Immunoregulatory Role of Myeloid-derived Cells in Inflammatory Bowel Disease

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Abstract: As the frontiers of immunological research expand, new insights into the pathogenesis of long poorly understood diseases, such as inflammatory bowel disease (IBD), are opening up new possible avenues for treatment. Myeloid-derived cells (i.e., monocytes, macrophages, neutrophils, and dendritic cells), long believed to be effector cells driving the initiation of inflammation, have been increasingly shown to have immunoregulatory effects previously underappreciated. Dysfunction in the immunoregulatory roles of these cells may play a part in the pathogenesis of a subset of patients with IBD. The role of myeloid-derived suppressor cells, initially described in cancer, have been shown to play an important role in the balancing of effector and regulatory T cells in inflammation as well, and their role in IBD is also explored. The potential for future cell-based therapies for IBD is enhanced by the advances being made in the understanding of the innate immune system in the intestine.

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Inflammatory bowel disease (IBD), comprised of Crohn's disease and ulcerative colitis (UC), is a chronic relapsing disease and is a manifestation of a dysregulated immune response against the microorganisms of the intestinal flora in genetically susceptible individuals.[1] Although the exact cause of IBD remains unknown, new pathogenic paradigms in IBD have highlighted that the interactions between various constituents of the innate and adaptive immune systems play key roles in the pathogenesis of IBD.[2] The review article will provide an overview of new insights into the immunoregulatory role of myeloid-derived cells (including monocytes, macrophages, myeloid-derived suppressor cells [MDSCs], neutrophils, and dendritic cells [DCs]) and the innate immune system in human IBD and animal models of colitis. Emerging evidence suggests an important protective role of these cells and possible homeostatic mechanisms to restrain acute and chronic intestinal inflammation. We will also discuss the relevance of understanding the contribution of myelopoietic responses for the development of future (cell-based) IBD therapies.

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MONOCYTES

Recent developments in the immunology and genetics of mucosal diseases suggest that monocytes and their derivative cells play an important role in the pathophysiology of IBD.[3] Intestinal macrophages derived from blood monocytes play a key role in sustaining the innate immune homeostasis in the intestine, suggesting that the monocyte/macrophage compartment might be an attractive therapeutic target for the management of IBD. After differentiation from myelomonocytic stem cells in the bone marrow, monocytes move into the bloodstream and from there differentiate into different subsets, comprising different functions. After trafficking to the intestines, monocyte subsets differentiate into macrophages and DCs. There is growing evidence that monocytes themselves not only demonstrate effector (proinflammatory) functions but also have inflammation-resolution functions, namely regarding tissue repair, immunomodulatory cytokine production, and in modulation of T-cell phenotype. Perhaps most interesting, from an IBD point of view, is the recent evidence of the induction of a regulatory monocyte phenotype under the influence of granulocyte macrophage colony-stimulating factor (GM-CSF) and glucocorticoids (GCs).

Murai et al[4] showed that in mice with experimental colitis, intestinal lamina propria mononuclear phagocytes produce anti-inflammatory interleukin (IL)-10, which act on forkhead box P3-positive (FoxP3$^+$) regulatory T cells (Tregs) in vivo to suppress colitis. Bain et al have shown through adoptive transfer of normally proinflammatory Ly6C$^+$ monocytes into *C-C chemokine receptor type 2* (*Ccr2*)–deficient mice (which have a selective defect in circulating Ly6C$^+$ monocytes) that there is a colonic in situ incremental change in the phenotype of newly arrived Ly6C$^+$ monocytes, with an increase in IL-10 production, loss of proinflammatory features, and desensitization to Toll-like

receptor (TLR) ligands. These Ly6C$^+$ monocytes differentiate into anti-inflammatory CX3C chemokine receptor 1 (CX3CR1)$^+$-resident macrophages through multiple transitional stages. Interestingly, in an inflamed colon, there seems to be a deviation in this differentiation to more TLR-responsive inflammatory CX3CR1^{int} macrophages.[5] Nevertheless, it should be noted that previous work has pointed towards a distinct subset of monocytes being the source of inflammatory macrophages in the intestine,[6] and more research to clarify this will be needed. Rivollier et al[7] had previously obtained very similar results and demonstrated the ability of Ly6C$^+$ cells to differentiate into both regulatory and proinflammatory populations. Although there was agreement that Ly6C$^+$ monocytes differentiated into regulatory macrophages in the colon, there was disagreement on whether the proinflammatory offspring were macrophages or DCs.[5,7] It is nevertheless suggested that the recruitment of newly arrived monocytes in the inflamed colon, which then differentiate into inflammatory macrophages are dependent on CCR2, an interesting potential target for the treatment of IBD.[6]

More recently, Grainger et al[8] have addressed the question of how the host regulates commensal-driven inflammation while under mucosal attack by a pathogen. This is a particularly important question to resolve given the long-held paradigm of IBD being an aberrant immune response to normally nonpathogenic commensals present in the fecal microbiota. Given the disruption of the intestinal epithelial barrier seen in both IBD and in infective enterocolitis, the ability of the innate immune system to differentiate between pathogen and commensal in an environment such as the gut is surely likely to yield important insights especially relevant to IBD. Ly6C$^+$ monocyte-derived prostaglandin E_2 (PGE_2) directly limits activation of neutrophils in a *Toxoplasma gondii*–infected mouse model. In fact, although all Ly6C$^+$ monocytes (such as those isolated from the spleen and gut) produced tumor necrosis factor alpha (TNF-α) during the acute phase of the infection, only Ly6C$^+$ monocytes located in the gut also produced PGE_2 and IL-10, which the authors suggested as showing a mixed phenotype of both inflammatory and regulatory features. Isolating the spleen monocytes and exposing them to a commensal-derived lysate caused them to upregulate PGE_2 and IL-10 suggesting that it is the exposure to the commensal intestinal milieu that triggers the regulatory functions of Ly6C$^+$ monocytes. In addition, limiting the accumulation of Ly6C$^+$ monocytes in *Ccr2*-deficient mice before the uncontrolled parasite expansion normally seen in previous studies with these mice led to a marked increase in neutrophil activation supporting the idea of mucosal Ly6C$^+$ monocytes limiting neutrophil activation. The use of selective blocking antibodies or inhibitors targeting other potential mediators (such as IL-10, transforming growth factor beta [TGF-β], IL-27, and adenosine) and the treatment of Ly6C$^+$ monocytes with a cyclooxygenase (COX)-1 and COX-2 inhibitor (indomethacin), which are the rate-limiting steps in PGE_2 synthesis, reversed the immunosuppressive phenotype of these monocytes. Thus, it is indeed likely that PGE_2 is a mediator in suppressing neutrophil effector function in vitro—an interesting finding, given the known clinical observation of COX-inhibitors being contraindicated in IBD due to their potential to initiate or potentiate a flare.

There is evidence that Gr1$^-$/Ly6C$^-$ monocytes are involved in tissue repair, namely through accumulation of myofibroblasts, angiogenesis, and deposition of collagen, and that they also express vascular endothelial growth factor at least in the injured myocardium.[9] Gr1$^-$/Ly6C$^-$ monocytes have been observed through intravital microscopy to crawl quite long distances along the luminal surfaces of blood vessels[10] and to enter the ischemic myocardium in quite a late phase,[9] adding to the evidence for their potential role in tissue repair. Indeed, Gr1$^-$/Ly6C$^-$ monocytes display a transcriptional profile reported to be similar to M2 macrophages,[11] which are believed to participate in tissue repair.[12]

Ehrchen et al[13] showed through microarray technology that GC-stimulated monocytes display increased transcription of genes relating to migration to inflammatory tissues, increased phagocytosis of proinflammatory agents, production of anti-inflammatory and antioxidant mediators, and increased longevity. These effects were subsequently confirmed by flow cytometry and real-time PCR, and independent functional assays confirmed these effects in GC-induced monocytes. Interestingly, genes, which are known to be upregulated by interferon gamma (IFN-γ), were downregulated after GC stimulation. In addition, genes with known anti-inflammatory functions were upregulated by GC stimulation (including IL-10, CD163, and IL-1 receptor type II). These effects are completely different from that induced by IL-10.[14] Indeed, the anti-inflammatory cytokines IL-4, IL-6 and IL-10 have either less or different anti-inflammatory effects on monocytes although there seems to be a potentiation effect seen when IL-6 or IL-10 is added to GC-induced monocytes mainly through enhanced survival.[15] Treatment of mouse monocytes with GC significantly improves the ability of these cells to interact with T cells. GC-stimulated monocytes (GCsMs) were found to be potent suppressors of both activated CD4$^+$ and CD8$^+$ T cells in vitro by reducing their proliferation. This was further confirmed when adoptive transfer of GCsMs was found to cure experimental T-cell–mediated colitis. In addition, GCsMs drive the induction of Tregs in vitro and in the colon of GCsMs-treated mice with experimental colitis. Also noted was that after transfer of GCsMs, there was a change in the cytokine pattern released by mucosal lamina propria, mesenteric lymph nodes (MLNs), and splenic T cells. Specifically, there was suppression of IFN-γ and IL-17 production by T cells in the MLNs and spleen, which correlated with the clinical response. Note that GCsMs express CD11b, Gr1 (Ly6C/G), and CD124 (IL-4Rα-chain),[16] as do MDSCs, which are known to be a potent suppressor of T-cell activation (discussed in detail in the Myeloid-derived Suppressor Cells section). Indeed, in vitro, GCsMs were shown to inhibit activation of naive T cells. The exact mechanism remains unknown; however it is interesting that GCsMs exert their inhibitory effects on T cells far more efficiently than Tregs with a 10:1 ratio (T cell/monocyte) for GCsMs compared with a 2:1 ratio (T cell/Treg).[17]

There is growing evidence that GM-CSF, or rather, the lack-thereof, is implicated in the pathogenesis of IBD (reviewed in Refs. 18,19). Human and murine studies showed that GM-CSF exerts beneficial effects in intestinal inflammation. To explore whether GM-CSF mediates its effects through myeloid regulatory cells, Däbritz et al[20] analyzed effects of GM-CSF on monocytes from humans (patients with IBD and healthy controls) and mice in vitro and assessed the immunomodulatory potential of GM-CSF–activated monocytes (GMaM) in experimental colitis models in vivo. They show that (1) GM-CSF provokes nonclassical monocyte activation, (2) drives monocytes towards an anti-inflammatory phenotype, (3) enhances innate immune functions (e.g., migration, chemotaxis, and oxidative burst), and (4) primes monocyte responses to secondary microbial stimuli in vitro. Additionally, GMaM accelerate epithelial healing in vitro. GMaM showed therapeutic activity in vivo and protected *Rag1*$^{-/-}$ mice from T-cell–induced experimental colitis. This was accompanied by accelerated gut homing of GMaM and increased production of IL-4, IL-10, IL-13 and decreased production of IFN-γ in lamina propria mononuclear cells in vivo. Confirming this finding, GMaM attract T cells and shape their differentiation towards T helper 2 (Th2) cells by upregulating T-cell–derived IL-4, IL-10, and IL-13 in vitro. In addition, cocultures of GMaM and naive T cells led to an induction of Tregs. In agreement with this, Kurmaeva et al[21] had shown that CD11b^{+}Ly6c^{+} immunosuppressive monocyte-derived cells expand during experimental colitis in mice and inhibit Th1 responses but enhance generation of Tregs. Thus, beneficial effects of GM-CSF in IBD may possibly be mediated through reprogramming of monocytes to simultaneously improved bacterial clearance and induction of wound healing, as well as regulation of adaptive immunity to limit excessive inflammation. These findings support the exploration of stimulating rather than suppressive therapies for patients with IBD and underpin that myeloid-derived cells might become a promising novel cell-based therapeutic option.

MACROPHAGES

It is clear that macrophages contribute to healing during the resolution stage of inflammation by removal of cellular debris and remnants of apoptotic cells[22]; however, this review article will focus only on the specific immunoregulatory roles of macrophages. Macrophages are located throughout the gut mucosa and mostly in the lamina propria in the entire gastrointestinal tract.[23] The nomenclature of macrophages, in particular, has been controversial and somewhat problematic given the spectrum of markers and stimulation conditions in use in experiments and their spectrum of activity.[24] As the field develops, it is hoped that a *lingua franca* will also be developed.

There is some evidence that the selective elimination of DCs and macrophages leads to a worsening of chemically induced dextran sulfate sodium (DSS) colitis, which has been suggested as being evidence for the protective role of mononuclear phagocytes in colitis.[25] However, in models where the epithelial barrier of the gut is breached, it is unclear whether the worsening of colitis in macrophage-depleted mice is due rather to the lack of required phagocytic bacterial and debris clearance or a fallback to more tissue-destructive innate defense (such as neutrophil accumulation and activation) versus any specific immunosuppressive effects of the mononuclear phagocytes themselves. Nevertheless, there is a large body of evidence that macrophages do have specific immunosuppressive functions. Certainly, in vitro activation of macrophages with GCs ± TGF-β, IL-10, certain immune complexes, and IL-4 can lead to degrees of immunosuppressive phenotypes.[24] For example, it is known that IL-4–treated murine macrophages will have upregulated expression of programmed death ligand 2 (prevents T-cell expansion) and arginase 1 (competitive inhibitor of inducible nitric oxide synthase [iNOS]).[26] However, the full scope of macrophage phenotypes in all tissues is beyond the scope of this review article; so, we will focus on their possible relationship to IBD.

The factors determining the differentiation and function of macrophages into pro- or anti-inflammatory phenotypes in the gut are being elucidated. TGF-β seems to be nonredundant with macrophage-specific TGF-β hyporesponsiveness showing exacerbated gut immunopathology in a DSS-induced mouse model, although whether this effect was at least partially explained by impaired IL-10 production is unclear, given that TGF-β induces macrophages to produce IL-10.[27] Hematopoietic cells mainly sense IL-10 by the dedicated IL-10 binding chain (IL-10Rα) and an accessory molecule (IL-10Rβ) shared with others in the IL-10 superfamily, including IL-22, IL-26 and IFN-γ.[28] Shouval et al[29] showed that IL-10 and IL-10R are integral factors in this for both bone marrow-derived and intestinal macrophages, and this is backed up by noting that there is impairment in the differentiation and function of pro- and anti-inflammatory phenotypes from monocyte-derived macrophages isolated from humans with loss of function mutations in IL-10RA and IL10-RB and early onset IBD, as well as diminished IL-10 expression and decreased generation of Tregs. In addition, the critical role that IL-10R signaling plays in regulating intestinal mucosal homeostasis was shown through the development of colitis after transfer of CD4^{+} T cells in mice with loss of IL-10R–dependent signaling. Shouval et al showed that in *IL10-rb*$^{-/-}$ mice, innate immune cells transmit a colitogenic signal to wild-type (WT) CD4^{+} T cells, and that loss of IL-10R signaling leads to exaggerated proinflammatory cytokine responses by innate immune cells. To summarize, they demonstrated that (1) the loss of IL-10R signaling on innate cells impairs these cells' cross talk with T cells leading to severe colitis; (2) IL-10R signaling suppresses the development of proinflammatory macrophages and facilitates not only the generation of anti-inflammatory intestinal macrophages but also their production of IL-10; and (3) the function and generation of WT Tregs are impaired in vivo with loss of IL-10Rβ signaling. Production of IL-10 in the gut is usually by B cells, T cells, macrophages, and probably some nonhematopoietic cells.[30] Murai et al have shown that IL-10 secretion from CD11b^{+} cells (likely macrophages given their expression of F4/80), rather than IL-10 secretion from Tregs

themselves, act in a paracrine manner to maintain FoxP3 expression of Tregs, whereas Zigmond et al found that loss of IL-10 secretion specifically from macrophages did not affect the gut homeostasis or Treg maintenance in the mouse.[4,31] Interestingly, they also found that the loss of macrophage-restricted IL-10Rα led to a spontaneous and severe colitis. However, one potential pitfall the authors identified in this study is that although they used a transgenic *Cx3cr1*^{cre} system to restrict the effects to the mouse macrophages, intestinal DCs would also be partially affected. Nevertheless, given the results of this study, the likelihood is that CX3CR1^{+} intestinal macrophages are crucial in the development of this type of colitis, and that an inability to sense IL-10 leads these macrophages to fail to develop an anti-inflammatory gene signature. In contrast, Li et al[32] also developed mice with a macrophage-selective deletion of IL-10Rα; however, these mice did not develop spontaneous colitis and required DSS administration for induction of colitis. It is unclear whether the difference was due to the mice in the two centers being housed in different specific pathogen-free environments (*Helicobacter* spp). We know that WT mice that do not bear *Helicobacter hepaticus* also do not develop a spontaneous colitis with antibody-mediated IL-10R blockage but that mice with this species do.[33] Nevertheless, Li et al found similar results using the DSS-induced colitis model, suggesting that the actions of IL-10 are predominant as a result of macrophage-specific effects. Interestingly, they reported that down-regulation of nitrite oxide and reactive oxygen species (ROS) were of central importance to the immunosuppressive functions of the IL-10–stimulated intestinal macrophages. Murai et al[4] also showed that CD11c^{+}CD11b^{+}F4/80^{+} cells are able to prevent the instigation of colitis after the adoptive transfer of CD4^{+}CD45RB^{+} T cells through their IL-10 production. Indeed, it has been shown in vivo that Tregs generation and expansion can be induced by CX3CR1^{+} intestinal macrophages.[34,35] This likely occurs locally in the intestinal mucosa rather than the MLNs,[35] as CX3CR1^{+} macrophages lack the ability to migrate due to their lack of expression of CCR7,[36,37] which is required for tissue egress.[38] In addition, IFN-γ–treated macrophages were shown to regulate CD4^{+} T-cell activation because of the induction of Tregs.[39]

The current M1/M2 macrophage paradigm does not seem to translate readily into gut macrophages: like M2 macrophages, they express CD206, CD163 and produce IL-10; but like M1 macrophages, they do not express arginase but express high levels of major histocompatibility complex class II molecules (MHCII) and produce TNFα.[23] There are also several differences between gut and nongut macrophages, including that CX3CR1^{+} macrophages in the intestinal lamina propria are relatively short lived with a 3-week half life[40]; another being the lack of a proinflammatory response upon exposure to bacteria or their products despite remaining avidly phagocytic and bactericidal.[41] This anergy is acquired during their maturation process from monocytes with intestinal macrophages downregulating TLR signaling molecules, such as TNF receptor-associated factor 6 (TRAF6) and myeloid differentiation primary response gene 88 (MyD88),[42] and upgregulating negative TLR and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB)–signaling regulators like the ubiquitin-modifying enzyme A20 and interleukin-1 receptor-associated kinase–M.[37] Their role in the noninflamed intestinal mucosa may be as an antigen-presenting cell, given their expression of major histocompatibility complex class II molecules and phagocytic abilities, given there is evidence that the mucosal cells that are known to sample luminal contents by transepithelial dendrites (originally believed to be DCs) are in fact CX3CR1^{+} macrophages and their ability to sustain local Tregs and facilitate their secondary expansion.[23] It seems that the gut resident macrophages maintain their immunoregulatory phenotype even in the inflamed colon in contrast to newly arrived monocyte-derived CX3CR1^{int} macrophages, which accumulate during colitis and have enhanced TLR responsiveness and express iNOS and TNFα.[43]

The in vivo local environment seems to be of utmost importance in shaping the phenotype of macrophages in the gut although the factors shaping intestinal mucosal macrophages to act in an inflammatory or immunosuppressive fashion remain to be elucidated. One recently discovered potential factor with a contribution to modulating intestinal mucosal macrophage phenotype is chemerin. Originally believed to be a chemoattractant protein involved with DCs or natural killer cells, in recent years, this protein has been shown to act on inflammation in either an anti- or pro-inflammatory fashion depending on the disease model.[44] Lin et al[44] were able to show that in a DSS-induced colitis model chemerin acted to potentiate inflammation, predominantly through the modulation of macrophage function away from the M2 type. The chemerin receptor, chemokine like receptor 1 (CMKLR1), is expressed on macrophages but has not been detected on neutrophils and inflammatory DCs.[45] Chemerin has been found to be elevated in the blood of patients with IBD,[46] in the colon of mice with DSS-induced colitis,[44] and chemerin mRNA expression was found to be elevated in the biopsies taken from human patients with UC. Interestingly, there was a significant difference found in the chemerin mRNA expression in the areas of inflammation versus macroscopically normal areas of the patients with UC. Lin et al found that although exogenous chemerin administered in the DSS colitis model had no effect on the proportion and magnitude of leukocytes in the colons nor on the secretion of proinflammatory cytokines, it did significantly decrease the expression of M2-associated genes. This effect was further confirmed after the administration of chemerin antibody (ChAb) in vivo with a significant improvement in histopathology from the colitic mice; again, the proportion of leukocytes in these colons remained unchanged. However, the clinical manifestations were not significantly different after ChAb administration, which is a limitation in this study; nevertheless, these results do suggest a role of chemerin in colitis through the shaping of macrophage phenotypes.

It has also been shown that in active IBD, there is a decrease in the production of IL-25, a constitutively produced cytokine, which has been shown in the gut to inhibit both IL-12 and

Th1-cell–driven inflammation,[47] although the exact mechanism remains elusive. Nevertheless, both macrophages and monocytes express functional IL-25 receptors, and there is some emerging evidence (1) that in vivo administration of IL-25 induces at least increased mRNA expression of arginase 1 (Arg1), found in inflammatory zone protein 1 (Fizz1) and chitinase-like 3 (Chil3, also known as Ym1) in macrophages, all of which have been associated with the immunoregulatory macrophage phenotype and (2) that transfer of IL-25–induced macrophages led to attenuation of murine colitis with concomitant reduction in IL-12, IL-6, TNF-α, and iNOS.[47,48]

Macrophages likely exert their anti-inflammatory effects through other modalities too. Certain anti-inflammatory lipid mediators, such as arachidonate 15-lipoxygenase and COX1, are upregulated in M2-like macrophages.[49] There is some evidence that colonic upregulation of ceruloplasmin, an acute-phase protein with ferroxidase properties, which limit ferrous ion-mediated production of ROS produced by macrophages also acts locally as an antioxidant to limit local tissue damage.[50] In the mouse, there is a critical role for ARG-1 in macrophage-mediated protection from colitis likely due to the competition between ARG-1 and iNOS for their common substrate, L-arginine, given that nitrite oxide is proinflammatory.[51] It also seems that some of the reported health benefits of helminth infection, such as improvement in airways hypersensitivity, allergy, and IBD, might be related to the stimulation of M2-like gut macrophages. Hunter et al[52] found that mice infected with the tapeworm *Hymenolepis diminuta* were protected from experimental colitis that they had increased IL-10 production and that there was increased mRNA expression for CD14, Arg-1, and Fizz1. It is speculated that the helminthes uses the ability of macrophages to develop an immunoregulatory phenotype to its survival advantage likely through its stimulation of IL-4 and IL-13. Interestingly, another study, while also showing that helminth infection confers protection from experimental colitis (DSS colitis infected with *Schistosoma mansoni*), found the protective effect to be due to induction of F4/80$^+$CD11b$^+$CD11c$^-$ macrophages.[53] Ziegler et al[54] identified a novel specific suppressive/regulatory macrophage population induced by a single parasite immunomodulator, which protects against mucosal inflammation in experimentally induced colitis and instructs IL-10 in CD4$^+$ T cells.

From a clinical perspective, it is also interesting that there is some in vitro and also in vivo evidence in patients with IBD that the anti-TNF-α agents (i.e., infliximab and adalimumab) that have revolutionized IBD treatment since the 1990s might owe at least some of their effect to the induction of immunoregulatory macrophages.[55,56] This is triggered by binding of anti-TNF-α to the membrane-bound TNF-α of activated T cells and with costimulation through the Fc receptor of a monocyte/macrophage antigen-presenting cell. This macrophage then produces IL-10, inhibits proliferation of activated T cells, and expresses CD206 (mannose receptor),[56] which is a commonly used marker for alternatively activated (M2) macrophages.[23]

MYELOID-DERIVED SUPPRESSOR CELLS

Growing evidence mounts on the role of MDSCs on colitis.[57] MDSCs are a phenotypically heterogenous myeloid-derived group of cells with a common biological activity, which includes potent suppression of various T-cell functions, increased production of ROS and reactive nitrogen species, and ARG1.

MDSCs have a phenotype in mice of CD11b$^+$Gr1$^+$ and in humans of LIN$^-$HLA-DR$^-$CD33$^+$ or CD11b$^+$CD14$^-$CD33$^+$. There is no human marker homologous to Gr1, and the phenotype of MDSCs in cancer can be quite diverse. In the steady state, MDSCs are not or only minimally present in lymphoid tissues; but in certain pathological conditions (notably cancer), MDSCs are found to a much greater extent in lymphoid tissues in response to several cytokines and growth factors and have low expression of F4/80 (as opposed to tumor-associated macrophages).[58,59] It is important to note, in terms of comparison of studies, that Ly6C and Ly6G are separate epitopes of Gr1, and indeed, they represent separate MDSC subsets: granulocytic MDSCs are Ly6G$^+$ and monocytic MDSCs are Ly6C$^+$.[58] Granulocytic MDSCs predominantly suppress CD8$^+$ T cells through ROS production and monocytic MDSCs through ARG1 enzyme production and NOS (reviewed in Ref. 59). Several other subsets of MDSCs have been found based on surface markers.[60]

Apart from suppression of T-cell function, MDSCs also appear to have the ability to promote the de novo development of Tregs in vivo in an IFN-γ and IL-10–dependent manner.[61,62] Other autoimmune models have added to our understanding of MDSCs beyond cancer, where it has been the focus of intense scrutiny. Immunosuppressive MDSCs have been found in autoimmunity, trauma, infection, and hypersensitivity reactions (reviewed in Ref. 57). Interestingly, it seems that CD4$^+$ T cells and IFN-γ are important for the accumulation of MDSCs in a model of autoimmune hepatitis with depletion of CD4$^+$ T cells or genetic ablation of IFN-γ decreasing the numbers of MDSCs.[63]

The mechanisms through which MDSCs exert their immunomodulatory effects in association with tumors have been recently been summarized.[59] Broadly, there are 4 main mechanisms that are relevant: (1) depletion of nutrients required by lymphocytes, such as L-arginine and L-cysteine, leading to down-regulation of the ζ chain in the T-cell receptor complex and subsequent arrest of antigen-activated T-cell proliferation; (2) oxygen stress generation leading to loss of T-cell receptor ζ-chain expression and interference with IL-12 receptor signaling and desensitization of the T-cell receptor; (3) interference with lymphocyte trafficking and viability; and (4) activation of Tregs. It has also been shown that IFN-γ upregulates genes involved in production of iNOS and ARG1, which are intimately involved in the immunosuppressive functions of MDSCs.[60] Other studies have shown that neutralizing IFN-γ abrogated the ability of MDSCs to suppress T-cell proliferation.[60,63–65] Indeed, the contribution of IFN-γ towards MDSC accumulation can be construed as being surprising given the large body of evidence linking the pathogenic role of Th1 cells to IBD.[2] There is also evidence that

MDSCs are able to switch macrophages from proinflammatory M1 to an anti-inflammatory M2 phenotype at least in cancer by inducing lower IL-12 production in macrophages and upregulating their own production of IL-10 in response to signals from macrophages.[66,67] Also, it seems that a subset of monocytic MDSCs are progenitors of $CD11b^+Gr1^-Ly6G^-F4/80^+MHC\text{-}II^+$ macrophages, which have quite potent immunosuppressive properties.[59]

Using a $CD8^+$ T-cell–mediated mouse model of IBD, Haile et al showed that repetitive transfer of $CD8^+$ T cells specific for a model antigen expressed in enterocytes leads to an increase in the frequency of $Gr1^+CD11b^+$ MDSCs in spleen and MLNs. MDSCs inhibited IFN-γ release by T cells and thus T-cell–mediated intestinal injury and protected mice from T-cell–mediated chronic enterocolitis, whereas depletion of Tregs had no effect on the induction of colitis. In addition, they showed an increase in ARG1-expressing MDSCs with immunosuppressive function in the peripheral blood from patients with IBD.[68] The immunosuppressive role of MDSCs was also shown in murine 2,4,6-trinitro benzene sulfonic acid (TNBS)–induced colitis with evidence that MDSCs are correlated with intestinal inflammation, and that adoptive transfer of MDSCs isolated from the spleen of mice with TNBS-induced colitis were able to ameliorate intestinal inflammation in naive mice who were then challenged with TNBS.[69] This correlated with decreased levels of TNFα, IFN-γ, and IL-17 as compared with control mice that were injected with saline instead. Also, this group showed that MDSCs could be induced in vitro by coculturing with hepatic stellate cells, and that the intravascular administration of these MDSCs also led to amelioration of murine colitis. Su et al[70] had similar results in a TNBS-induced murine model but specifically showed the colitis-amelioration effects of granulocytic MDSCs. They also showed that the transferred MDSCs predominantly localized not only to the colon but also specifically to the inflamed areas of the colons (as well as liver and spleen) through the use of sex cross-transplantation and subsequent Y chromosome staining. This demonstrates the in vivo tendency of these cells to accumulate at sites of active inflammation.

The evidence for a potentially important role of MDSCs in chronic colitis was elaborated in experiments on LysMcre/$Stat3^{flox/-}$ mice, which have a targeted knockout of the signal transducer and activator of transcription 3 (STAT3) gene in myeloid cells only.[71] Whereas the majority of factors known to trigger MDSC expansion seem to converge on the activation of Janus kinase (JAK) protein family members and STAT3, the latter is arguably the main transcription factor.[72] STAT3 is a cytoplasmic downstream transcription factor for the IL-6 family of cytokines, granulocyte colony-stimulating factor receptor, and IL-10 receptor. LysMcre/$Stat3^{flox/-}$ mice spontaneously develop T-cell–mediated colitis, unless they are crossed with $Rag1^{-/-}$ mice.[73] This suggests that myeloid–lymphocyte interaction is the critical point in the spontaneous development of chronic colitis in these mice. Note that in this study, the clinical outcome of DSS-induced acute colitis was similar to that seen in WT mice. Nevertheless, $CD11b^+Gr1^+$ cells have been shown to be upregulated in the spleen of DSS-induced colitic mice.[74] Anti-Gr1 treatment led to exacerbation of colitis in these mice demonstrating the immunosuppressive effects of these cells. Adoptive transfer of $CD11b^+Gr1^+$ cells, harvested from mice previously treated for 5 days with DSS, are able to alleviate the disease parameters of colitis in mice treated with DSS if given in the early phase of disease induction.[75]

The specific factors that recruit MDSCs to the inflamed colon are yet to be ascertained. Oh et al had compared 3 mouse models of colitis, one of which was using a caspase-1 knockout mouse. Caspase-1 is involved in the final step of inflammasome activation, which leads to the cleavage of the inactive pro-IL-1β to the active form, IL-1β. They found that despite TNBS challenge, *caspase-1*$^{-/-}$ mice did not have a significant increase in MDSCs ($CD11b^+Gr1^+$ cells) in the lamina propria or Peyer's patches.[76] The authors suggest that IL-1β might be involved potentially corroborating the results that Tu et al[77] saw in gastric inflammation and cancer, which found that IL-1β was correlated with early recruitment of MDSCs. However, it remains unclear whether MDSC recruitment is due to a factor further downstream in the intestinal inflammation cascade than the inflammasome and IL-1β, given that caspase-1 knockout mice also did not show the massive bowel edema and disruption of epithelial cells seen in the other colitis models and was accompanied by an increase in the number of Tregs. Zhang et al[78] however, were able to show an expansion of MDSCs in a colitis model (using WT and *protein tyrosine phosphatase 1B* (PTP1B) null mice) concomitant with decreased inflammation. Recent studies have suggested that inhibition of PTP1B can lead to an amelioration of obesity-associated inflammation, and PTP1B is known to be expressed in immune cells and is a major negative regulator of leptin receptor-associated JAK2.[79–81] Recall that JAK protein family members are known to be a factor that triggers MDSC expansion. *PTP1B*$^{-/-}$ mice were more resistant to DSS-induced colitis and showed a clinical response that was less severe. Indeed, the serum levels of proinflammatory cytokines (including IL-17, TNFα, IL-1β, IL-12, and IL-6) were all far lower in *PTP1B*$^{-/-}$ mice compared with WT mice, whereas the serum levels of anti-inflammatory IL-10 were higher. They also found that although the frequency of MDSCs in the bone marrow of both WT and *PTP1B*$^{-/-}$ mice were almost the same before administration of DSS, the increase in the frequency of granulocytic and monocytic MDSCs was significantly higher in *PTP1B*$^{-/-}$ mice. Adoptive transfer of MDSCs ameliorated DSS-induced colitis in WT mice. Adding to the possible mechanism in which lower PTP1B levels can enhance MDSCs expansion, beyond the known negative regulation of JAK2, Zhang et al[78] also found that PTP1B deficiency increases STAT3 activity and hence promotes MDSC expansion. This is a potentially important finding in terms of IBD, in context of previous evidence showing that TNF-α can increase or activate PTP1B,[82] given the major role that TNF-α plays in IBD and the success of anti-TNF-α in terms of treatment. Zhang et al also found that by treating bone marrow cells from WT mice with

TNF-α, the expression of PTP1B increased in a dose-dependent manner and this impaired the frequency of MDSC expansion. Furthermore, inhibition of PTP1B led to a strong induction of MDSCs. Taken together, the authors suggest a positive feedback loop in intestinal inflammation that may be relevant in IBD: initial inflammation increases the level of PTP1B through inflammatory factors (such as IL-17 or TNF-α), which subsequently suppresses MDSC production by JAK2/STAT3 suppression with prolongation of intestinal inflammation.

Singh et al[83] published further evidence from a mouse IL-$10^{-/-}$ model that correlates a decrease in colitis with an increase in MDSCs. This article showed that giving resveratrol, a naturally occurring polyphenolic phytoalexin previously found to exhibit strong anti-inflammatory properties, to *IL-*$10^{-/-}$ mice with chronic colitis led to its amelioration. The clinical improvement was correlated with (1) a significant increase in ARG1-expressing MDSCs, at least in the lamina propria, and likely also the spleen; (2) an impaired recruitment of inflammatory $CXCR3^+$ T cells into the lamina propria; and (3) a reduction in the percentage and number of activated T cells in the spleen, MLN, and lamina propria. The clinical course was consistent with previous studies that had shown that resveratrol can suppress colitis,[84–86] but this was the first study to link the effects to an increase in MDSCs.

Given the multifaceted function of MDSCs in the amelioration of IBD models associated with the suppression or induction of specific types of the immune response, MDSCs not only have immunosuppressive functions but could also belong to the network of myeloid regulatory cells with immunoregulatory functions.[87]

NEUTROPHILS

Although neutrophils have traditionally been seen as inflammatory effector cells, it is becoming increasingly apparent that this is not the whole story in the gut. For example, although depletion of polymorphonuclear leukocyte (PMN) by using Gr1 antibodies resulted in diminution of inflammation in a lung injury model,[88] the opposite has been seen colitis models.[89] Indeed, Kuhl et al showed that in both DNBS-/TNBS-induced colitis and $CD4^+CD45RB^+$ T-cell–induced colitis, neutrophil depletion potentiated colonic inflammation. One clear issue with observations such as these is that depletion of neutrophils by antibodies, such as anti-Gr1, might also deplete MDSCs, the importance of which in the resolution of colitis has already been explored in this article (see Myeloid-derived Suppressor Cells section). Indeed, despite multiple reports of different surface markers being able to distinguish between granulocytic MDSCs and nonimmunosuppressive neutrophils, no single or combined surface marker has been reliably and consistently shown to be able to accurately differentiate between these 2 functionally different populations in mice or humans.[90] It is clear that human neutrophils can produce some anti-inflammatory cytokines (such as IL-1RA, TGF-β1, and TGF-β2) and immunoregulatory cytokines (such as IL-12 and IL-23); however, it is important to note that there is some controversy over whether human neutrophils do produce other anti-inflammatory and immunoregulatory cytokines (such as IL-4, IL-10, IFN-α, and IFN-γ).[91]

The mechanisms through which neutrophils can contribute to inflammatory resolution in the gut have not yet been elucidated, but there are 3 models reviewed by Colgan et al.[92] In summary, one model postulates that the production of an inflammatory hypoxic milieu due to the large amounts of localized oxygen consumption in areas of inflammation by neutrophils (it is estimated that activated PMNs can consume up to 10 times as much oxygen as any other cell in the body) leads to stabilization of hypoxia-inducible factor (HIF). Campbell et al[93] have shown that PMNs can, by nicotinamide adenine dinucleotide phosphate burst, lead to hypoxia in nearby intestinal epithelial cells, and that the severity of the inflammatory response in vivo is influenced by the degree of hypoxia produced. It is believed that the stabilization of HIF leads to increased transcription of a variety of genes that potentiate the barrier function of epithelial cells, mainly through increased mucin production, modification of the mucin produced, nucleotide signaling, and metabolism and xenobiotic clearance.[92,93] These roles of HIF on intestinal epithelial cells have been shown in microarray analysis, animal models, and human intestinal tissues. Indeed, Campbell et al[93] showed not only that inducement of colitis by TNBS in mice that lack respiratory burst leads to severe and nonresolving colitis, which is coupled with a lack of mucosal hypoxia but also that HIF stabilization through pharmacological intervention (administration of an HIF stabilizer) ameliorates colitis severity in these mice. The second model reviewed by Colgan et al is the role that PMN cells play in building up extracellular adenosine, which then is either recycled or interacts with epithelial cell surface Ado receptors, a subset of which has been recently implicated as being a potent inhibitor of NF-κB–mediated inflammatory signaling cascades through proteasomal degradation of IκB proteins. The third model reviewed by Colgan et al is the resolution of inflammation through a process of transcellular biosynthesis, in which lipid mediators act to initiate the resolution phase of acute inflammation. The lipid mediators of most interest are resolvins (Rv) and maresins (macrophage mediator in resolving inflammation, MaR), but PMNs also produce, or contribute to the production of, growth factors (such as vascular endothelial growth factor), lipoxins, and protectins too.[94] These lipid mediators have been shown to inhibit neutrophil recruitment and tissue infiltration, attenuation of NF-κB responses, stimulation of CCR5 expression by apoptotic neutrophils, which act as scavengers for CCL3 and CCL5, and the expression of CC-chemokine receptor D6 (a decoy receptor and scavenger for almost all inflammatory CC-chemokines).[91,92] Specifically for IBD, patients with UC have been shown to produce less lipoxin A_4 as controls,[95] and murine DSS- and TNBS-induced colitis was ameliorated with lipoxin A_4 analog treatment.[96,97] A more detailed description of the mechanisms of action of these lipid mediators are beyond the scope of this review article, but the critical role of PMNs in generating these molecules through their interaction

with epithelial and endothelial cells add to the evidence of the contribution of PMNs to the resolution of intestinal inflammation. Neutrophils have also been shown to limit the proinflammatory effects of IL-1 by expression of membrane-bound and released type 2 IL-1 decoy receptor (IL-1R2).[91] This expression is potentiated by anti-inflammatory signals such as GC hormones.[98] IL-1R2 mops up IL-1, and furthermore, neutrophils that have been activated by IL-10 release IL-1RA, which binds to IL-1R1 without inducing any intracellular signals.[91] Finally, the functional phenotype of macrophages is shaped by the recognition and ingestion of apoptotic neutrophils, mediated by so-called "eat me signals." These trigger an anti-inflammatory phenotype in the engulfing phagocytes, stimulating an IL-10^{+}IL-12^{-} M2-like phenotype.[99–101]

DENDRITIC CELLS

Although DCs are located throughout the lamina propria of the gut, they are mainly found within intestinal lymphoid tissues, including Peyer's patches and solitary isolated lymphoid tissues and in MLNs where they initiate adaptive immune responses.[102] The realization that surface markers traditionally used to differentiate DCs and macrophages can be expressed by multiple cell types has led to some confusion over the correct identification of these 2 functionally distinct mononuclear phagocytes. As discussed earlier in this article, it seems that intestinal macrophages are more efficient in their uptake of luminal antigens compared with DCs.[102] It is now generally accepted that both DCs and macrophages in the intestinal mucosa display both $MHCII^{+}$ and $CD11c^{+}$; and recent studies have shown that DCs are $CD103^{+}$ (integrin $\alpha1$), whereas macrophages are $CD103^{-}$ but display $CX3CR1^{+}$, F4/80, and CD64 (high affinity IgG receptor FcγRI) (reviewed in Ref. 43). In the gut, $CD103^{+}$ DCs comprised 2 separate populations, based on the expression of CD11b, which have different proportions in small bowel ($CD11b^{+}$) versus large bowel ($CD11b^{-}$) in the colon.[43]

Two recent studies using multiphoton microscopy elucidated 2 different methods of how intestinal DCs gain access to luminal antigens. McDole et al found goblet cells passing luminal antigens to $CD103^{+}$ DCs in the small intestine,[103] whereas Farache et al[104] found a small population of $CD103^{+}$ DCs in the intestinal epithelial layer itself extending dendrites towards the lumen. DCs are able to migrate from the gut to the draining MLNs in a CCR7-dependent manner.[105] Intestinal DCs' anergy is, to a certain extent, controlled by A20, a protein with known deubiquitinating E3 ligase and ubiquitin-binding functions, which is a regulator of NF-κB.[106] Mice with DC-specific lack of A20 develop spontaneous colitis, seronegative arthritis, and enthesitis, a group of manifestations that can be seen in IBD, and noncoding A20 single nucleotide polymorphisms have been found to be associated with Crohn's disease.[106] Intestinal $CD103^{+}$ DCs are able to induce $FoxP3^{+}$ Treg differentiation in a retinoic acid- and active TGF-β–dependent manner.[107,108] $CD103^{+}$ lamina propria DCs are able to metabolize vitamin A to retinoic acid by their expression of aldehyde dehydrogenase enzymes[107]; and latent TGF-β can be converted to its active form by their expression of $\alpha v\beta8$ integrin.[109] In addition to the role of RA and TGF-β in inducing $FoxP3^{+}$ Tregs, they also have been shown to have the potential to actually alter the colitogenic potential of $CD4^{+}$ intestinal T cells.[110] In addition, certain factors in the local environment in the gut mucosa have a contributory role in DCs' ability to develop tolerogenic T cells, including thymic stromal lymphopoietin, bile and dietary retinoids, signals derived form the MLNs, and soluble mediators such as PGE2 and vasoactive intestinal peptide.[43] It also seems that microanatomical location has some influence on the effectiveness of antigen sampling and T-cell activation of tolerogenic intestinal $CD103^{+}$ DCs (reviewed in Ref. 111). Beyond their contribution to inducing tolerance to oral antigens, there is evidence that intestinal epithelial cells influence DCs in the development of tolerance to the intestinal microbiota (reviewed in Ref. 112), and that intestinal DCs tolerate the microbiota at least partially through a TRAF6-dependant mechanism leading to IL-2–mediated induced Treg generation.[113]

CONCLUSIONS, THERAPEUTIC IMPLICATIONS, AND FUTURE PERSPECTIVES

Far from the traditional view that the innate system is predominantly involved in effector functions and proinflammatory effects, it has become clear over the last decade that these myeloid-derived cells have important immunoregulatory functions as well, and this is especially true in inflammation and in the specialized tissues of the gut (Fig. 1). Our expanding knowledge of this area will help our understanding of the pathogenesis of IBD and helping to put into context the evergrowing data being generated from genetic and microbiota studies. Indeed, although IBD has traditionally been seen as predominantly a Th1-mediated disease, the likelihood is that at least some of our patients with IBD may have a primary defect in a myeloid-derived subset with subsequent dysregulated immunoregulatory effects and that this is the trigger that starts intestinal inflammation in IBD. The potential to use some of these insights to improve our treatment options in IBD also beckons.

Because of their specialized ability to induce $FoxP3^{+}$ Tregs, DCs have been suggested as having potential as immunotherapeutic agents. Indeed, in vitro studies[114] and some in vivo studies in mice have had quite promising results in experimentally induced colitis,[115] but it has proven difficult to translate this to human clinical trials. Given the low numbers of DCs in human tissues, monocyte-derived dendritic cells, generated from circulating monocytes and then reinjected, have been proposed as a method for individualized immunotherapy in humans. Unfortunately, the ability to induce gut homing markers in monocyte-derived dendritic cell is proving difficult and may be why the in vitro results are proving to be difficult to translate in vivo.[116] However, conditioning with RA has recently been shown in vitro to produce monocyte-derived dendritic cells that home to the gut,[116] which may finally produce the hoped-for positive results for this potential future therapy in humans.

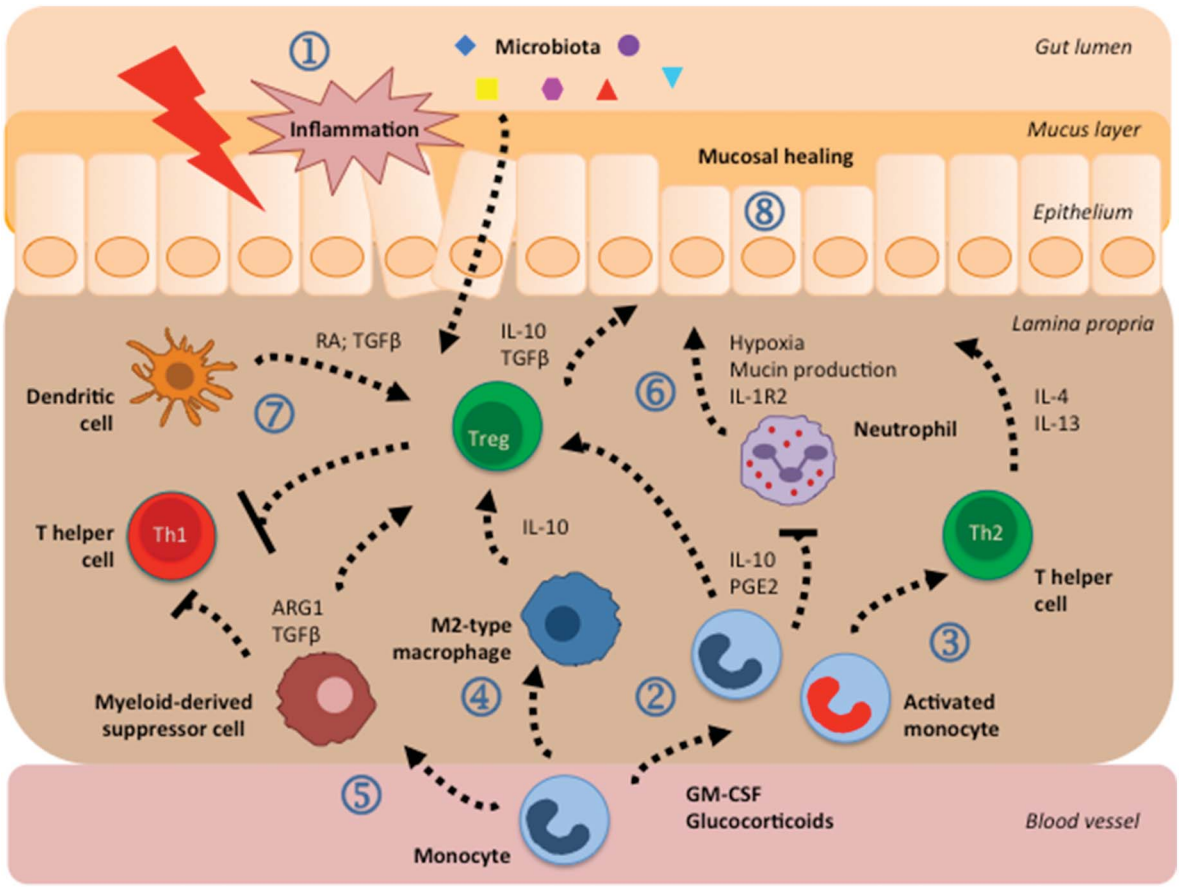

FIGURE 1. Mechanisms of innate cell immunoregulation in IBD. 1, Genetically defined factors lead to colitis susceptibility due to a dysregulated immune response against the microorganisms of the intestinal flora. 2, Under basal conditions, an immunoregulatory phenotype predominates in lamina propria monocytes with increased production of IL-10 and PGE2 (which limits neutrophil activation), modulation of T-cell phenotype, and possibly tissue repair. 3, With exposure to GCs or granulocyte macrophage colony-stimulating factor, monocytes obtain a regulatory phenotype and induce T helper 2 (Th2) cells and FoxP3$^+$ Tregs. 4, Local factors, under basal conditions, induce immunoregulatory M2 type-like gut-specific macrophages to differentiate from monocytes; IL-10 production from macrophages helps maintain Treg induction. 5, MDSCs, induced by inflammation, produce ARG1 and TGF-β and have both T-cell suppressive effects and Treg stimulatory effects. 6, Respiratory burst by activated neutrophils leads to localized inflammatory hypoxia, stabilization of HIF, which leads to increased mucin production and mucin modification and release of IL-1 decoy receptor (IL-1R2). 7, Lamina propria DCs are able to metabolize vitamin A to retinoic acid and inactive TGF-β to active TGF-β, which assist in inducing Treg. 8, The immunoregulatory role of myeloid-derived cells have important protective and homeostatic effects to restrain acute and chronic intestinal inflammation.

Although GC-stimulated monocytes have been shown to have immunoregulatory effects as described above, extracorporeal stimulation would be required if the systemic side effects of steroid administration were to be avoided. However, the molecular basis for GC-mediated gene transcription in monocytes has been explored with the identification of the A3 adenosine receptor being the initial trigger in this pathway, suggesting the possibility of using this or its downstream signaling pathways as potential targets.[117]

There is also expanding evidence that cells from the lymphocytic lineage not traditionally believed to have immunoregulatory roles in colitis, actually do. These include the newly described innate lymphoid cells (reviewed in Ref. 118) and natural killer cells, which have been shown to be protective in DSS-induced colitis through reducing neutrophil activation and recruitment and modulating their inflammatory phenotype through direct contact.[119]

Apoptotic neutrophils release their own signals, which limit further neutrophil infiltration, such as annexin A1 and lactoferrin, and these and other molecules recruit scavenger macrophages, which themselves release mediators that suppress inflammation. Given the centrality of neutrophil apoptosis in this mechanism of inflammation resolution, it has been suggested that the induction of neutrophil apoptosis might be a potential future target for IBD.[120]

The possibility of using activated macrophages as a treatment modality in IBD is coming closer to a clinical reality. Recent in vivo evidence has raised the tantalizing possibility that macrophages with distinct colitis-suppressing functions can be induced through interaction with soluble factors produced from

adipose tissue-derived mesenchymal stem cells (ASC), at least in DSS- and TNBS-induced colitis murine models.[121] Bone marrow-derived macrophages activated with IL-4 and IL-13 have been found to reduce colitis in DNBS-treated mice.[26] Another potential pitfall of this emerging therapy will be the question of whether these activated macrophages might put patients at higher risk of cancer, given their similarities to tumor-associated macrophages and the already higher risk of colon cancer in patients with IBD. We are beginning to see trials targeting macrophages in an attempt to manipulate their phenotype for many disease states. Although currently most of these trials are for cancer (with manipulation of macrophage recruitment, switching to M1 or macrophage depletion), there are some trials ongoing for other autoimmune conditions such as asthma, atherosclerosis, and diabetes.[49] If these trials show promise, it will be only a matter of time before we see innate cell-targeted therapies being trialed in IBD.

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