

# Origin and Function of Monocytes in Inflammatory Bowel Disease

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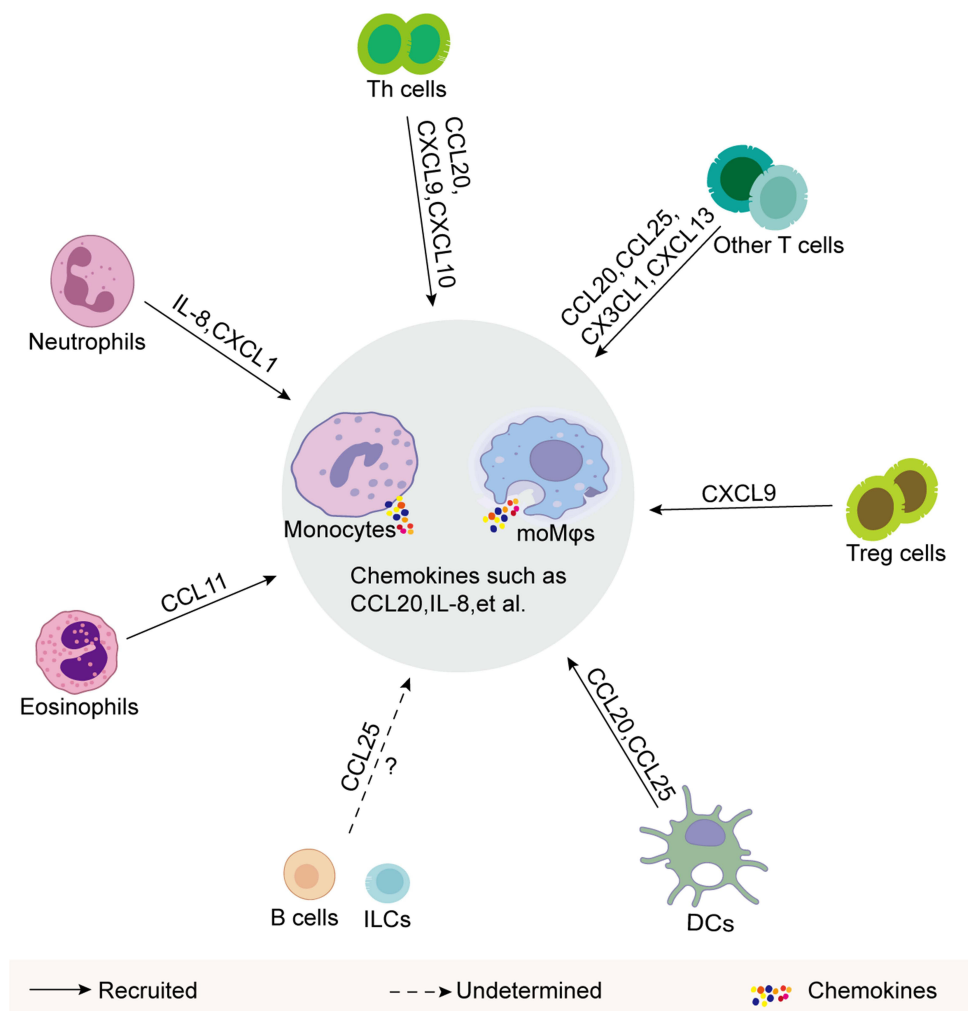
**Abstract:** Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic disease resulting from the interaction of various factors such as social elements, autoimmunity, genetics, and gut microbiota. Alarming, recent epidemiological data points to a surging incidence of IBD, underscoring an urgent imperative: to delineate the intricate mechanisms driving its onset. Such insights are paramount, not only for enhancing our comprehension of IBD pathogenesis but also for refining diagnostic and therapeutic paradigms. Monocytes, significant immune cells derived from the bone marrow, serve as precursors to macrophages (Mφs) and dendritic cells (DCs) in the inflammatory response of IBD. Within the IBD milieu, their role is twofold. On the one hand, monocytes are instrumental in precipitating the disease's progression. On the other hand, their differentiated offsprings, namely moMφs and moDCs, are conspicuously mobilized at inflammatory foci, manifesting either pro-inflammatory or anti-inflammatory actions. The phenotypic spectrum of these effector cells, intriguingly, is modulated by variables such as host genetics and the subtleties of the prevailing inflammatory microenvironment. Notwithstanding their significance, a palpable dearth exists in the literature concerning the roles and mechanisms of monocytes in IBD pathogenesis. This review endeavors to bridge this knowledge gap. It offers an exhaustive exploration of monocytes' origin, their developmental trajectory, and their differentiation dynamics during IBD. Furthermore, it delves into the functional ramifications of monocytes and their differentiated progenies throughout IBD's course. Through this lens, we aspire to furnish novel perspectives into IBD's etiology and potential therapeutic strategies.

**Keywords:** IBD, monocytes, inflammatory response

## Introduction

Inflammatory Bowel Disease (IBD) is a chronic and complex intestinal inflammatory disorder. Recent clinical data have shown promising results in IBD treatment through the combination of Granulocyte-Monocytes Apheresis with certain pharmacological agents.<sup>1-4</sup> This emerging evidence highlights the potential efficacy of monocytes-based interventions in IBD, despite the absence of well-established therapeutic guidelines. Moreover, extensive basic research has elucidated the pivotal role of monocytes in the pathogenesis and progression of IBD.

Monocytes, integral components of the immune system, are produced in the bone marrow and play a vital role in maintaining intestinal homeostasis through processes such as recruitment, activation and differentiation.<sup>5-8</sup> In patients with IBD, there is typically an overabundance of highly active monocytes in the intestinal milieu. These monocytes contribute significantly to the inflammatory cascade by releasing pro-inflammatory cytokines and chemokines, thereby recruiting additional immune cells to the site of inflammation.<sup>9-14</sup> For example, monocytes-derived cytokines, including



**Figure 1** Recruitment of Immune Cells by Monocytes in IBD. Through the secretion of cytokines, including chemokines and other inflammatory mediators, monocytes facilitate the congregation of these immune cells. These cells collectively contribute to either the amplification or the regulation of the inflammatory response integral to the pathogenesis of IBD, thereby influencing the disease's progression and outcomes.

IL-1 $\beta$ , IL-6, and IL-23, have the capacity to activate T cells within the innate layer of the intestinal mucosa. This, in turn, results in the production of additional inflammatory cytokines, thereby amplifying the inflammatory response within the intestinal tract.<sup>14–16</sup> Furthermore, chemokines released by monocytes, such as CCL11, can attract other immune cells, including neutrophils and eosinophils, to sites of inflammation, exacerbating tissue damage within the intestine (Figure 1).<sup>17,18</sup>

Throughout the course of IBD, monocytes process a plethora of signals, such as inflammatory mediators and pattern recognition receptors.<sup>1–11</sup> These signals subsequently lead to the release of cytokines, which play a crucial role in regulating tissue damage and repair, as well as various cellular activities, including differentiation, activation, apoptosis, phagocytosis, and immune responses.<sup>12–17</sup> Given the central role of monocytes in the pathogenesis of IBD, they have emerged as a focal point in pathological studies aimed at elucidating the onset and progression of the disease. Consequently, there is a burgeoning interest in delineating the immunobiology of monocytes in IBD, and unraveling the intricacies of their functional alterations in the context of the disease.

## Originate of Monocytes

The conventional model of monocytes generation posits that hematopoietic stem cells (HSCs) in the bone marrow differentiate into multipotent progenitors (MPP), which subsequently give rise to common myeloid progenitors (CMP).

These CMPs then differentiate further into granulocyte-monocytes progenitors (GMP), monocytes-dendritic cell progenitors (DMP), and common monocytes progenitors (cMoP), ultimately resulting in the development of monocytes.<sup>19,20</sup> However, recent studies in mice have challenged this linear model, proposing two parallel pathways originating from the CMP stage: one pathway leads to the formation of neutrophil-like monocytes (NeuMo) and neutrophils via GMP and monocytes progenitors (MP); the other pathway leads to dendritic cell-like monocytes (DCMo) and dendritic cells (DC) via DMP and cMoP. Furthermore, *in vitro* studies have shown that human GMPs failed to produce DCs, suggesting a potential dual-pathway in human monocytes development as well.<sup>21,22</sup> This raises the question of whether MP and cMoP, derivatives of GMP and DMP respectively, can generate additional monocytes subgroups.

While non-classical monocytes are known to evolve from classical monocytes,<sup>23–25</sup> evidence suggests other precursor cells might be involved.<sup>26–28</sup> Their survival in the bone marrow is dependent on the nuclear receptor subfamily 4 group A member 1 (Nr4a1), a transcription factor essential for their development in blood and tissues.<sup>29</sup> An intermediate monocytes subset, bridging classical and non-classical monocytes, has been identified in both the bone marrow and blood.<sup>24,30,31</sup> Upon reaching a certain developmental stage in the bone marrow, CCR2 and its ligands CCL2 and CCL7 direct these monocytes to migrate into blood and tissues, playing innate immune roles against invading antigens.<sup>32</sup> In summary, monocytes mature in the bone marrow, enter circulation, and are recruited to various tissues based on ecological demands, thus providing essential innate immune functions. However, the developmental relationships between different monocytes subsets remain unclear and require further investigation (Figure 2).

## Clinical Relevance of Monocytes in IBD

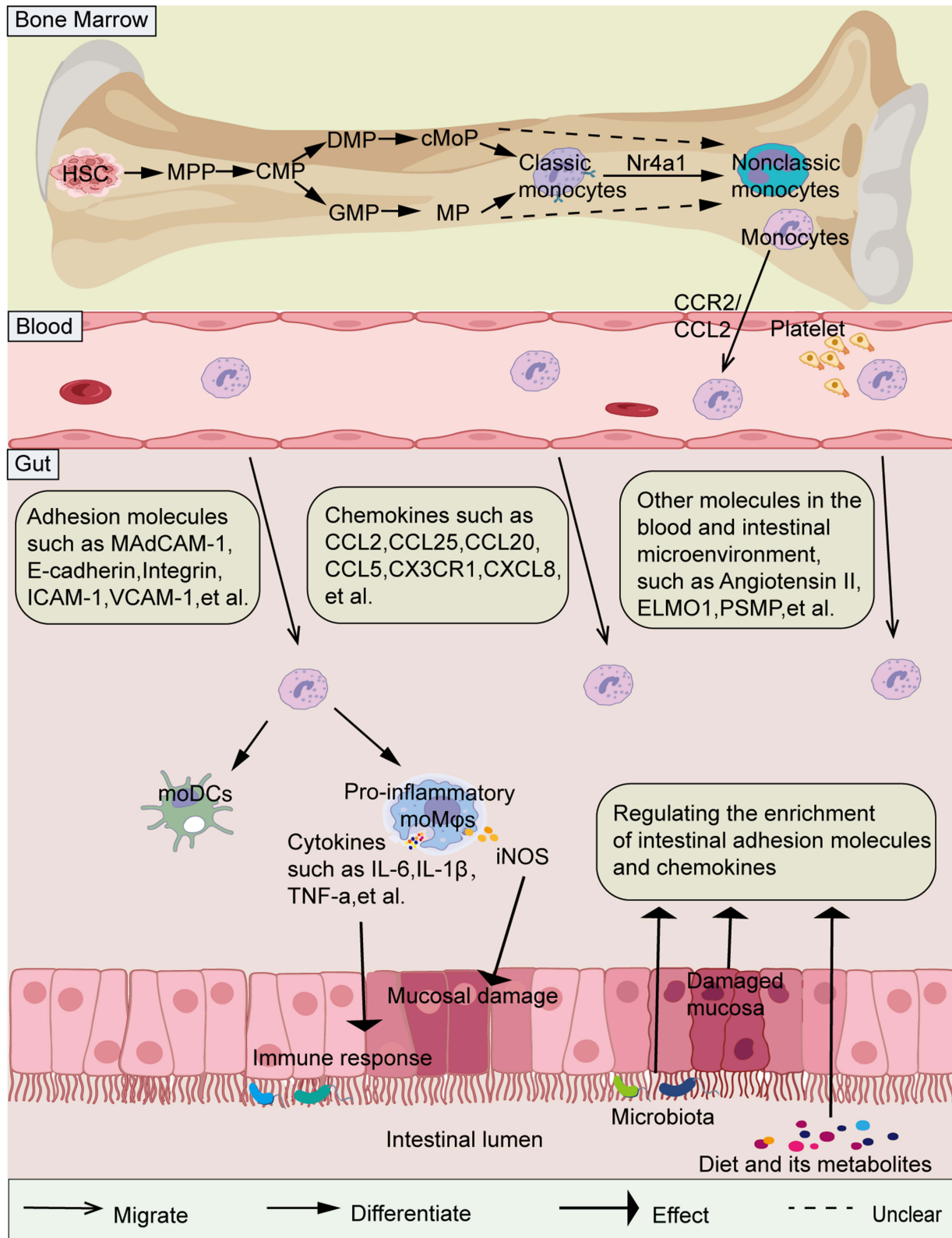
Grimm et al identified an increase in CCL2 production by macrophages, smooth muscle cells, and endothelial cells in IBD patients. Elevated CCL2 levels recruited monocytes to the intestinal mucosa, where they differentiated into macrophages, releasing inflammatory mediators like MIP, RANTES, and CCL2, exacerbating mucosal inflammation. These monocytes also showed increased sensitivity to LPS, contributing to IBD's persistent inflammation.<sup>33–35</sup> Clinical data from CD patients show higher monocytes counts during relapses compared to remission.<sup>36</sup> Patients with monocytes counts over 8.15% are more likely to relapse within six months, even if in deep remission.<sup>37</sup> In UC patients with low CRP levels, higher monocytes counts correlate negatively with mucosal healing.<sup>38</sup> Hence, monocytes counts and lymphocyte-to-monocytes ratios could predict disease activity in UC.<sup>39</sup>

Further research identified RhoB, CTSD, and ZYX as key genes in UC, associated with monocytes infiltration.<sup>40</sup> Polymorphisms in IBD-related risk genes affect cytokine secretion and signaling in monocytes-derived macrophages, regulating inflammation in IBD.<sup>41–43</sup> Frame-shift mutations in CSF2RB and CARD15 reduce monocytes response to GM-CSF, increasing IBD susceptibility.<sup>44,45</sup> Autophagy gene variants ATG16L1 and NOD2 enhance monocytes phagocytic capacity in IBD patients.<sup>46</sup> These findings highlight altered monocytes recruitment and differentiation in IBD and show how genetic markers affect monocytes functions, disrupting mucosal barriers and intestinal homeostasis.

## Migration and Recruitment of Monocytes During IBD

### Important Mediators of Monocytes Migration and Recruitment in the Course of IBD

The migration and recruitment of monocytes within the intestine differ markedly between homeostatic and inflammatory conditions. Under homeostatic conditions, monocytes utilize CCR2 and  $\beta$ 7-integrin to facilitate their homing to the intestine. Conversely, during episodes of intestinal inflammation, monocytes amplify their recruitment through enhanced expression of CCR2 and no longer rely on  $\beta$ 7-integrin for this process.<sup>6</sup> In animal models of acute colitis, CCR2 expression has been found to be pivotal in recruiting Ly6C<sup>hi</sup> monocytes to the inflamed intestine, rendering Ly6C<sup>hi</sup> monocytes the predominant cell type within the lamina propria.<sup>47</sup> CCL2, a well-documented ligand for CCR2, is primarily produced by monocytes and “classically activated” pro-inflammatory macrophages, although CCL7 and CCL8 are also recognized as ligands for CCR2.<sup>48–50</sup> Researches indicate that macrophage-expressed Dectin-1 and the highly expressed Engulfment and Cell Motility protein 1 in intestinal tissues facilitate the infiltration of Ly6C<sup>hi</sup>CCR2<sup>hi</sup> monocytes subsets from the blood into inflamed colons by upregulating CCL2.<sup>51–53</sup> Furthermore, studies have shown that pathogen infection-induced activation of NOD2 is associated with the development of CD, partially attributed to NOD2-mediated recruitment of CCL2-CCR2-dependent inflammatory monocytes.<sup>54</sup> Additionally, CD30L has been shown to



**Figure 2** Development and Migration of Monocytes in IBD Pathogenesis. Monocytes originate from hematopoietic stem cells (HSC) in the bone marrow and undergo a sequential process of differentiation, culminating in the formation of monocytes. These monocytes primarily access the circulation through the CCL/CCR2 axis. In the context of IBD, a range of cytokines, chemokines, integrins, adhesion molecules, and gut microenvironmental cues mediate the migration of circulating monocytes to sites of inflammation. Once monocytes infiltrate the gut, they differentiate into macrophages and dendritic cells, ultimately leading to immune response.

activate circulating classical monocytes and upregulate CCR2 through the NF- $\kappa$ B pathway. This, in turn, induces monocytes homing in a colitis mouse model via the CCL2/CCR2 axis.<sup>55,56</sup> Importantly, researches have indicated that the chemotactic cytokine PSMP is upregulated earlier than CCL2 in experimental colitis and promotes the expression of CCL2. This suggests that PSMP may initiate the early recruitment of circulating Ly6C<sup>hi</sup>CCR2<sup>+</sup> monocytes to the tissue, working in concert with CCL2 and CCL7 to drive colitis. Nevertheless, the chemotactic action remains dependent on CCR2.<sup>50</sup> Therefore, CCR2 emerges as a crucial regulator in directing monocytes chemotaxis to lesion sites in IBD.

Monocytes migration in IBD is a complex process that extends beyond the CCL2/CCR2 axis. In active IBD, there is an observed upregulation of  $\alpha$ 4 integrin and CX3CR1, which facilitates the infiltration of CD14<sup>+</sup>CD16<sup>+</sup> monocytes into the mucosa.<sup>57</sup> Furthermore, CD14<sup>+</sup> monocytes with high HLA-DR expression can re-localize to the intestinal mucosa via interactions with CCR9 and CCL25.<sup>58</sup> Employing a TNBS-induced chronic colitis rat model, Ajuebor et al demonstrated that RANTES plays a role in promoting monocytes recruitment to inflammatory sites during the transition from acute to chronic colitis.<sup>59</sup> In studies involving DSS-induced colitis and bone marrow transplantation, Fpr2/3 was shown to modulate the CCL20-CCR6 interaction, thereby driving monocytes chemotaxis to intestinal mucosa.<sup>60</sup> Moreover, GM-CSF activation of monocytes enhances their migration, chemotaxis, adhesion, and recruitment to inflamed sites, which also correlates with the upregulation of chemokines.<sup>7</sup> Thus, a comprehensive understanding of monocytes chemokine expression in IBD could better address their recruitment dynamics, beyond a singular pathway focus.

Beyond the influence of chemokines and their receptors on monocytes migration, cell adhesion molecules play a pivotal role in monocytes recruitment in IBD. Early research identified significant monocytes migration to the intestines in CD patients, with  $\beta$ 2 integrins playing a crucial role.<sup>61</sup> Recent findings indicate that  $\alpha$ 4 $\beta$ 7 integrin regulates non-classical monocytes adhesion to MAdCAM-1 and E-cadherin, influencing intestinal homing.<sup>62</sup> Furthermore, compounds derived from chemical and traditional herbal medicines that inhibit the expression of adhesion molecules such as ICAM-1, VCAM-1, and MAdCAM-1 have been shown to obstruct monocytes adhesion to inflamed intestines, providing relief from IBD.<sup>7,63–65</sup> Moreover, in a DSS-induced murine colitis model, Abe et al demonstrated that TLR9-activated conventional dendritic cells regulate monocytes transport to the inflamed colon through the induction of IFN-1.<sup>66</sup> Additionally, the glucocorticoid-induced TNF receptor family-related protein ligand, GITR-L, modulates the transport of monocytes from splenic reservoirs to inflammatory sites.<sup>24</sup> Notably, recent research on experimental colitis revealed that the impaired migratory capability of Trim33<sup>-/-</sup> circulating monocytes was not related to defects in the CCL2/CCR2 axis, but rather to the diminished migratory ability of bone marrow-derived precursor cells with a Trim33 deficiency.<sup>60</sup> These findings highlight the necessity for research on monocytes recruitment in IBD to extend beyond the CCL2/CCR2 axis and proteins expressing chemotactic or adhesive properties at inflammatory sites. Furthermore, there is a need to consider potential abnormalities in the differentiation of monocytes precursor cells.

### Effect of Blood Compositions on Monocytes Migration and Recruitment

Blood components such as platelets and angiotensin affect monocytes migration in intestinal inflammation. PDE-3 inhibitors in murine models reduce monocytes recruitment by interrupting platelet-monocytes interactions.<sup>67</sup> Angiotensin II limits CCL2 production, hindering Ly6C<sup>+</sup>CCR2<sup>+</sup> monocytes recruitment.<sup>68</sup> The peptide SRSRY reduces inflammatory monocytes recruitment to inflamed tissues.<sup>69</sup> Cobalt protoporphyrin IX increases monocytes entry into the bloodstream but disrupts the CCL2 gradient in the colon, reducing monocytes recruitment and inflammatory cytokine expression.<sup>70</sup> Apolipoprotein AI mimetic peptide 5A downregulates plasma CCL2 levels, reducing pro-inflammatory monocytes and suppressing monocytes adhesion and migration in human intestinal microvascular endothelial cell layers.<sup>71</sup> These findings show that blood components impact monocytes migration, but their roles and mechanisms during IBD are not fully understood. The potential of blood analogues targeting monocytes infiltration for IBD therapy requires further research.

### The Intestinal Microenvironment and the Migration and Recruitment of Monocytes During IBD

The intestinal microenvironment plays a crucial role in the migration and recruitment of monocytes in IBD. Structural disruptions to tight junction proteins such as occludin and impaired epithelial barrier function can enhance monocytes migration.<sup>8</sup> Mucosal injuries stimulate the production of chemokines, such as RANTES, CCL20-CCR6, and CCL8,

promoting monocytes recruitment to the colon.<sup>59,60,72</sup> From a microbiota perspective, commensal Gram-positive bacteria can attract monocytes into the colon, inducing inflammation.<sup>73</sup> Bacterial infections can stimulate NOD2-mediated CCL2-CCR2-dependent inflammatory monocytes recruitment.<sup>54</sup>

Dietary and metabolic product studies indicate that non-digestible polysaccharides stimulate macrophages to produce chemokines like CCL5 and CXCL8 in vitro, enhancing monocytes recruitment.<sup>67</sup> Conversely, polyphenols significantly inhibit CCL2 expression and the NF- $\kappa$ B pathway,<sup>74,75</sup> and butyrate suppresses TNF- $\alpha$ -induced VCAM-1 expression,<sup>76</sup> reducing monocytes adhesion to intestinal epithelial cells (IECs). In the SAMP3/Yit ileitis mouse model,  $\Omega$ -3 polyunsaturated fatty acids mitigate monocytes recruitment by decreasing intestinal CCL2 expression,<sup>77</sup> highlighting the importance of dietary intake in clinical IBD management. In terms of metabolic products, spermine-treated cells exhibit reduced IFN- $\gamma$ -induced CCL2 expression in THP-1 cells, subsequently decreasing monocytes recruitment.<sup>78</sup> Furthermore, cholecystectomy-induced accumulation of secondary bile acids regulates chemokines like CCL2, CCL7, and CCL8 to suppress monocytes recruitment.<sup>79</sup> In summary, alterations in intestinal structure, microbiota, diet, and metabolic byproducts influence monocytes recruitment to the colon. Although the intestinal microbiota appears to be a dominant factor in this process, further research is needed to validate these findings. [Table 1](#)

**Table 1** Cellular Molecules Associated with the Migration and Recruitment of Monocytes in IBD

| Cellular Molecules            | Migration and Recruitment of Monocytes   | References |
|-------------------------------|--|------------|
| <b>Chemokines</b>             |  |            |
| CCL2                          | Promote via CCL2 and CCR2 axis   | [48–52]    |
| CCL5(RANTES)                  | Promote by binding to CCR1 or CCR5   | [59]       |
| CCL7                          | Promote by binding to CCR2   | [48–50]    |
| CCL8                          | Promote by binding to CCR2   | [48–50]    |
| CCL20                         | Promote via CCL20 and CCR6 axis  | [60]       |
| CCL25                         | Promote via CCL25 and CCR9 axis  | [58]       |
| CX3CR1                        | Promote via CX3CL1/CX3CR1 axis   | [57]       |
| <b>Cytokines</b>              |  |            |
| IFN1                          | Promote via cDCs secrete CCL5  | [66]       |
| PSMP                          | Promote by cooperating with CCL2 and CCL7  | [50]       |
| <b>Protein</b>                |  |            |
| TRIM33                        | Promote by Changing the deformability and migration ability of bone marrow-derived precursor cells | [60]       |
| GITRL                         | Control the transportation of monocytes from spleen to inflammatory sites                          | [24]       |
| Dectin-1                      | Promote via Upregulation of CCL2   | [51]       |
| ELMO1                         | Promote via Upregulation of CCL2   | [51]       |
| FPR                           | Promote by regulating CCL20/CCR6   | [60]       |
| NOD2                          | Promote via CCL2 and CCR2 axis   | [54]       |
| TLR9                          | Promote via cDCs secrete CCL5  | [66]       |
| GM-CSF                        | Promote by Upregulation of chemokines  | [7]        |
| <b>Adhesion molecule</b>      |  |            |
| $\beta$ 2 integrin            | Promote via $\beta$ 2 integrin and ICAM-1  | [61]       |
| ICAM-1                        | Promote by combining with integrin ligands   | [7,63–65]  |
| VCAM-1                        | Promote by combining with integrin ligands   | [7,63–65]  |
| MAdCAM-1                      | Promote by combining with integrin ligands   | [7,63–65]  |
| $\alpha$ 4 $\beta$ 7 integrin | Promote via Monocytes adhere to MAdCAM-1 and E-cadherin  | [57]       |

Changes in both the blood and intestinal microenvironments, largely mediated by chemokines and adhesion molecules, are critical factors influencing monocytes migration during the progression of IBD. Banerjee et al discussed the role of biomechanical forces in regulating integrins in autoimmunity, shedding light on the importance of mechanical forces in autoimmune conditions.<sup>80</sup> Studies have demonstrated that monocytes migration and adhesion are closely related to ICAM1/VCAM1 expression as well as the intrinsic mechanical strength of the cells themselves.<sup>81</sup> However, this field remains relatively underexplored. The intrinsic biomechanical movement capabilities of monocytes and their impact on migration are intriguing and represent a novel avenue of investigation. Delving deeper into the field of biomechanics, including the effects on monocytes stiffness and uncovering the mechanisms of dysregulation during IBD, will provide valuable insights into monocytes migration and recruitment in IBD. Understanding these biomechanical aspects may offer new opportunities for therapeutic intervention, ultimately contributing to better management and treatment of IBD.

## Differentiation of Monocytes During IBD

The intestinal inflammatory environment during IBD profoundly impacts the fate of monocytes. Once recruited from the bloodstream, these monocytes exhibit their unique subset characteristics, but they also further differentiate into intestinal macrophages and dendritic cells within specific tissue microenvironments.<sup>82</sup> This process mirrors the adaptive response of monocytes to immunological stimuli. However, the complexity of IBD arises from the interplay of multiple factors. The heterogeneity observed in monocytes differentiation within the IBD milieu suggests that they may adopt diverse cellular fates influenced by various determinants.<sup>83</sup> While our current understanding is limited regarding whether monocytes differentiate into cell types other than macrophages and dendritic cells, available evidence suggests that their differentiation is intricately linked with factors such as the intestinal microenvironment, inflammatory responses, bio-signaling molecules, genetic predispositions and immunoregulation. For a comprehensive understanding of the role and functionality of monocytes in IBD, in-depth studies focusing on their differentiation pathways and mechanisms in inflammatory settings are crucial. These studies will shed light on their pivotal role in the pathogenesis of IBD and could provide essential insights for developing novel therapeutic strategies.

## Effect of Inflammatory Microenvironment on Monocytes Differentiation

Under physiological homeostasis, monocytes predominantly replenish the pool of intestinal macrophages, typically differentiating into tolerogenic macrophages.<sup>6,83</sup> However, the delicate balance between monocytes and macrophages is perturbed in IBD, resulting in a substantial influx of monocytes to the intestines and mesenteric lymph nodes. Once recruited, these monocytes differentiate into inflammatory macrophages, characterized by robust phagocytic capabilities and the capacity to produce inducible nitric oxide synthase (iNOS).<sup>84,85</sup> This shift is hypothesized to be a consequence of an interruption in the monocytes maturation process, culminating in the accumulation of intermediate form macrophages. This aberration subsequently leads to an augmented population of inflammatory macrophages following Toll-like receptor (TLR) stimulation.<sup>83</sup> Intriguingly, this disruption in equilibrium may be intricately linked to the absence of IL-10 receptor (IL-10R) expression.<sup>86</sup> Furthermore, it has been demonstrated that IFN- $\gamma$  plays a pivotal role in maintaining the inflammatory macrophages within the inflamed intestinal milieu.<sup>87</sup>

The process of monocytes differentiation extends beyond the simple production of inflammatory macrophages, as demonstrated by experimental mouse colitis models. In these models, in the presence of CD4<sup>+</sup> T cells, IFN- $\gamma$ -stimulated monocytes-derived cells represent a distinct population of newly activated macrophages.<sup>88</sup> Recent research has elucidated that during the resolution phase of gut muscular inflammation, activated enteric glial cells facilitate monocytes infiltration via the release of CCL2 and CSF1, ultimately leading to their differentiation into anti-inflammatory macrophages.<sup>89</sup> Moreover, it has been observed that non-classical monocytes tend to differentiate into macrophages that play a pivotal role in promoting wound healing.<sup>90,91</sup> Over time, monocytes also possess the capacity to differentiate into migratory antigen-presenting cells with dendritic cell characteristics, referred to as moDCs.<sup>47</sup>

Consequently, within the inflammatory milieu of IBD, monocytes differentiation emerges as a complex and multifaceted process. While contemporary researches suggest that differentiated inflammatory macrophages are predominant in such inflammatory conditions, a comprehensive examination of additional subsets is indispensable. A meticulous investigation of these various subsets could shed light on the intricacies governing the diverse differentiation pathways of

monocytes, thereby elucidating the intricate mechanisms underpinning this process. Such insights could potentially pave the way for novel therapeutic interventions aimed at modulating monocytes differentiation to ameliorate IBD pathology.

## Relationship Between Intestinal Microbes and Monocytes Differentiation

During acute inflammation in IBD patients, infiltrating monocytes within the lamina propria alter tight junctions, inducing epithelial cell apoptosis and disrupting mucosal integrity through inflammatory factors. This leads to the exposure of the intestinal mucosa to gut microbiota.<sup>92</sup> In the case of animal models with acute colitis, Ly6C<sup>hi</sup>CX3CR1<sup>int</sup> monocytes accumulate and activate TLR and NOD2 recognition pathways. They respond to bacterial products and differentiate into pro-inflammatory effector cells secreting IL-6 and IL-23, as well as cells with antigen-presenting characteristics,<sup>47</sup> potentially referred to as moMφs and moDCs respectively. Research indicates that fecal bacteria from CD patients induce monocytes differentiation into macrophages that express high levels of pro-inflammatory cytokines.<sup>93</sup> Conversely, the probiotic strain *Saccharomyces boulardii* can induce the proliferation of classical monocytes, which, upon infiltrating the lamina propria, differentiate into CX3CR1<sup>+</sup>Mφ.<sup>94</sup> Moreover, gut microbiota like *M. Capsulatus Bath* affect the activation and maturation of moDCs.<sup>95–97</sup> Due to the rich diversity of gut microbiota, combined with the heterogeneity of monocytes differentiation, examining a single microbial group or species might not sufficiently elucidate their interrelationships.

## The Relationship Between Cytokines and Monocytes Differentiation

Recent research highlights the role of cytokines and growth factors in directing monocytes differentiation. Classical monocytes, when activated by CD30L, tend towards inflammatory monocytes through the CCL2/CCR2 and NF-κB signaling pathways.<sup>56</sup> Schridde et al demonstrated that TGF-β is pivotal for intestinal monocytes differentiation into macrophages.<sup>98</sup> Furthermore, during IBD inflammation, moMφs' TGF-β activation ability via integrin αβ8 diminishes.<sup>10</sup> Recent findings emphasize GM-CSF-induced STAT5 tetramerization as critical for monocytes differentiation. STAT5 tetramers are essential for monocytes to become moDCs. Aberrations in these tetramers shift differentiation towards functionally distinct moMφs, with heightened arginase I expression and reduced LPS-induced NO synthesis.<sup>99</sup> A noteworthy observation is that moMφs, when treated with GH within a GM-CSF milieu, demonstrate a pronounced bias towards anti-inflammatory gene signatures. This shift is attributed to a decline in activin A mediated via the PI3K pathway and an upsurge in MAFB expression, collectively impeding the polarization towards pro-inflammatory macrophages.<sup>100</sup>

In-depth examinations of experimental colitis paradigms suggest that IFN-γ orchestrates the differentiation trajectory of monocytes towards macrophages. This orchestration occurs via an epigenetic mechanism, specifically through the acetylation of the promoter region of the NOS2 gene, mediated by the STAT-1 signaling pathway.<sup>87</sup> Within the monocytes-macrophage axis, the expression of IRF5 predominantly channels the differentiation of Ly6Chi monocytes into the CD11c<sup>+</sup>moMφs phenotype.<sup>101</sup> Interestingly, when exposed to GM-CSF, monocytes exhibiting IRF4 anomalies also favor macrophage differentiation. Contextualizing this within the broader cytokine-mediated modulation landscape, it is postulated that IRF4 may function downstream of the STAT5 tetramer assembly, though this intricate mechanism merits comprehensive exploration.<sup>99,102</sup> Moreover, the genetic backdrop characterized by miR-223 deficiency manifests in a pronounced decrement in the CR3CX1<sup>+</sup>MΦ population, contrasted by an augmentation in moDCs differentiation trajectory.<sup>103</sup> Recent discoveries underscore that in monocytes, NOD2 activation exerts an inhibitory effect on macrophage differentiation, operating through the mTOR signaling cascade and modulated by the TNF-α axis.<sup>104</sup> This insight potentially elucidates the pathophysiological accumulation of deleterious moMφs observed in CD patients harboring risk-associated NOD2 alleles or specific missense mutations. Lu et al using murine models, shown that the Monocytes Chemotactic Protein-Induced Protein 1 is upregulated through the ATF3-AP1S2 pathway, promoting pro-inflammatory polarization of moMφs in the intestinal mucosa.<sup>105</sup> Conversely, Zhou et al reported that the herbal compound, Xianglian Wan, restores colonic immune balance by disrupting the STAT1 and PPARγ interaction, reducing moMφs production, and favoring anti-inflammatory macrophage polarization, validated in IBD patients.<sup>106</sup> Table 2



**Table 2** Differentiation of Mouse Monocytes During Intestinal Inflammation

| Cell Type              | Inflammatory Environment                          | Signal or Mechanism                                   | Reference     |
|------------------------|---|---|---------------|
| <b>Monocyte subset</b> | DSS induce acute colitis                          | CD30L, CCL2/CCR2, NF-κB                               | [23–25,56]    |
| <b>moMφs</b>           |   |   |               |
| Inflammatory Mφ        | T cell-mediated colitis/ DSS induce acute colitis | IL-10R deficiency; IFN-γ support; TGFβ downregulation | [10,83–85,93] |
| IFNγ-MdC               | DSS induce acute colitis                          | CD4+T cell/IFN-γ, M-CSF                               | [88]          |
| Anti- Inflammatory Mφ  | Small intestinal muscularis inflammation          | CSF-1   | [89]          |
| Reparative Mφ          | In vivo wound healing                             | <i>Nr4a1</i>  | [90]          |
| CX3CR1 <sup>+</sup> Mφ | Infectious colitis                                | Probiotics  | [86,94,103]   |
| CD11c <sup>+</sup> Mφ  | Helicobacter hepatica + aIL-10R colitis           | IRF5  | [101]         |
| <b>moDCs</b>           | DSS induce acute colitis                          | TLR-NOD2; Tetramerization of STAT5                    | [47,99]       |

In summary, monocytes differentiation within the ambit of IBD embodies a multifaceted biological trajectory. Contemporary research avenues have yet to distinctly demarcate whether moMφs and moDCs possess overlapping developmental continuums. A long-standing focal point in the discourse remains the identification of pivotal signaling events that underpin the heterogeneity in monocytes differentiation. The pertinent query centers on whether these signals arrest moMφs and moDCs at specific developmental junctures or if they directly modulate the differentiation trajectory of monocytes.

## Function of Monocytes in IBD

In 2010, the International Federation of Immunological Societies' Nomenclature Committee formally classified human monocytes into three subgroups: classical (CD14<sup>++</sup>CD16<sup>-</sup>), intermediate (CD14<sup>++</sup>CD16<sup>+</sup>), and non-classical (CD14<sup>+</sup>CD16<sup>++</sup>).<sup>107</sup> The primary functions of classical monocytes include potent phagocytosis, tissue repair, production of inflammatory mediators such as TNF-α, IL-1β, ROS in response to microbial pathogens, and the capability to migrate to inflamed lesions. Intermediate monocytes display production of inflammatory mediators such as TNF-α, IL-1β, IL-6, proliferation during infections, and antigen-presentation roles. Meanwhile, non-classical monocytes mainly perform “patrolling” of endothelial cells, Fcγ-mediated phagocytosis, and secretion of TNF-α, IL-1β, CCL3 under immunogenic stimuli.<sup>108</sup>

Though all three subgroups can produce pro-inflammatory cytokines, classical monocytes are the best producers, followed by intermediate monocytes, and the least effective are the non-classical monocytes.<sup>109</sup> This further elucidates the functional heterogeneity of monocytes. For instance, the deficiency of COMMD10 enhances the inflammatory mediator activity of classical monocytes,<sup>110</sup> the downregulation of Tim-3 leads to higher expression of pro-inflammatory cytokines in classical monocytes.<sup>111</sup> Furthermore, in inflamed colonic venous endothelium, non-classical monocytes accelerate subsequent leukocyte activation and infiltration by locally producing inflammatory cytokines and chemokines.<sup>112</sup> They also significantly express α4β7 integrins, promoting wound healing at the lesion sites.<sup>62,113</sup> Notably, in UC patients with anxiety and depression symptoms, the percentage of intermediate and non-classical monocytes in peripheral blood is higher, their phagocytic function is reduced, and these cells' functions are impaired.<sup>114</sup> This indicates that the phenotype of monocytes subgroups can vary with or without coexisting diseases. Due to the significant phenotypic and functional differences between monocytes subgroups, the immune response mechanisms induced by monocytes remain intricate.

## Monocytes Directly Regulate Intestinal Inflammation

Monocytes occupy a pivotal position in orchestrating the inflammatory response characteristic of IBD, primarily through the induction of iNOS/NO and the secretion of pro-inflammatory cytokines including IFN-γ, TNF-α, IL-1β, IL-6, IL-8, IL-12 and IL-23.<sup>9–14,115–117</sup>

On the one hand, IBD is marked by a surge of monocytes that release oxygen radicals and enzymes, culminating in tissue damage.<sup>118</sup> The resultant injury to the mucosal tissue, when exposed to the diverse microbial milieu of the gut, leads to an augmented activation of monocytes STAT3. This, in turn, compromises the patient's innate defenses, potentiates low-level bacterial infections, and serves as a catalyst for the disease.<sup>119</sup> Illustratively, chronic infection with *Toxoplasma gondii* intensifies monocytes activation, thereby escalating the release of the inflammatory mediator NO and the concomitant secondary environmental damage.<sup>120</sup> The activation of the iNOS/NO pathway by monocytes amplifies the inflammatory response in IBD, perpetuating tissue damage. Notably, the attenuation of iNOS/NO activity generated by monocytes has been shown to mitigate experimental colitis.<sup>121,122</sup> Conversely, VEGFR1<sup>+</sup> cells, derived from the monocytes lineage, foster the accumulation of Treg cells in the ulcerated regions of DSS-induced colitis via tyrosine kinase signaling.<sup>123</sup> In the inflamed milieu, monocytes release microparticles that express pro-coagulant tissue factors, thereby facilitating the healing of the damaged mucosa.<sup>124</sup>

On the other hand, alterations in the surface expression of cytokine receptors on monocytes (eg, IL-1R, CXCR3, TNF-related receptors),<sup>9,125,126</sup> the activation of inflammatory cytokine pathways (eg, NF- $\kappa$ B, MAPK, JAK/STAT signaling pathways),<sup>115,125,127–132</sup> and the subsequent regulation of pro-inflammatory genes<sup>12,14</sup> collectively contribute to an amplification of the inflammatory response mediated by monocytes.<sup>110,133</sup> However, the intricacies of the molecular mechanisms governing the dysregulation of cytokine secretion in monocytes during IBD remain to be fully elucidated. While the administration of anti-inflammatory drugs and certain synthetic compounds that inhibit inflammatory mediators has demonstrated efficacy in ameliorating experimental colitis, the translatability of these findings to clinical IBD treatment necessitates further exploration.<sup>63,134–136</sup> This exploration may potentially unravel the interplay between inflammatory cytokines and extrinsic factors that modulate the inflammatory regulatory role of monocytes. Exogenous IL-10 significantly inhibits IL-12 release from LPMC stimulated with IFN- $\gamma$ -treated LPS. Yet, PGE2's inhibition of IL-12 could only be partially reversed by an anti-IL-10 monoclonal antibody,<sup>137</sup> highlighting the intricate interplay among inflammatory cytokines. Studies also indicated that platelet-derived hyaluronidase 2 cleaves HA into fragments that directly stimulate monocytes in the inflammatory milieu to produce pro-inflammatory cytokines.<sup>138</sup> In murine colitis models, GM-CSF modulates monocytes to upregulate cytokines like IL-4, IL-10 and IL-13, promoting Th2 T-cell differentiation.<sup>7</sup> Vagus nerve stimulation ameliorates colonic damage, attributed to enhanced epithelial barriers and suppressed monocytes JAK1/STAT6 signaling.<sup>139–141</sup> In light of these complex networks and interactions that characterize the interplay between inflammatory cytokines, the ideal therapeutic strategy for IBD would encompass compounds that restore or recalibrate the delicate balance between pro-inflammatory and anti-inflammatory cytokines. This balanced modulation has the potential to substantially mitigate the inflammatory cascade characteristic of IBD, thereby ameliorating the clinical manifestations of the disease (Table 3).

**Table 3** The Main Inflammatory Cytokines Produced by Monocytes During IBD

| Cytokines     | Function          | Role in IBD   | Reference         |
|---------------|-------------------|---|-------------------|
| TNF- $\alpha$ | Pro-inflammatory  | Promote inflammatory cell infiltration and intestinal tissue damage                               | [10,14,104,108]   |
| IL-1 $\beta$  | Pro-inflammatory  | Promote inflammation and stimulate the production of other cytokines                              | [10,12,16,108]    |
| IL-6          | Pro-inflammatory  | Participate in the process of inflammatory response   | [12,14,47,108]    |
| IL-10         | Anti-inflammatory | Inhibiting the release of inflammatory mediators and inflammatory reactions                       | [7, 86, 137, 142] |
| IFN- $\gamma$ | Pro-inflammatory  | Activating macrophages and promoting inflammatory processes                                       | [10,87,137]       |
| GM-CSF        | Duality           | Improving bacterial clearance and inducing wound healing, as well as regulating adaptive immunity | [7,16]            |
| TGF- $\beta$  | Anti-inflammatory | Regulating the life process of monocytes and suppressing excessive immune responses               | [10,98,145]       |
| IL-12         | Pro-inflammatory  | Regulate immune cells and stimulate the production of other cytokines                             | [16]              |
| IL-23         | Pro-inflammatory  | Promote Th17 cell differentiation, thereby promoting inflammation                                 | [13]              |
| IL-4          | Anti-inflammatory | Suppress excessive immune response and alleviate inflammatory response                            | [7,142]           |
| IL-8          | Pro-inflammatory  | Related to the severity of colitis  | [9,17]            |
| IL-1ra        | Anti-inflammatory | Related to the severity of colitis  | [9]               |

## Regulation of Leukocyte Function

In the context of IBD, monocytes regulate other immune cells (eg, T lymphocytes, neutrophils, eosinophils) primarily through antigen presentation and cytokine secretion. Experiments using peripheral blood mononuclear cell isolated from UC patients have shown that CD14<sup>+</sup> monocytes expressing CD1a stimulate the activation and differentiation of CD4<sup>+</sup> T cells into Th cells.<sup>15</sup> Furthermore, when treated with the *Hymenolepis diminuta* antigen HdAg, monocytes present antigens that enhance the production of IL-10 and IL-4 by activated T cells, alleviating DSS-induced colitis.<sup>142</sup>

In IBD, there is a significant inverse correlation between the expression of miR-374a-5p in monocytes and pro-inflammatory genes (eg, TNF $\alpha$ , IL1A, IL6, and OSM), as well as the ability to activate T cells.<sup>14</sup> Early studies postulated that in the pathogenesis of CD, lamina propria monocytes produce IL-12, which, through an unknown mechanism, drives a pathogenic Th1-associated immune response.<sup>143</sup> IL-12, IL-1 $\beta$ , and CD163-negative monocytes-like cells induce the expression of IL-8 in colonic CD4<sup>+</sup> T cells.<sup>16</sup> Similarly, monocytes-derived IL-12 and IL-23 contribute to the promotion of Th1/Th17 immune responses in the colonic mucosa.<sup>144</sup> Moreover, IECs induce monocytes TGF- $\beta$  expression via thrombospondin-1, fostering the generation of induced regulatory T cells and mitigating experimental colitis in mice.<sup>145</sup>

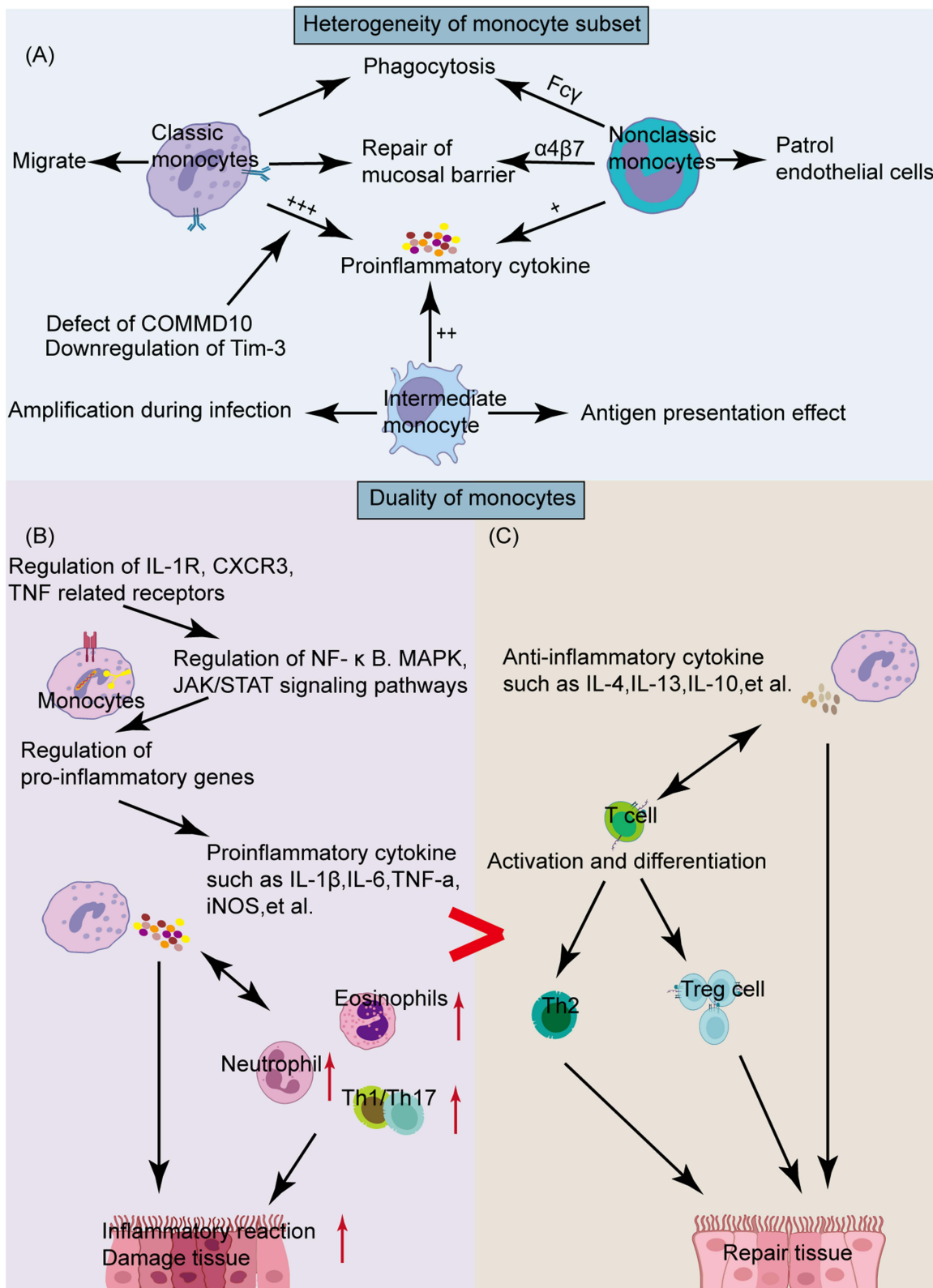
In addition to modulating T lymphocytes, monocytes also participated in regulating other innate immune cells. For example, low concentrations of Clostridium difficile toxin effectively stimulate monocytes to release IL-8, promoting neutrophil extravasation and tissue infiltration.<sup>17</sup> In studies of DSS-induced colitis, inflammatory monocytes express CCL11, leading to an increase in eosinophilic granulocytes.<sup>18</sup> These findings underscore the complexity of monocytes-mediated immune regulation in IBD, encompassing cytokines, chemokines, T cells, and a myriad of interacting mechanisms (Figure 3).

## Conclusion

Monocytes, pivotal constituents of the immune system, play an indispensable role in the pathogenesis of IBD. Originating in the bone marrow, these cells navigate through the bloodstream, targeting inflamed sites where they orchestrate inflammatory responses. Within the IBD milieu, monocytes undergo further differentiation, engaging in inflammatory reactions, tissue repair, and immune modulation through their recruitment, tissue infiltration, and cytokine release.

A particularly noteworthy aspect of monocytes in IBD is their role in bridging intestinal inflammation with the neuroendocrine system. Recent evidence from colitis mouse models reveals that  $\alpha 4\beta 7$  integrin-expressing monocytes are instrumental in recruiting neutrophils to the brain vasculature. This interaction precipitates heightened cytokine concentrations, with a marked surge in IL-1 $\beta$  levels—a cytokine implicated in mediating anxiety-like behaviors.<sup>146</sup> Furthermore, specific commensal bacteria, namely *B. vulgatus* and *F. varium*, incite human moDCs, culminating in augmented corticotropin-releasing factor (CRF)/Urocortin 1 (UCN1) 2 levels. As modulators of brain stress networks, CRF/UCN1 exacerbates anxiety-like behaviors.<sup>147,148</sup> Corroborating this link, IBD patients exhibit infiltration of monocytes, along with other immune cells, in the enteric ganglia.<sup>149</sup> External stressors, via the hypothalamic-pituitary-adrenal axis, escalate glucocorticoid concentrations. Prolonged exposure to these elevated glucocorticoid levels catalyzes the genesis of pro-inflammatory subsets of intestinal glial cells, which in turn, amplify TNF- $\alpha$ -mediated inflammation in monocytes via CSF1.<sup>150</sup> This revelation poses implications for the clinical administration of corticosteroids in IBD management, suggesting that while they may transiently dampen inflammation, their chronic use could potentially exacerbate the disease.

The intricate crosstalk between the neuroendocrine system and gut immunity, orchestrated by monocytes, underscores their paramount significance in IBD. As we chart the future course of research, it becomes imperative to probe deeper into the regulatory dynamics governing monocytes differentiation and function, and their interplay in IBD. Such insights could unveil novel therapeutic strategies and pathways for the prevention and management of IBD. Understanding the nuanced roles and functionalities of monocytes and their progenies can illuminate the pathogenesis of IBD, heralding innovative therapeutic avenues. Elucidating the regulatory and operational mechanisms of monocytes can potentially unveil therapeutic targets, thereby catalyzing the design of inhibitors or activators that modulate their activity in intestinal inflammation. The ongoing clinical development of novel therapeutic agents—including selective Janus kinase inhibitors,



**Figure 3** Functional heterogeneity and duality of monocytes in IBD. **(A)** Monocytes exhibit functional heterogeneity, with different subtypes displaying distinct functional characteristics. **(B)** The stimulation of various cytokine receptors, triggered by the underlying causes of IBD, activates downstream inflammatory signaling pathways, which increasing pro-inflammatory gene expression. This results in heightened inflammation and, through interactions with other immune cells, exacerbates intestinal damage. **(C)** Monocytes also produce anti-inflammatory cytokines during IBD, fostering immune regulatory interactions that aid in intestinal repair.

sphingosine-1-phosphate receptor modulators, SMAD7 antisense oligonucleotides, phosphodiesterase 4 inhibitors, IL-12/IL-23 inhibitors, and integrin inhibitor biologics—coupled with advances in drug combination strategies and nanoparticle targeting technologies, promises to significantly enhance the treatment landscape for patients with IBD. Additionally, insights into the reparative role of monocytes in tissue injury could pave the way for therapeutic interventions focused on tissue repair in IBD. An expanded understanding of how monocytes modulate systemic immunity may also engender pioneering immunotherapeutic approaches, enhancing the overall treatment efficacy for IBD.

## Data Sharing Statement

No new data were generated or analyzed in support of this research.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no competing interests in this work.

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