The authors speculated whether increased VEGF affects the formation of the subepithelial collagen band in CC through its ability to suppress tissue inhibitor of metalloproteinase [TIMP-1], thereby increasing matrix metalloprotease [MMP]-1 activity. Colonic perfusates, but not serum samples, from patients with active disease showed increased VEGF.[90] In patients with active disease, an increased VEGF expression was demonstrated in lamina propria fibroblasts. Connective tissue growth factor [CTGF], which also plays a role in fibrotic disorders, was studied in CC and LC. *CTGF* transcripts were increased in CC compared with LC, and its expression was located in fibroblasts at the subepithelial band in CC, and scattered in lamina propria cells and along the endothelium.[91]

Changes in arachidonic acid metabolism has been associated with MC, after finding overexpression of cyclooxygenase-2 [COX-2] located in the macrophages in CC, as also found in UC and Crohn's disease. Increased COX-2 was also demonstrated by immunohistochemical staining in both CC and LC.[92–94] The mRNA of prostaglandin E4 receptor was found upregulated in colonic mucosa of LC.[85] Involvement of the complement system involved in MC has been demonstrated by the finding of increased mRNA expression of complement factor B.[68] However, C3 and C4 levels were not significantly different in CC and healthy controls.[95]

3.1.3.5. Innate immune receptors

Toll-like receptor [TLR] signalling was as a preliminary investigated in MC by assessing key downstream regulators: increased expression of miR-155 and miR-21 was demonstrated in CC, and active LC presented upregulated IRAK-M, miR-146a, and miR-21 compared with controls,[30] overall indicating increased TLR signalling. CD1d is a molecule belonging to the major histocompatibility complex [MHC] class I-like family, presenting glycolipids from microbial surfaces to NK cells. Reduced expression of CD1d compared with controls was found in colonic epithelium of CC and LC.[96]

3.1.3.6. Conclusion

There is evidence that several components of the innate immune system are involved in the pathogenesis of MC; these are summed up in Figure 3. However, the exact role of involvement is not known and there is no evidence that changes in innate immunity primarily cause MC.

3.1.4. Is adaptive immunity altered in MC?

The intestinal mucosa is the largest lymphoid organ, with high numbers of activated immune cells. Compared with IBD, immune changes in MC are more subtle, although an increasing number of studies describe changes in local immune responses [Figure 3].

3.1.4.1. Cell subset distribution in the lamina propria

Colonic lymphocytes were thoroughly characterised by flow cytometry, immunohistochemistry, and real-time polymerase chain reaction [RT-PCR].[97–100] In LC, the vast majority of $CD8^+$ lamina propria lymphocytes [LPL] were conventional T cells expressing TCRαβ and CD8αβ, and their proportion compared with controls was not increased. In CC, the proportion of proliferating $Ki67^+$, as well as activated/memory $CD45RO^+CD8^+$ cells, increased significantly. Elevated proportions of $CD45RO^+CD4^+$ T cells in lamina propria were found in CC patients, and both CC and LC patients had higher proportions of $Ki67^+CD4^+$ LPL. No changes were noted in $CD4^+8^+$ double-positive [DP], $CD19^+$ B cells, $Ki67^+CD19^+$ cells, nor $CD38^{++}CD138^+$ plasma cells.[97] An increased proportion of $CD8^+$ and a decrease in lamina propria $CD4^+$ T cells were confirmed by immunohistochemistry; $CD45RO^+$, $FoxP3^+$, and $CD30^+$ cells were also more abundant. Increased areas of $CD20^+$ B lymphocytes, albeit scarce, were demonstrated.[98] $CD25^+FoxP3^+$ cells were found in the lamina propria of 63% of LC and 70% of CC patients.[102] Increased $CD8^+/FoxP3^+$ ratios in both LC and CC were also reported, being highest in the latter.[102]

3.1.4.2. Cell subset distribution in the epithelium

Increased numbers of colonic $CD3^+$ intraepithelial lymphocytes [IELs] were found in MC, being higher in LC than in CC.[102,103] These cells were predominantly $CD8^+$.[96,102, 104,105] Increased numbers $CD3^+$ T lymphocytes have been also described in the terminal ileum.[106] $CD8^+$ IEL in MC patients were predominantly conventional $TCR\alpha\beta^+CD8\alpha\beta^+$ T cells. Proliferating $Ki67^+CD8^+$ IELs were significantly increased in CC but not LC patients, with no differences in memory type $CD45RO^+CD8^+$ IELs.[97] CC patients presented increased proportions of $CD4^+8^+$ DP IELs. Reduced proportions of $CD4^+$ IELs were found in in LC compared with CC, with no different expressions of CD45RO, CD45RA, or Ki67.[97] Immunohistochemistry confirmed these data, demonstrating increased numbers of $CD8^+$ and decreased $CD4^+$ IELs. $CD45RO^+$, $FoxP3^+$, and $Ki67^+$ cells were all more abundant within the epithelium.[98]

CC patients also presented with significantly higher numbers of cells expressing MUM1/IRF4 protein, found on activated T cells, committed B cells, and plasma cells.[107]

3.1.4.3. Colonic cell subset distribution not divided into IELs and LPLs

Increased proportions of $CD8^+$ and a reduction in $CD4^+$ T cells were found in LC patients, together with significantly increased proportions of $TCR\gamma\delta^+$ cells among the $CD4^+$ subset. Double-negative [DN] $CD4^-CD8^-$ T cells were higher in both LC and CC, whereas a lower proportion of $CD4^+CD8^+$T cells was found in LC compared with CC and controls.[99,100] A trend towards higher proportions of $CD25^+FoxP3^+$ T cells in both CC and LC, and a decrease of late apoptotic and dead/necrotic T lymphocytes, were also noted.[100] Increased proportions of $CD8^+$ and $CD4^+$ T lymphocytes, both with reduced expression of CD69, were demonstrated by flow cytometry in CC patients. Budesonide treatment normalised CD69 expression.[80] A case report of a CC patient undergoing repeated FMTs found no major changes in the proportions of $CD4^+$ and $CD8^+$ lamina propria T cells from baseline compared with after the second FMT. However, the proportion of both $CD4^+$ and $CD8^+$ $CD45RO^+$ activated/memory cells decreased, whereas naïve $CD45RA^+$ T cells increased or remained unchanged, respectively. Proliferating $Ki67^+$ $CD4^+$ and $CD8^+$ T cells were increased, as well as $CD4^+FoxP3^+$ T_{reg},

whereas $CD8^+FoxP3^+$ T_{reg} decreased. Within the epithelium, $CD8^+$ T cells decreased and $CD4^+$ T cells increased.[30]

Single-cell RNA sequencing and digital mRNA quantification in colonic biopsies revealed two clusters of cells unique for MC patients: one representing an epithelial cell population, the other representing $CD8^+$ CTLs characterised by high expression of CD3D, CD8A, NKG7, PRF1, and CD7 genes,[84] corroborating findings from previous studies.

3.1.4.4. Other types of T cell distribution analyses

T cell receptor excision circles [TRECs] levels reflect the amount of recent thymic emigrants. In MC, TRECs were reduced in colonic biopsies, indicating local expansion of resident T cells rather than T cell migration to inflammation sites.[108]

Targeted next generation sequencing demonstrated that both MC and UC patients showed an oligoclonal TCRβ distribution in the colon and a distinctive diversity between CC, LC, and UC patients, suggesting different pathophysiological mechanisms.[109] LC patients showed less diverse and less evenly distributed TRBV-J combinations with reduced richness compared with controls and CC, indicating a more selective T cell response in LC toward certain antigens.[109]

3.1.4.5. Th/Tc1 and Th/Tc17 deviation in MC?—cells, cytokines, and gene transcripts

Colonic mucosa of both LC and CC presented an upregulated gene expression of IFN-γ, TNF-α, and IL-15 compared with controls,[65,85] a non-significant trend for upregulating IL-10, and no changes in IL-2, IL-4, and IL-5, with no differences between LC and CC.[86] A mixed Th1/Th17 and Th1/Tc1 cytokine profile was reported, with significantly upregulated mRNA but not protein levels of IFN-γ and IL-12, in both CC and LC. mRNA levels for IL-17A, IL-21, IL-22, and IL-6 were all significantly upregulated in both CC and LC patients, and correlated with higher numbers of bowel movements per day. Significantly enhanced IL-21 protein levels were also noted in both groups.[86]

After *in vitro* culture, higher levels of IL-10, but not TGF-β mRNA and secreted protein, was found in both LC and CC colonic samples.[99] Additional studies of CC patients revealed enhanced expression of genes involved in inducing [IL-12A, IL-12B, IL-12Rβ1] and executing [IFN-γ, TIGIT, TBX21] Th1 immunity, but also FoxP3 involved in immune modulation. Differently from IBD, IL-22, IL-22RA2, and TNF-α expressions were unchanged.[66]

To investigate the impact of soluble factors from the colonic mucosa, peripheral blood $CD4^+$ T cells were polyclonally activated in the absence or presence of conditioned media from colonic biopsies from CC patients or controls: the production of both pro-inflammatory [IFN-γ, IL-17A, IL-6, IL-1β] and anti-inflammatory [IL-4 and IL-10] cytokines was significantly enhanced, and a trend towards reduced inhibition of T cell proliferation was observed in the presence of conditioned media from CC patients.[110]

Upregulated gene expression[93] and immunohistochemical staining[100] of IL-17 and IFN-γ were found in both CC and LC colonic biopsies, but flow cytometry showed decreased proportions of Th1 and Th17 cells.[99] A positive correlation between the number of daily stools and mRNA levels of IL-15, IL-17, and IFN-γ, but not cell proportions or protein levels, was found.[100] Gene expression of IL-23 was also increased in both LC and CC.[100]

In a case report, faecal stream diversion in a CC patient significantly reduced mucosal protein levels of IL-2, IL-17A, IL-23, TNF, IFN-γ, IL-4, IL-5, IL-10, and IL-13, whereas IL-21 remained unchanged. After restoration of bowel continuity, symptoms relapsed and IL-2, IL-23, and IL-21 levels increased to higher levels than before faecal stream diversion.[111]

A study of MC patients who evolved into IBD demonstrated increased numbers of cells expressing IFN-γ, T-bet, TNF-α, and GATA-3, but not IL-17 or RORc compared with MC-resolved cases. Former LC patients had more $TNF\text{-}\alpha^+$ and $RORc^+$ cells than former CC patients. The increased ratio of mucosal T effector/T_{reg} lymphocytes seemed to be the key characteristic feature of MC patients subsequently transforming to IBD.[112]

3.1.4.6. Transcription factor expression

The T helper/cytotoxic cell differentiation into different subtypes is regulated by different transcription factors. In colonic biopsies from LC, all IELs were $CD8^+$, 10–20% of which expressed the Th2-associated GATA-3 and the remaining the Th1-associated T-bet.[113] Among the lamina propria T cells [65–70% $CD4^+$; 30–35% $CD8^+$] the majority of the $CD4^+$ T cells were $GATA\text{-}3^+$, and T-bet and GATA-3 were expressed at a similar frequency by the $CD8^+$ T cells. T-bet was also found to be significantly enhanced in CC patients, and there was a tendency [$p = 0.0055$] in LC patients.[86] Thus, LC shows features of a mixed Th1/Th2 immune response.

3.1.4.7. Antibody levels

The only paper that investigated serum antibody levels reported higher IgM in CC, with no differences found for other Ig isotypes.[5] Therefore so far there are no data to support significant changes in antibody levels in MC.

3.1.4.8. Drug-induced MC and treatment of MC with immunotherapy

NSAID- and PPI-induced MC has been covered in the first PEO. Acarbose induced LC in a patient with increased expression of CD25 and HLA-DR.[114] Immune checkpoint inhibitors, targeting natural brakes in the adaptive immune system, are used to enhance antitumour immunity. Several reports have described development of MC following this therapy.[115–117] Also, vedolizumab [anti-integrin-α4β7] successfully induced remission in two CC patients by modulating the lymphocyte trafficking into the gut mucosa.[118,119]

3.1.4.9. Conclusion

A large number of studies have described changes in adaptive immune responses in MC, but it is difficult to clearly recognise a pattern. Studies have focused on T lymphocytes, and most report increased proportions of $CD8^+$ but reduced or unchanged proportions of $CD4^+$ T cells, both subsets showing activated phenotypes. Most studies indicate a predominance of cytokines and/or transcription factors associated with Th1 and Th17 [or $CD8^+$ Tc1 and Tc17] responses. Some studies support LC and CC being two different entities.

3.1.5. Are extracellular matrix remodelling [ECM] alterations involved in MC?

The presence of a subepithelial collagen band represents the landmark to differentiate CC from LC.[120] Capillaries, fibroblasts, eosinophils, mast cells, inflammatory cells, and increased numbers of lymphocytes can be found within this collagen band,[121–126] some of these cells mediating abnormal collagen deposition.[79,88,122–124,127–130] The composition of the subepithelial collagen band has provided heterogeneous findings:[131,132] some reports mostly identified type VI

collagen, and others demonstrated type I and III subtypes. Whereas the former points towards a primary alteration in collagen synthesis,[125,127] the latter represents a repair attempt after chronic inflammatory damage.[16,125] Immunohistochemical staining and *in situ* hybridisation analyses on the immediate pericryptal ECM composition suggest that pericryptal myofibroblasts express minor amounts of collagen types I, III, and VI in the deep parts of the crypts,[123] whereas they express and deposit increased amounts of type VI collagen in the upper pericryptal areas and the subepithelium, which suggests deposits of physiological products of subepithelial myofibroblasts.[127]

Tenascins were also identified together with collagen.[127] Although they are weakly expressed in normal mucosa, non-specific chronic inflammation and, in LC,[127,133] prominent tenascin immunostaining [measuring 12–28 µm] were found in the collagen band characterising CC,[133–135] which can be used as routine staining in suspected CC. Other ECM components, such as laminin and fibronectin, were not expressed or distributed uniformly in the lamina propria of normal and inflamed tissues, thus failing as diagnostic markers for CC.[133]

The factors that trigger chronic inflammation and the subsequent collagen accumulation in CC remain unclear. Inflammation preceding fibrosis appears mandatory, but contributes little to its progression. Therefore, the mechanisms that regulate fibrosis and inflammation appear to be different,[129,136] and collagen abnormally accumulates exclusively in CC, despite LC also involving chronic inflammation. Better understanding of the cellular and molecular mechanisms underlying fibrosis is changing the conception of intestinal fibrosis as an inevitable and irreversible process of chronic intestinal inflammation, including MC.[129,136] Faecal stream diversion represents a model of the reversibility of collagen deposition in CC.[28,137,138] As stated previously, temporary ileostomy and faecal stream diversion significantly downregulated pro-inflammatory and profibrotic cytokine expression, including IL-1β, IL-6, IL-12, IL-17A, IL-23, TNF-α, INF-γ, IL-4, IL-5, and IL-13; restoration of intestinal continuity led to clinical relapse and histological recurrence, and to several cytokines being upregulated [IL-23, IL-2, and IL-21].[111]

An abnormal collagen deposition depends on the balance between the production and degradation of ECM proteins [Figure 4]. ECM is produced by a transient or permanent numerical expansion of activated myofibroblasts, which are modulated by profibrotic and antifibrotic factors.[122,124,127,129,136,139,140] Numerous pro-inflammatory and profibrogenic cytokines are overexpressed both in CC and LC, including TNF-α, IFN-γ, IL-15, IL-6, IL-1β, IL-21, IL-22, IL-12, IL-23, and IL-17A.[15,65,86,87,99] In contrast, IL-37, a newly described member of the IL-1 family which exerts anti-inflammatory effects by suppressing innate immune responses through attenuating the production of TLR agonist-induced inflammatory cytokines, is downregulated in MC.[141]

Several growth factors, cytokines, chemokines, products of oxidative stress, components of the renin-angiotensin system. and angiogenic factors, as well as NO, are involved in intestinal fibrosis in IBD.[129,136,140] Which of these mediators triggers and maintains accumulation of subepithelial collagen in CC is unknown. The differences in mucosal profile of T cells and cytokines between LC and CC may partly explain differences in subepithelial collagen pattern between both MC variants.[99]

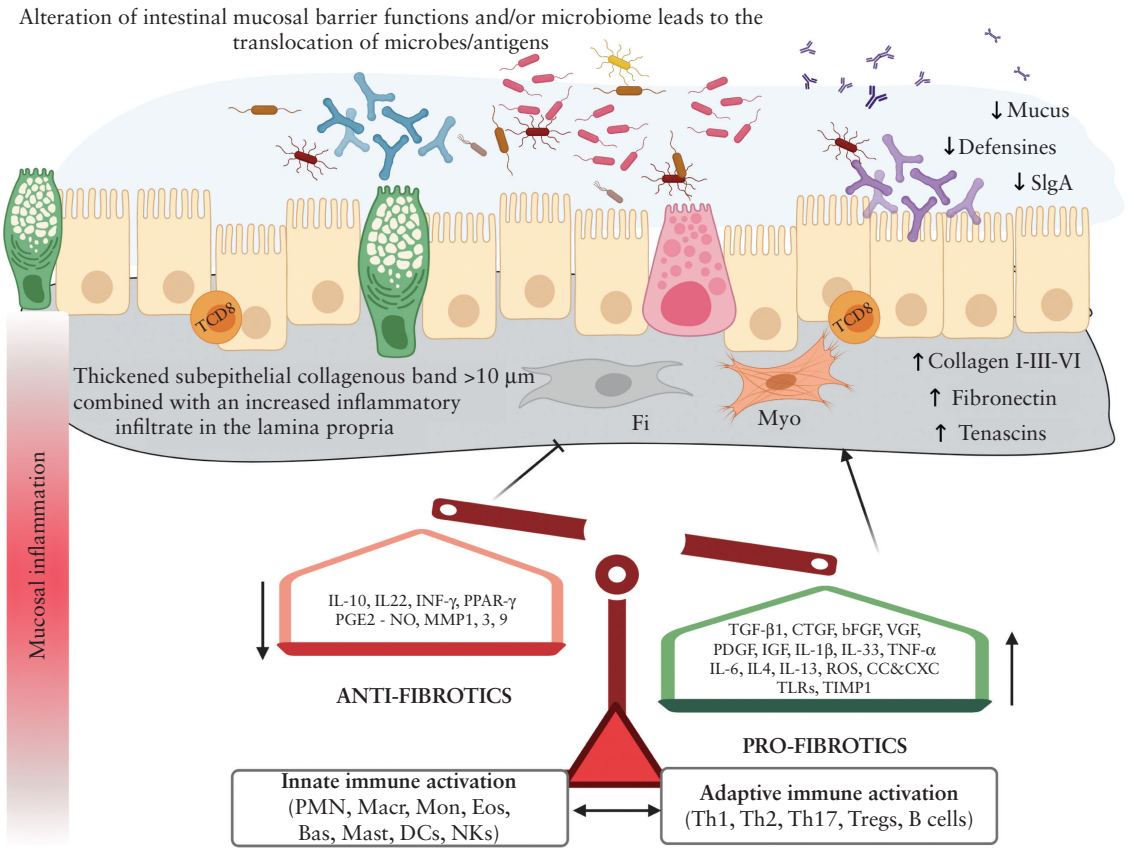


Figure 4. Extracellular matrix in microscopic colitis [MC].

ECM is degraded by MMP; a fine balance between MMP and TIMP determines ECM deposition. In addition to promoting ECM turnover, MMPs degrade a variety of non-matrix substrates including chemokines, cytokines, growth factors, and junctional proteins. Thus, MMPs are increasingly recognised as essential components in the inflammatory response and in fibrogenesis.[127,129,140] Thereby, the imbalance due to reduced MMP activity and/or increased TIMP expression leads to excessive ECM deposition and fibrosis. Specific factors involved in collagen deposition in CC have been identified. TGF-β and TIMP-1 expression are upregulated in the colonic mucosa of patients with CC as compared with healthy controls,[128,142] and smoking, which is disproportionately associated with CC compared with LC,[143–145] has been shown to directly upregulate TGF-β and TIMP-1.[146] PPI, another risk factor for CC, have been shown to increase the expression of profibrogenic factors ssuch as TGF-β and FGF-2. PPI also downregulate the expression of replication factor C1 [RFC1], a negative regulator of collagen production, resulting in increased production of collagen III and IV, in association with lipid peroxide.[147] Connective tissue growth factor [CTGF], the downstream effector of TGF-β, was markedly increased in the subepithelial tissue of CC samples.[91] CTGF colocalises in areas with excessive collagen deposition, suggesting it acts as an end-stage mediator of local fibrosis in CC.

Mucosal secretion and expression of basic fibroblast growth factor [bFGF] is markedly increased in CC patients,[148] which promotes fibroblasts' proliferation and differentiation. A strong expression of VEGF within the epithelium, inflammatory cells, and fibroblasts compared with normal controls is found in CC.[89,90] VEGF enhances angiogenesis, mitogenesis, permeability, and fibrosis. As stated previously, prostaglandins are also involved in CC. COX-1 is constitutively expressed and its prostaglandins are involved in maintaining gastrointestinal integrity. In contrast, COX-2 is induced by a variety of stimuli [including cytokines, growth factors, and hormones] and its prostaglandins contribute to inflammation. Increased amount and activity of COX-2 are found in CC,[93,94] a persistent inhibition of which promotes myofibroblast-associated fibrosis.[149,150] This provides an explanation for the increased risk of MC, and especially of CC, with the use of NSAID.[151,152]

MMPs play an important role in tissue remodelling during chronic colitis.[153] Differential expression MMPs has been involved in abnormal accumulation of collagen in CC. Among the MMPs, MMP-1 and MMP-9 seem relevant in CC.[66,142] A restricted MMP-1 expression, counteracted by increased TIMP-1 expression, suggests locally impaired fibrolysis in CC,[142] and a defective activation of MMP-9 CC further contributes to collagen deposition.[154,155]

The thickness of the collagen band in CC does not correlate with duration and severity of symptoms nor with clinical response to treatment, according to results of clinical trials[1] [Table 2].

3.1.5.1. Conclusion

ECM components, especially collagen, are markedly increased in CC, but not in LC. However, their pathogenetic role is unclear. The activation of myofibroblasts, the imbalance between profibrotic and antifibrotic molecules, including cytokines, chemokines, growth

Table 2. Results of randomised controlled trials in collagen colitis: effects of treatments on changes in the thickness of the collagen band.

Authors, year [ref.]	No. of patients in treatment groups	Treatment duration	Clinical response/remission [Active drug vs placebo]	Significant reduction of inflammation grade	Significant reduction of collagen band thickness
Wildt S, 2006[162]	Probiotics: 21[a]	12 weeks	29%	No	No
	Placebo: 8		13%		
Madisch A, 2007[163]	*Boswellia serrata*: 16	6 weeks	44%	No	No
	Placebo: 15		27%		
Baert F, 2002[156]	Budesonide [9 mg/day]: 14	8 weeks	57%	Yes	No
	Placebo: 14		21%		
Bonderup OK, 2003[157]	Budesonide [9 mg/day]: 10	8 weeks	100%	Yes	Yes
	Placebo: 10		20%		
Miehlke S, 2002[158]	Budesonide [9 mg/day]: 23	6 weeks	87%	Yes	No
	Placebo: 22		14%		
Bonderup OK, 2009[159]	Budesonide [6 mg/day]: 14[b]	24 weeks	76%	Yes	Data not reported
	Placebo: 14		12%		
Miehlke S, 2014[160]	Budesonide [9 mg/day]: 30	8 weeks	80%	Yes	Data not reported
	Mesalamine [3 g/day]: 25		32%		
	Placebo: 37		38%		
Miehlke S, 2008[161]	Budesonide [6 mg/day]: 23[c]	6 months	74%	Yes	Yes
	Placebo: 23		35%		

[a]*Lactobacillus acidophilus* and *Bifidobacterium animalis* subsp. lactis BB12.

[b]34/42 collagenous colitis [CC] patients who achieved clinical remission after 6 weeks' induction therapy with budesonide [9 mg/day] were subsequently randomised to maintenance therapy with budesonide [6 mg/day] or placebo.

[c]46/48 collagenous colitis [CC] patients who achieved clinical remission after 6 weeks' induction therapy with budesonide [9 mg/day] were subsequently randomised to maintenance therapy with budesonide [6 mg/day] or placebo.

factors, MMP, and TIMP, contribute in multiple ways to subepithelial collagen deposition in CC. The thickness of the subepithelial collagen band does not correlate with symptoms' duration or severity. Response to treatment does not correlate with collagen band thickness in CC.

3.1.6. Are there genetic risk factors in MC?

Genetic predisposition to MC has been scarcely evaluated. Classical twin [monozygotic vs dizygotic] or large population-based studies have been lacking, though first-degree familial clustering has been described, also in the context of other autoimmune disorders.[164–169] A recent nationwide survey in Sweden provided further evidence of familial aggregation in MC, as well increased prevalence of comorbid autoimmune diseases with known genetic origin [UC, coeliac disease, rheumatic and thyroid diseases].[75]

Genetic predisposition to MC has been studied in the past mainly through candidate-gene approaches, including the HLA region, nucleotide-binding oligomerisation domain-containing protein 2 [*NOD2*], *TNF*, adrenergic receptor alpha 2A [*ADRA2A*], *MMP-9*, *IL6*, FERM domain containing 4B [*FRMD4B*], serotonin transporter solute carrier family 6 member 4 [*SLC6A4*], and phosphatase and tensin homologue [*PTEN*].[6,38,53,75,87,154,170–174] However, reported associations from all these studies were at best of borderline significance, based on sample sizes as small as a few dozens of individuals, and lacked replication. Whereas the analysis of hundreds of thousands of individuals is becoming the norm in modern genetic studies of complex diseases, none of these studies can be considered conclusive, and they may only contribute to a historical perspective of genetic investigations in MC. On the contrary, compelling evidence has been obtained for a role of the HLA region and the extended haplotype 8.1 in the pathogenesis of MC, particularly CC. HLA alleles encoded from this haplotype and known to be relevant to other immune-mediated disorders [HLA-DQ2 in coeliac disease, a known comorbidity in MC, as exposed before] were initially studied in small surveys from the late 1990s,[6,38,53,171] where preliminary evidence of association was reported. A more recent multicentre study from Sweden and Germany unequivocally demonstrated haplotype 8.1 association with collagenous colitis, reporting array-based [Immunochip] analyses focused on immune-related genes in several hundred patients.[49] This study also highlighted partial genetic overlap with inflammatory bowel diseases Crohn's disease and UC, based on enrichment of concordant genetic risk effects at immune-related loci. These findings were further corroborated in subsequent large analyses.[175] The latest large research related to this topic has been published outside the current period of this systematic review.[176] Of note, a later survey from the same group highlighted how HLA associations may be CC-specific, as they were not observed in a cohort of patients with adequate statistical power to detect them also in LC.[50] Although this is an observation that requires confirmation in larger datasets, it is important because it may provide important clues as to a differential aetiopathogenesis of the two major MC subtypes.

3.1.6.1. Conclusion

Compelling evidence indicates that genetic risk factors play a role in MC, although these appear to be confined to the HLA region. Subtype-specific [CC vs LC] HLA associations may be of value to identify pathogenetic mechanisms of disease predisposition, and to contribute to genotype-driven CC and LC patient stratification.

3.1.7. What is the mechanism of diarrhoea in MC?

Mechanisms of watery diarrhoea in MC are poorly understood, and might respond to one or a combination of the following: [1] osmosis; [2] reduced absorption or increased active secretion; [3] passive leakage flow due to impaired epithelial barrier [e.g. swollen from denuded mucosa, congenital or acquired epithelial barrier deficiency]; and [4] abnormal motility. Indeed, excluding abnormal motility and increased active secretion, the pathogenetic pathways of

Table 3. Main pathophysiological mechanisms of diarrhoea in patients with active microscopic colitis.

Major evidence	Study type	MC Patients involved	Plausible clinical relevance
Osmotic			
A normal stool weight [<200 g/day] is restored by fasting[177] and the faecal osmotic gap is abnormal only in some MC patients[177,178]	Cohort[177] and case-control study[178]	67	+/-
Secretory			
A decrease in net absorptive fluxes of sodium and chloride was found in CC[74] and faecal sodium and chloride concentrations are increased in either CC or LC.[178] Active electrogenic chloride secretion is also present in CC[74]	Case-control studies[74,178]	66	++
Leak flux			
Transmembrane strand-forming proteins of the colonic epithelial tight junction [E-cadherin, occluding, and claudins] and epithelial resistance are diminished in both CC and LC[65,74,182]	Case-control studies[65,74,182,185–189]	33	+
Dysmotility			
The role of abnormal motility in the watery diarrhoea of patients with MC is uncertain and poorly investigated	No full-text article	Missing data	Unknown
Bile acid malabsorption			
Bile acid malabsorption is common in patients with either CC or LC, and more plausible during relapse[185–189]	Cohort[185,187] and case-control study[186,188,189]	149	+
Aquaporins			
Expression of colonic water-selective channel aquaporine 8 is decreased in CC patients[190]	Case-control study[190]	40	+

MC, microscopic colitis; CC, collagenous colitis; LC,lymphocytic colitis;

watery diarrhoea are generally driven by osmotic forces. Aquaporin dysregulation has been recently proposed as a novel potential diarrhoeal mechanism. Bile acid malabsorption might play a role by preventing water absorption and increasing water secretion through intracellular mediators or increased permeability. Table 3 summarizes these mechanisms.

3.1.7.1. Osmosis

Pure osmotic diarrhoea stops during fasting; stool analysis reveals a wide osmotic gap. Osmotic diarrhoea usually associates with small bowel involvement with nutrient malabsorption, two conditions that have never been demonstrated in MC. However, some cases of active CC patients restore a normal stool weight [<200 g/day] by fasting only,[177] and the faecal osmotic gap in MC patients has been shown variable.[177,178] An altered intestinal bacterial fermentation with accumulation of osmotically active organic anions could secondarily cause osmotic diarrhoea in MC.

3.1.7.2. Reduced absorption

A marked decrease in the absorptive net flow of sodium and chloride is observed in CC compared with healthy subjects.[74] Epithelial Na^+ channels are inhibited in human sigmoid colon of LC patients compared with controls, despite aldosterone stimulation.[179] Consistently, faecal sodium and chloride concentration are significantly increased in these patients.[178] As stated previously, iNOS are induced in the epithelium of MC, therefore NO levels are increased in LC and CC.[64,65] In addition to mediating inflammation, NO may exert secretory actions[180] and impair colonic absorption of fluid.[181]

3.1.7.3. Increased secretion

A slight active electrogenic chloride secretion has been suggested in CC patients.[74]

3.1.7.4. Leak flux

Colonic epithelial resistance was found reduced in both CC and LC, related to a decreased expression of epithelial tight junction transmembrane strand-forming proteins [E-cadherin, occludin, and claudins].[65,74,182] Epithelial apoptosis is normally seen in MC patients but it does not contribute to barrier dysfunction.[74,182] Leak flux in MC represents a passive mechanism, secondary to active inflammation and epithelial barrier dysfunction.

3.1.7.5. Abnormal motility

A role for abnormal motility in the watery diarrhoea of patients with MC is uncertain and poorly investigated.[182–184]

3.1.7.6. Bile acid malabsorption

Bile acid malabsorption is found in 27–70% of patients with CC and LC.[185–187] Bile acids eincrease water secretion and prevent water absorption, by acting through intracellular mediators or altering intracellular and epithelial barrier permeability.[188] Reduced ileal reuptake of bile acids is found in CC, which normalises after controlling disease activity.[189] Whether bile acid diarrhoea is a consequence of inflammation in the right colon [or the terminal ileum] or a coexisting disorder is still unclear.

3.1.7.7. Aquaporins

Aquaporin dysregulation has recently been suggested to be involved in watery diarrhoea in CC.[190] Aquaporins are transmembrane proteins that work as water-selective channels to regulate water absorption and homeostasis in colonic and other cells. A decreased expression of colonic aquaporin-8 in active CC patients compared with healthy controls has been shown; expression improved in cultured cell lines following corticosteroid treatment.

3.1.7.8. Conclusion

Evidence suggests a multifactorial cause for watery diarrhoea in active MC, with secretory mechanisms appearing dominant. The reduced absorption of electrolytes [mainly Na^+] and water together with an increased secretion of Cl^- appear prominent in inducing diarrhoea in patients with active MC. Colorectal mucosal inflammation is directly responsible for both reduced water absorption and increased secretion, which are corrected after anti-inflammatory treatment-induced disease remission.

4. Discussion

The amount of knowledge available on the pathogenesis of MC is scarce compared with other immune-mediated gastrointestinal disorders. Most data derive from low-profile studies, such as case series or experimental studies with small numbers of individuals. However, MC is as frequent as IBD and considerably impairs the patients' quality of life.

This review systematically assessed current evidence on MC pathophysiology and provided a narrative report. Its major strengths include exhaustive literature searches in Pubmed, Embase, and Web of Science. Different researchers selected references per PEO with independent extraction of data from studies, reducing the inclusion bias. No restrictions were used on language or time frame. Limitations of this research to be acknowledged is that a quantitative pooling of data was not possible because lack of enough comparable studies and heterogeneous results. At the time of wrapping up collected data and writing the paper, new studies on MC pathogenesis are being published, which address the relevance of aquaporins,[190] faecal microbiota transfer effects,[191] the relevance of intestinal dysbiosis,[192] apoptosis phenomena in paediatric patients with LC and genetic mutations associated with autoimmune entheropathy,[193] the expansion of FoxP3+ T helper cells,[194] and a role for the HLA haplotype 8.1 in additional case-control samples[176] and much larger population-based cohort.[175] In an emerging field as MC, the key question—what is the pathogenesis of MC—remains and the breakthrough study is yet to come.

In conclusion, MC is a multifactorial disease with insufficient research performed so far to address its pathogenesis. A big knowledge gap remains, which should be filled with high-quality research.

5. Research Agenda

This systematic review has revealed that knowledge gaps should be addressed by the following future research proposals: [a] microbiota's role, composition, and metabolic function in active, inactive, and treatment-naïve MC; [b] physical barriers in MC, and its regulation by iNOS and additional molecules; [c] cytokines that trigger and maintain subepithelial collagen deposition in CC; [d] anti-inflammatory mechanisms that block gene expression in MC to prevent IBD development; [e] dysmotility as potential cause of watery diarrhoea in MC patients; [f] genetic predisposition to MC, including large-scale genetic studies exploring genetic variation at

the whole-genome level and comparing CC and LC subtypes; [g] identification and impact of aquaporins blockers and stimulators on chronic diarrhoea.

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Conflict of Interest

All authors declare that there is no conflict of interest .

Author Contributions

YZ coordinated the systematic review. YZ, GT, EHH, KS-Z, GL, AEØ, WM, Md'A performed the systematic review and wrote the original manuscript. AA gave statistical support. YZ, EHH, KS-Z, GL, and AEØ designed the figures. KS-Z edited the figures. SM, AM, FF-B, and AJL performed a critical review of the manuscript, with important intellectual contribution. All authors approved the final version of the manuscript.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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