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REVIEW

Resolution of ulcerative colitis

Markus F. Neurath [1] · Moritz Leppkes [1]

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Abstract
Ulcerative colitis designates an idiopathic chronic inflammatory bowel disease leading to bloody diarrhea and inflammatory alterations mostly restricted to the large intestine. Many studies continue to unravel important aspects of its etiopathogenesis, and recent pharmaceutical developments broaden the arsenal of therapeutic opportunity. In this review, we delve into the cellular and molecular determinants of successful resolution of ulcerative colitis, describing novel insights in each of the phases of mucosal healing starting from damaging insults to the mucosa, epithelial restitution, and its adaption to inflammation as well as lymphocyte-driven maintenance and resolution of chronic inflammation. Additionally, molecular switches from inflammation to resolution are explored, paving the way for future avenues to resolve ulcerative colitis.

Keywords Ulcerative colitis · Resolution of inflammation · Intestine · Epithelium · Lymphocytes

Introduction

Ulcerative colitis typically affects the large intestine in a continuous fashion starting from the rectum possibly leading to pancolitis, a continuous inflammation of the whole large intestine [1] (Fig. 1). The patients may suffer from abdominal pain and bloody diarrhea as well as rectal excretion of mucus and pus. This may lead to up to more than ten bowel movements during flares of the disease, thus strongly affecting quality of life. Additionally, extraintestinal manifestations of the skin, liver, eyes, or joints may occur [2]. Complication of the disease may arise in the form of toxic megacolon, when inflammation impedes large bowel movement and induces extensive bowel extension and a systemic inflammatory response syndrome [3]. Moreover, long-standing inflammation may lead to fibrotic stenosis of the gut or colitis-associated malignancy [4]. For many years, a stepwise therapeutic approach has been implemented depending on the severity of the disease. Topical or systemic steroids or aminosalicylates are successful in many cases to reduce acute inflammation [5]. Additionally, immunosuppression by azathioprine or 6-mercaptopurin helps to maintain remission [6, 7]. Cyclosporin A or tacrolimus is used in acute steroid-refractory cases to induce remission [8]. A relevant number of patients fail classical therapies and require biological approaches including anti-TNF therapies (infliximab, adalimumab, or golimumab) [9] or anti-α4β7-integrin therapies targeting gut-specific lymphocyte trafficking (vedolizumab) [10]. The most recent addition to the medical management of ulcerative colitis is oral JAK inhibition by tofacitinib, which has been successfully introduced into clinical practice [11]. An anti-IL-12/23-directed therapy (ustekinumab) currently awaits FDA approval for its use in ulcerative colitis, while its use in Crohn's disease is already ongoing [12]. The defining features of disease are the result of a largely stereotypic pathogenesis in a wide variety of patients. Yet, the etiologic basis of disease stays unknown in most cases. Mostly, the initial insults to mucosal integrity remain unknown as well as their potential continued presence [13]. Even successful studies still show relatively low responder rates. This heterogeneity of clinical response to established therapies shows that there is still a dire medical need to advance the understanding of environmental mucosal irritants, to identify factors that hamper mucosal restitution and to improve the understanding of the cellular and molecular mechanisms of mucosal wound healing in

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✉ Markus F. Neurath
Markus.Neurath@uk-erlangen.de

Moritz Leppkes
Moritz.Leppkes@uk-erlangen.de

[1] Department of Medicine 1, Translational Research Center and Kussmaul Campus for Medical Research, Deutsches Zentrum Immuntherapie (DZI), University of Erlangen-Nürnberg, Erlangen, Germany

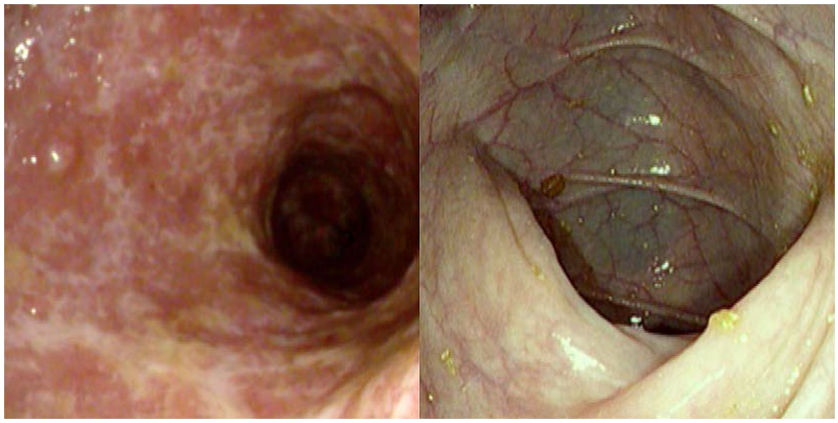

Fig. 1 The resolution of ulcerative colitis. Endoscopic pictures from the colon of a patient suffering from ulcerative colitis. Pictures before (left) and after (right) successful resolution of inflammation, 15 months after a change in treatment, are presented. Inflammatory changes of the mucosa include edema, erythema, fibrinous layers, and an altered vascularization (left). After resolution of inflammation, translucency of the mucosa is increased, edema and erythema vanished, and the vascular pattern normalized (right)

ulcerative colitis [14]. Apart from continuous exposure to pro-inflammatory factors, which might hamper mucosal healing, novel avenues of research have focused on mediators, which actively resolve inflammation [15]. Pro-resolving factors limit neutrophil influx, counterregulate chemokines and cytokines, reprogram myeloid cells to regulatory phenotypes, support egress of leukocytes, instruct suppressive immune cell populations, and guide tissue repair without fibrosis or scar formation [16]. In the following, we will describe phases of colonic mucosal healing in ulcerative colitis to systematically highlight novel and established elements in the resolution of inflammation in the context of this disease.

Insults

A rich microbial ecosystem is present in the intestinal lumen. This microbial ecosystem consists of bacterial, fungal, and viral elements. In some individuals, parasites and helminths populate the human gut. The intestinal microbiota is constantly challenged by various dietary factors. Constituents of the intestinal lumen may damage the mucosa in multiple ways: (I) pathogenic bacteria may outnumber the indigenous commensals; (II) the overall constitution or the metabolic balance of the microbiota may be altered (dysbiosis); (III) dietary factors could promote dysbiosis or (IV) harm the mucosa directly [17].

Under homeostatic conditions, a mucus barrier limits the interaction of the luminal microflora with epithelial cells. Disturbed mucus function has been observed in ulcerative colitis exemplified by a reduction in mucus glycosylation and sulfation [18–20], a decreased thickness of the mucus layers [21], increased mucinolytic properties of the feces [22], or a reduced bactericidal capacity of the mucus [23]. Areas of acute inflammation are mostly denuded of the mucus layer [21]. These alterations might facilitate flares of disease or simply complicate resolution of inflammation in affected patients. Mice defective in mucin-2, the major constituent of colonic mucus, demonstrate a strongly enhanced susceptibility to mucosal irritants [24]. Desai et al. nicely connected dietary fiber deprivation to increased mucus consumption by the commensal flora: In this study, mucus alterations facilitate increased bacterial invasion and a direct, potentially toxic, interaction of the microbiota with intestinal epithelial cells [25].

The intestinal epithelium may be harmed by physicochemical stressors directly, including radiation or medications. In the context of IBD, it is well-known that a damage induced by non-steroidal anti-inflammatory drugs such as ibuprofene may trigger a flare of the underlying immune-mediated disease [26]. Rodent models have characterized the role of many elements of the mucosal barrier using strong physicochemical stressors. These include direct chemical damage to the epithelium as in (I) acetic acid–induced colitis or (II) dextran sodium sulfate–induced colitis [27]. (III) Oxazoles activate epithelial IDO1, increase tryptophan-derived aryl hydrocarbon receptor ligands, and thus trigger epithelial damage and an inducible NK T cell response [28, 29]. (IV) Trinitrobenzoic acid is known as a haptenizing agent inducing colitis by eliciting immune responses, when bound to carrier proteins [30]. Furthermore, (V) pathogenic bacteria can severely damage the intestinal mucosa. The most common bacterial pathogens are pathogenic *E.coli* strains, *Salmonella*, *Clostridium difficile*, *Yersinia*, and *Shigella* [31]. Especially in the setting of ulcerative colitis, concomitant viral infection is observed: (VI) CMV enterocolitis may aggravate a preexisting ulcerative colitis leading to pathognomonic owl-eye inclusion bodies [32].

Coagulation and immunothrombosis

A damaging insult leads to areas of epithelial tears or areas of denuded epithelia. Such areas lack epithelia and mucus and are, thus, prone to microbial translocation. Secondary emergency barriers and a quick and timely epithelial restitution are needed. First, sites of mucosal damage may bleed, so coagulation takes place supported by plasmatic and cell-based mechanisms leading to a blood clot on the damaged mucosa. Neutrophils and other myeloid cells are consequently called to the site of injury as first responders [33]. Neutrophils act on the blood clot and replace the primary clot with a secondary whitish material consisting of live aggregated neutrophils, extracellular chromatin of dead neutrophils, and also designated neutrophil extracellular traps (NETs) and fibrin and thus form a fibrinoid layer [34, 35]. This fibrinoid layer is developing hours after the insult and is only removed once epithelial restitution was successful. The fibrinoid layer proteolytically degrades the blood clot and remaining tissue debris and provides a superficial border with powerful antimicrobial capacity to limit microbial influx and guide epithelial restitution on intact mesenchyme [36].

Epithelial restitution

Recent studies continue to explore the mechanisms of epithelial restitution: Breaches in the colonic epithelial barrier induce a defined cellular program in adjacent epithelial cells. These cells respond to altered cellular contact and local mediators including Wnt5a, TGF-β, and prostaglandin E2 to form wound-associated epithelia characterized by the expression of claudin-4, Dpcr1, and CD55b [37, 38]. Recently, Kaiko et al. demonstrated that reconstituting epithelia make use of tissue plasminogen activator expression (tPA) to activate plasminogen to plasmin [36]. This establishes two effects: On the one hand, it enables fibrinolysis at the edge of the fibrinoid cap by the restituting epithelial cells. On the other hand, activated plasmin achieves maturation of latent TGF-β to allow epithelial regeneration. Plasminogen activator inhibitor-1 (PAI-1) inhibits sufficient plasmin activation and its deficiency improves colonic wound healing [36]. Once an even sheath of epithelia has sealed the mucosal barrier, increased proliferation by neighboring crypts and crypt fission induced by Wnt5a furthers the regeneration of epithelial crypts in the injured area [37]. Increased proliferation of transit-amplifying cells in neighboring crypts is mediated in part by interferons via STAT1 [39, 40], interleukin-22 via STAT3 [41], and newly recognized cytokines of the IL-1 family such as IL-36 via MyD88 [42].

The intestinal epithelium is characterized by a high cellular turnover, even under homeostatic conditions. The increased proliferation induced by inflammatory states is paralleled by a state of energy deficiency in the intestinal epithelium [43]. Colonic epithelial cells have been shown to make use of short-chain fatty acids (SCFA), like butyrate, as energy substrate [44]. SCFA are catabolized via beta-oxidation, which partly takes place in mitochondria [45]. Indeed, multiple studies now suggest that the metabolism of colonic epithelial cells might be disturbed in the context of ulcerative colitis [46]. Luminal SCFA are produced by fermentation of dietary fiber by the intestinal microbiota. A lack of microbial fermentation products is most obvious in diversion colitis, in which surgical measures bypass the colon, leading to a reduction of the luminal microflora. Diversion colitis can be successfully treated by (smelly) butyrate enemas [47] or potentially coconut oil, which features rather short medium-chain fatty acids [48]. In ulcerative colitis, SCFA metabolism might be disturbed on multiple levels. Firstly, a lack of dietary fiber decreases the microbial production of SCFA [25]. Secondly, transcriptomic signatures [46], electron microscopy studies [49], and experimental models of colitis [50] suggest that mitochondrial morphology and function are disturbed in the context of ulcerative colitis. Improved understanding of the energetic demands of regenerating epithelia might substantially support mucosal healing.

It is likely that in active flares of ulcerative colitis, already this early phase of mucosal healing may be disturbed on multiple levels. Without successful epithelial restitution, resolution of inflammation cannot properly occur. The delicate process of epithelial restitution may be disturbed by continuous insults, insufficient immunothrombosis, and metabolic or regulatory deficits of regenerating epithelia (Fig. 2).

Microbial disturbance of epithelial regeneration

In the case of gastric ulcers, it is well known that microbial colonization with specific microbes sustains disease and inhibits mucosal healing. It is well established that *Helicobacter pylori* harbors a large number of virulence factors disturbing epithelial regeneration [51]. In the case of the extreme environmental conditions of the stomach, the luminal flora features limited diversity and *H. pylori* is one of few species capable of colonizing gastric ulcers. In ulcerative colitis, the colon harbors a plethora of microorganisms, which come into direct contact with ulcerated tissue and regenerating epithelia [52]. Many of the bacterial species and their respective virulence factors are not sufficiently characterized; thus, their influence on mucosal healing remains speculative. Recent years have seen a large expanse of studies on the intestinal microbiome in ulcerative colitis and other inflammatory bowel conditions [53, 54]. Specific changes associated with inflammation have been identified. Various reports have observed a reduced biodiversity, as well as a reduction in firmicutes and an expansion of gammaproteobacteria [55, 56]. For a more detailed description of the advances in microbiota research in the context of IBD, other current reviews are suggested [54, 57].

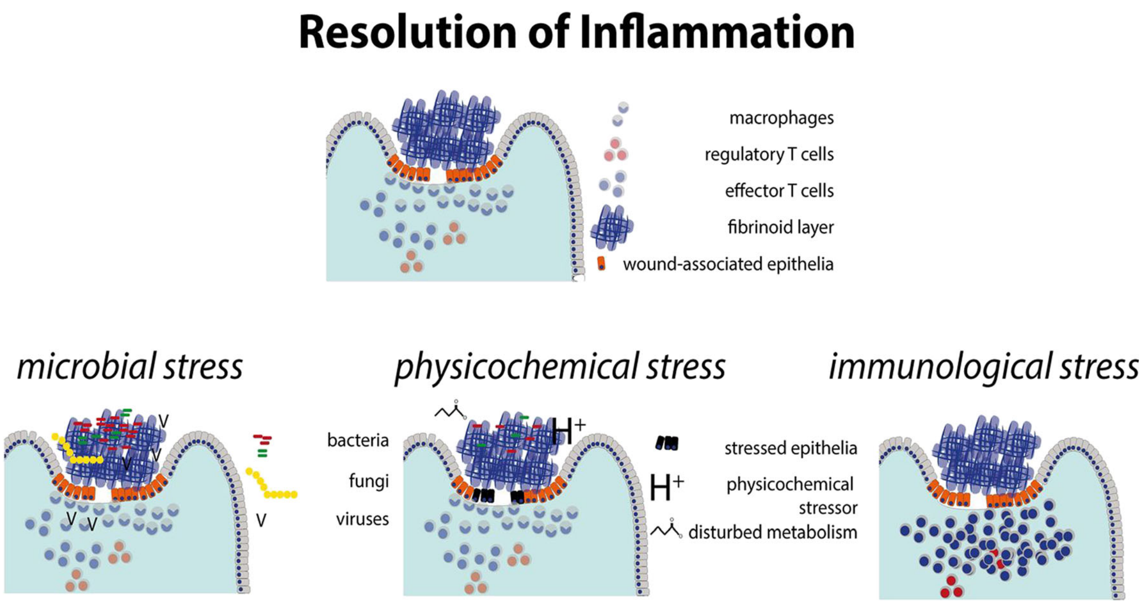

Fig. 2 Factors disturbing the resolution of ulcerative colitis. Ulcerative colitis is characterized by areas of denuded epithelia covered by fibrinoid layers and increased leukocytic infiltration. Epithelial restitution takes place derived from neighboring epithelia by the formation of specialized wound-associated epithelia. This epithelial restitution is the basis for a successful resolution of ulcerative colitis mediated by a plethora of metabolically related inflammatory mediators. Epithelial restitution is a delicate process possibly disturbed by microbial, physicochemical, or immune-mediated stress

Recent studies have addressed the role of the fungal composition in the course of IBD using sequencing technology. An increased fungal diversity was observed in IBD samples as compared with healthy controls [58]. Yeasts colonize gastrointestinal ulcers and *Candida* spp. are well known to cause esophagitis. It has been addressed in the past, whether *Candida* species can be detected in colonic ulcers. In one study, fungal colonization has been observed in up to 53% of colonic ulcers in ulcerative colitis [59]. However, the potentially pathogenic mycelia phase was never observed in these cases. Thus, fungal colonization rather than infection was observed whenever detected. Antifungal treatment has been used in experimental colitis models to functionally address the role of commensal fungal communities in mucosal wound healing: mice deficient in fungal immune recognition (Clec7a-deficient mice [60] and CX3CR1^{hi} mononuclear phagocyte–deficient mice [61]) suffer from increased severity of acute dextran sodium sulfate (DSS)–induced colitis in the presence of luminal commensal fungi. This increase in disease severity can be rescued by short-term treatment with fluconazole. This shows that, indeed, commensal fungal species may inhibit mucosal healing under specific circumstances. A long-term treatment with fluconazole, however, alters both the intestinal commensal fungal and bacterial communities and exacerbates acute DSS-induced colitis in wild-type mice [62]. In essence, it seems unlikely that yeast colonization has a significant impact on epithelial regeneration in the majority of cases in ulcerative colitis. Yeast infection, however, may also occur in UC patients in rare cases: In a recent case report, it was described, how, indeed, immune modulatory treatment of ulcerative colitis facilitated severe fatal fungal infection [63].

Inflammatory changes to the epithelium

In parallel to restitution of epithelial layer breaches, the inflamed mucosa undergoes structural changes after an inflammatory insult. The proliferation of the intestinal epithelium is enhanced leading to crypt elongation and, thus, a significant epithelial hyperplasia [64]. One important cytokine in this regard is interleukin-22, in part produced by T helper cells, innate lymphoid cells [65], and neutrophils [66]. IL-22 may induce proliferation of intestinal epithelial cells via STAT3 [41]. Additionally, antimicrobial properties of the regenerating epithelium are enhanced via induction of the antimicrobial peptides Reg-3β and Reg-3γ [67]. A T cell–derived IL-22 binding protein was shown to be expressed in the context of inflammatory bowel diseases and inhibited protective IL-22-mediated responses [68]. Blockade of STAT signaling is now achieved therapeutically using JAK1/3 inhibition by tofacitinib. This compound blocks various inflammatory cytokines including IL-6, IL-7, IL-10, IL-15, IL-21, IL-22, and IFN-γ among others and successfully treats active ulcerative colitis [11].

Under homeostatic conditions, goblet cells are a frequent cell type in the colonic epithelium. In ulcerative colitis, elongated crypts in inflamed areas typically show a loss of mucin and altered goblet morphology [69, 70]. In parasitic and helminth infections, cytokines of the type II immune response have been shown to regulate epithelial differentiation [71]. IL-4Rα and STAT6 are important to induce goblet cell hyperplasia in the small intestine [72]. Recently, IL-33 expression was observed in crypt-based subepithelial myofibroblasts. IL-33 can also influence epithelial differentiation and enhance secretory cell formation and epithelial hyperplasia [73], in part via IL-13 [74]. In ulcerative colitis, however, goblet cell loss is observed with underappreciated consequences for the restoration of the mucus barrier. This is apparently at odds with a proposed type II–biased immune response in ulcerative colitis [28]. Clearly, a more differentiated analysis of the temporal changes of epithelial morphology in ulcerative colitis is warranted [75].

Switching inflammation to resolution

Various mediators of diverse chemical nature decide the fate of inflammation. Many mediators of inflammation are metabolically linked and function as molecular switches between upholding inflammation versus its termination once the breach in mucosal integrity is closed. Many pro-inflammatory mediators are released as a consequence of cellular demise, subsumised with the term alarmins [76]: Dying cells release arachidonate-derived or polyunsaturated fatty acid–derived lipid mediators, adenosine trisphosphate, nuclear basic proteins with cytotoxic properties, proteases, and cytokines such as IL-1α or IL-33 among others.

Lipid mediators

A large variety of lipid mediators with divergent functions are derived from arachidonic acid. On the one hand, pro-inflammatory mediators are produced when cyclooxygenases (COX) mediate the formation of prostaglandins, and lipoxygenase activity leads to leukotrienes, which support acute inflammation in various ways. On the other hand, in later phases, lipoxins serve as pro-resolving mediators and occur as a consequence of 5-, 12-, or 15-lipoxygenase activities [15]. In the case of trinitrobenzene sulphonic acid–induced colitis, oral lipoxin A4 promoted the resolution of inflammation [77].

Similar to arachidonic acid, potent mediators of inflammation are also derived from omega-3 polyunsaturated fatty acids (PUFAs): resolvins, protectins, and maresins [78]. Resolvins of the D family are derived from docosahexaenoic acid (DHA), whereas the E series are metabolites of eicosapentaenoic acid (EPA). Protectin D1 (PD1) is a product of 15-LOX-mediated conversion of a PUFA substrate. Potent immunoregulatory actions of resolvins and protectins have been observed in vitro and in vivo: Administration of synthetic resolvin E1 reduced colitis-associated mortality and protected animals from weight loss and shortening of the colonic mucosa [79, 80]. Similarly, protectin $D1_{n\text{-}3\ DPA}$ and resolvin $D5_{n\text{-}3\ DPA}$ are mediators of mucosal protection as demonstrated in DSS-induced colitis [81]. Protective effects of maresin 1 have been observed in both DSS- and TNBS-induced colitis [82]. While an increasing number of pro-resolving lipid mediators are described, a conclusive picture regarding their relative contribution to the resolution of intestinal inflammation is lacking.

Purinergic signaling

Extracellular ATP is a well-studied mediator of inflammation. It is released from dying cells and can function on various immune cells. It was shown to increase adhesion of neutrophils, allow the (pyroptotic) release of inflammatory cytokines, activate the inflammasome [83], induce maturation of dendritic cells, or support the differentiation of IL-17-producing T helper cells [84]. Thus, extracellular ATP functions as an important mediator governing acute inflammatory responses [85]. However, ATP is biologically unstable and dissociates spontaneously and enzymatically via 5′-ectonucleotidases such as CD39 and CD73. The resulting adenosine functions in a more regulatory fashion allowing increased IL-10 release by macrophages, decreased expression of IL-12 or TNF, and decreased superoxide anion generation by neutrophils [86]. In the setting of colitis, pro-inflammatory effects of extracellular ATP signaling via P2X7 have been observed [87]: Supporting ATP degradation attenuated colitis, whereas blocking it exacerbated disease. Thus, extracellular ATP functions as a strong activator of colitis, whereas its metabolites support the resolution of colonic inflammation.

Arginine/NO

Another well-described molecular switch is determined by metabolites of arginine in the course of inflammation. Arginine can be metabolized to nitric oxide by various isoforms of nitric oxide synthases, which are either constitutively expressed or inducible upon inflammatory stress. NO can be cytotoxic in high concentrations and modulated vasodilation in inflammatory foci. On the other hand, arginases are capable of competing with nitric oxide synthases and limit substrate availability. Thus, arginase expression is considered an immunoregulatory pro-resolving tool. The hypothesis that L-arginine represents a key mediator in acute inflammation is corroborated by the finding that tissue L-arginine levels are inversely correlated with disease activity in ulcerative colitis [88]. The picture in experimental models is not unequivocal. In *Citrobacter rodentium*–induced colitis, a protective role of arginase has been observed: Arginase inhibition by S-(2-boronoethyl)-l-cysteine worsened the outcome of treated mice [89]. On the other hand, DSS-induced colitis was ameliorated by arginase inhibition via N(ω)-hydroxy-nor- arginine (nor-NOHA) [90].

Heme

Ulcerative colitis is characterized by repetitive mucosal bleeding. Thus, the ulcerated intestinal mucosa has to be equipped to break down coagulated blood. Interestingly, metabolites of hemoglobin-derived heme have recently been shown to impact the expression of the macrophage transcription factor Spi-C and to favor local immunoregulation [91]. These findings are corroborated by immune regulatory effects of carbon monoxide which are mediated by heme-oxygenase-1 [92].

Resolving lymphocytic inflammation

So far, this review focused on early phases of intestinal inflammation and mechanisms that govern acute flares of intestinal inflammation, when epithelial damage and neutrophil infiltration characterize the disease. While the antimicrobial properties of the mucus and epithelial-derived antimicrobial responses hold off the majority of luminal bacteria from entering the tissue, the mucosal adaptive immune system is vital to protect the body from pathogenic microorganisms. Pathogenic microorganisms are equipped with virulence factors to surpass these aforementioned innate defense mechanisms. Adaptive immunity, mainly performed by effector lymphocytes, provides tailored antigen-specific responses to rid the mucosa of invading microorganisms [93]. At the immunological synapse between antigen-presenting dendritic cells and T lymphocytes, co-stimulation with danger signals is needed to induce an effective adaptive immune response. Under homeostatic conditions, luminal antigens are presented to the adaptive immune system together with a paucity of danger signals. Thus, a tolerogenic response ensues [94]. In the setting of a breached barrier in ulcerative colitis, luminal antigens are presented in conjunction with strong stimulatory danger signals, and thus, inappropriately intense adaptive immune responses may be raised against typically non-pathogenic commensals or against inflammation-associated neoepitopes, including neutrophil cytoplasmic antigens [95]. The continued presence of these antigens, a dysregulated mucosal immunity and repetitive breaches in the epithelial barrier may, thus, form a vicious cycle to maintain chronic intestinal inflammation in the setting of ulcerative colitis. Therapies, which suppress T cell immunity, have been successfully used to maintain remission in this disease. Efforts in the last decades more closely defined effector mechanisms of T cell pathogenicity in ulcerative colitis, as well as properties and potential of regulatory T cell populations which limit disease. Much of these advances are deeply rooted in the use of experimental models of colitis [30]. Pathogenic T cell populations in ulcerative colitis are characterized by the expression of various effector cytokines. Th1/Th17 cells expand in the setting of IBD and express TNF-α, IFN-γ, IL-17A, and IL-17F. Their differentiation is directed by the transcription factors T-bet [96] and RORγt [64] and guided by the cytokines IL-12 and IL-23, respectively. IL-12 and IL-23 both share a common subunit p40 [12]. IL-9, partly derived from T helper cell populations, has pro-inflammatory effects in oxazolone-induced colitis [97]. Tissue retention of pro-inflammatory tissue-resident effector memory T cells is regulated by CD69 surface expression and controlled by the transcription factors Hobit and Blimp1 [98]. Effector T cell responses are controlled by regulatory T cell populations. There is ample evidence that Foxp3-positive regulatory T cells are capable of suppressing pathogenic effector T cell responses in the intestine [99]. Additionally, IL-10-expressing Tr1 cells can effectively resolve lymphocytic inflammation in the gut [100] as shown in the adoptive transfer model of colitis. Clinical studies are underway to analyze the efficacy of autologous ex vivo expanded regulatory T cells in ulcerative colitis [101, 102].

One of the most prominent histological features to distinguish ulcerative colitis from acute self-limiting colitis is the presence of plasmocytosis in proximity to the crypt base [103]. The functional role of these plasma cells has been difficult to address in animal models of colitis as this is not a typical feature in rodent models. In a case report, salvage therapy of severe ulcerative colitis using B cell–depleting rituximab apparently aggravated the course of the disease [104].

Conclusions

Resolution of inflammation is a complex biological process involving several phases. It encompasses the control of persistent insults to the damaged mucosa. For successful epithelial restitution, its metabolic requirements must be met and control of invading microorganisms must be achieved in part by structural and immunological adaption of the epithelium. Additionally, pro-inflammatory mediators of inflammation need to be balanced by active pro-resolving mediators supporting the orderly termination of inflammation and the return to tissue homeostasis. Failure of timely resolution may provide the basis for an aberrant lymphocyte-driven adaptive immune response capable of maintaining chronicity of IBD. The currently ongoing detailed study of these processes paves the way for future therapies in ulcerative colitis.

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Compliance with ethical standards

Conflict of interest M.F.N. has served as an advisor for Pentax, Giuliani, MSD, AbbVie, Janssen, Takeda, and Boehringer. M.L. has no conflict of interest to report.

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