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Macrophage interactions with fungi and bacteria in IBD

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Abstract

Purpose of the review—In this review, we discuss recent advances into delineating the dual role of intestinal phagocytes in health and during intestinal disease. We further discuss the key role of gut-resident macrophages in recognition of bacterial and fungal microbiota in the gut.

Recent findings—Inflammatory bowel disease (IBD) commonly manifests with pathologic changes in the composition of gut bacterial and fungal microbiota. Intestinal macrophages are key regulators of the balance between tolerogenic immunity and inflammation. Recent studies have highlighted the role of resident intestinal macrophages in the control of commensal fungi and bacteria in the steady state and during dysbiosis. The dual role of these cells in maintaining intestinal homeostasis and responding to microbiota dysbiosis during inflammation is being increasingly studied.

Summary—It is becoming increasingly clear that an aberrant pro-inflammatory response to microbiota by infiltrating monocytes plays a role in the development of intestinal inflammation. Intestinal mononuclear phagocytes with characteristics of macrophages play an important role in limiting fungal and bacterial overgrowth under these conditions, but can be influenced by the inflammatory environment to further propel inflammation. Better understanding of the interaction of intestinal macrophages with host microbiota including commensal fungi and bacteria, provides an opportunity for the development of more targeted therapies for Inflammatory Bowel Disease.

Keywords

Intestinal macrophage; mycobiota; bacterial microbiota; intestinal inflammation

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Introduction

The yin and yang of intestinal macrophages

Due to their functional role and location in close proximity to the intestinal epithelium mononuclear phagocytes have been historically considered as both “sensors” and “responders” to the intestinal environment. Macrophages in the gastrointestinal tract of both human and mouse share a similar distribution, a high threshold to activation upon stimuli, and the expression of phagocytic and pattern recognition receptors. Yet, they are characterized by different combination of surface markers including CD11b, the fractalkine receptor CX3CR1, F4/80 and CD11c [1–3]. Mononuclear phagocytes expressing the CX3CR1 and displaying a macrophage phenotype, have been shown to play a key role in the uptake of food antigen, an in the sampling of bacterial and fungal antigens from the intestinal lumen [3–7]. The majority of these intestinal lamina propria macrophages differentiate from CCR2⁺CX3CR1^{int}Ly6C^{hi} monocytes and are constantly replenished during the steady state [1] (Fig. 1). Their ability to sense the intestinal environment during steady state and the innate capacity to overdrive inflammatory immunity during intestinal disease put intestinal macrophages at the crossroad between protective immunity and inflammation. Understanding the mechanisms controlling this dual function holds major promise for improving therapeutic outcomes for inflammatory bowel disease (IBD) by targeting specific pathways.

Role on gut resident macrophages in the maintenance of intestinal immune homeostasis

Consistent with their role in controlling immune responses to microbiota, diet and other environmental cues, mononuclear phagocytes have been shown to play a role in restriction of intestinal inflammation through direct control of the microbiota or through the release of local anti-inflammatory molecules (Fig. 1).

Studies in children with very early onset IBD have underlined the importance of IL-10 in preventing intestinal inflammation with macrophages being key responders to this cytokine [8–10]. Recent study further defined a subset of IL-10 producing CD11c⁺ mononuclear phagocytes in the human colon [11]. These tolerogenic CD11c⁺ phagocytes originated from monocytes following mucosal conditioning in the intestine and were decreased in inflamed colons of IBD patients [11, 12]. In contrast to the colon, IL-10 producing macrophages are less common in the small intestine. Transcriptional and functional profiling of macrophages in duodenal transplants defined four distinct populations of these cells, albeit none of them produced IL-10 [13]. Although the response to IL-10 rather than its production seems to be important for the maintenance of tolerogenic properties of macrophages [10], these findings hint at a compartmentalization of IL-10 producing macrophages in the human gut that correlates with dietary factors and specific microbial distribution.

Other molecules, such as TGF- β and retinoic acid (RA), are important for the anti-inflammatory properties of intestinal macrophages (Fig. 1). However, major differences between human and mouse macrophages have been described in this regard. While human gut-resident macrophages are able to produce RA, in mice this property is restricted to conventional dendritic cells (cDCs) [14–17]. Furthermore, RA might have different impact

on macrophages during the steady state and during inflammation. Indeed, RA production by infiltrating monocytes and macrophages has been reported in patients with Crohn's Disease (CD) while blockade of RA receptor signaling reduced TNF- α production by these cells in vitro [17]. Similarly, in human gut-resident macrophages TGF- β might play a more central role in inducing hypo-responsiveness of those cells to microbial products than in mice [2].

Numerous reports have established an important role of GM-CSF in the control of monocyte dependent mucosal homeostasis in IBD. GM-CSF enhances both antimicrobial and immunoregulatory properties of intestinal monocytes and macrophages [18]. Loss of GM-CSF signaling through either production of GM-CSF autoantibodies [19], decreased cell surface abundance of the GM-CSF receptor alpha chain subunit CD116 [20] or frameshift mutations leading to reduced GM-CSF dependent STAT5 activation [21] have been associated with increased risk for CD.

In addition to secretory molecules, the peroxisome proliferator-activated receptor gamma (PPAR γ) axis was recently shown to play critical roles in the polarization of tolerogenic intestinal macrophage. Inhibition of the mammalian target of rapamycin (mTOR) or loss of semaphorin 6D (Sema6D), both leading to loss of PPAR γ signaling, caused a metabolic reprogramming and promoted an inflammatory phenotype in CX3CR1⁺ macrophages thus contributing to development of colitis [22].

Gut resident macrophages and intestinal inflammation

During inflammation in both mice and humans, mononuclear phagocytes expand in the intestinal lamina propria [1, 2, 17, 23]. Inflammation can also profoundly affect the differentiation of monocytes to fully mature and functional macrophages (Fig. 1). CD11c^{high}CCR2⁺CX3CR1⁺ monocytes that infiltrated in the colonic intestinal mucosa of IBD patients in a CCR2-dependent manner did not differentiate fully to macrophages and produced the pro-inflammatory cytokine IL-1 β [11]. Macrophages isolated from patients with CD produced higher levels of IL-1 β upon stimulation, which correlated with decreased SHIP levels [24]. Consistently, macrophages from SHIP-deficient mice showed increased *Il1b* levels, which contributed to spontaneous ileal inflammation [24]. Increased monocyte infiltration and production of large amounts of pro-inflammatory mediators including TNF α , IL-1, IL-23, nitric oxide (NO) by monocytes and macrophages is a key characteristic of IBD [1, 2, 16, 17, 23, 25] (Fig. 1).

In addition to the pro-inflammatory cytokine IL-1, IL-23 produced by CD11c⁺ MNPs was also identified as a strong inflammatory mediator to trigger intestinal inflammation in *Helicobacter hepaticus* induced IL-10R deficiency colitis model [26, 27]. Cyclic induction of IL-23 production by CX3CR1⁺ MNPs predisposed mice to diet-induced colitis [28]. This, together with recent clinical study conducted in CD patients treated with ustekinumab (p40 subunit blockade, targeting both IL-12 and IL-23) [29], suggest that IL-12/IL-23 blockade might act by targeting monocytes and macrophages to suppress intestinal inflammation in IBD.

Bacterial interactions with mononuclear phagocytes in health and during intestinal disease

Gut microbiota plays an important role in maintenance of the tolerogenic function of intestinal macrophages (Fig. 1). Bacterial dysbiosis is strongly associated with intestinal inflammation and IBD [30][31, 32]. Microbial sensing by macrophages promotes GM-CSF production by type 3 innate lymphoid (ILC3) cells [33]. Disruption of this regulatory loop led to reduced regulatory T cell (Treg) numbers and increased intestinal inflammation [33]. Similarly, the interaction between microbiota, macrophages and ILC3 has been shown to control IL-22 release and play a role in intestinal epithelial cell healing [34].

Intestinal epithelium-adhering bacteria can interact with CX3CR1⁺ MNPs to modulate the immune balance in health and diseases. Segmented filamentous bacteria (SFB) interaction with the gut epithelium induced Th17 responses through CX3CR1⁺ MNPs [35, 36]. Expansion of adherent-invasive *Escherichia coli* (AIEC) has been reported in the ileal mucosa during active CD [37][38]. AIEC was capable to induce IL-10 production by CX3CR1⁺ MNPs and suppressed Th17 immune responses [36, 38]. In the absence of IL-10 signaling AIEC induced Th17 immune responses and aggravated intestinal disease in IL-10 knockout mice, but not in wild-type mice [38]. Similarly, loss of IL-10 signaling resulted in severe colitis in mice upon diet-driven expansion of pathobionts such as *B. wadsorthia* [39]. The role of CX3CR1⁺ MNPs in the maintenance of non-inflammatory state is further emphasized by depletion experiments leading to the expansion of Th1 and Th17 cells in mice colonized with intestinal epithelium-adhering bacteria [36]. Tolerogenic responses seem to be further controlled by the presence of healthy commensal microbiota, as antibiotic-induced dysbiosis abrogated the tolerogenic effect of CX3CR1⁺ MNPs on Treg differentiation [36].

Recently, oral cavity-derived *Klebsiella* species have been shown to colonize the intestine of IBD patients [40]. Intestinal colonization with patient-derived *Klebsiella spp.* has been shown to induce severe colitis upon IL-10 deficiency via the induction of Th1 pro-inflammatory immune response [40]. However, *Klebsiella* failed to exacerbate intestinal inflammation in wild-type, indicating that IL-10 is required to restrain the *Klebsiella*-induced pathogenic Th1 immune response. Although it has been suggested that intestinal phagocytes (CD11b⁺CD103⁺ DCs) can sense *Klebsiella spp.* and induce Th1 cells polarization, whether intestinal phagocytes, such as CX3CR1⁺ MNPs are involved to control immune homeostasis balance when ectopically bacteria colonize the gut of healthy individual remains to be investigated. Altogether, these studies suggest that CX3CR1⁺ MNPs are crucial to regulating the balance between effector T cells and Tregs under immune homeostatic condition to limit intestinal pathology development.

Fungal interactions with mononuclear phagocytes in health and during intestinal disease

Two major Phyla, Ascomycota and Basidiomycota, dominate the intestinal mycobiota in human and in mice. Among the Ascomycota, *Candida* and *Saccharomyces* are among the most prevalent and abundant genera in the human intestine. Intestinal fungi have been shown to affect the intestinal niche both directly or through the modulation of the intestinal microbiota [3, 41–43]. Mono-colonization of germ-free mice with *Candida albicans* or

Saccharomyces cerevisiae promotes the establishment of intestinal homeostasis. Importantly, both species exert a striking protective effect against mucosal injury in a model where bacteria are depleted with a combination of broad-spectrum antibiotics [44]. Targeting the healthy fungal community can also lead to undesired consequences. We have shown that in specific-pathogen-free (SPF) mice, perturbation of the fungal microbiota using anti-fungal drugs has a detrimental impact on the development of intestinal inflammation [41]. These studies suggest that intestinal fungi are not intrinsically detrimental. Rather, fungal communities contribute to the maintenance of intestinal homeostasis in healthy hosts but can worsen the disease outcome in conditions permissive of the overgrowth of potentially pathogenic fungal species.

Several factors including diet, oral hygiene or medications can influence the composition of the mycobiota without altering intestinal homeostasis [45]. More dramatic perturbations of the fungal communities have been observed in IBD patients and have been associated with the disruption of the epithelial barrier and the shift to a pro-inflammatory environment that could favor the development of intestinal inflammation. In particular, an increased abundance of *Candida* spp. is associated with both experimentally induced intestinal inflammation and IBD [3, 46–50]. Intestinal colonization with *Saccharomyces cerevisiae* and *C. glabrata* has been shown to exacerbate the outcome of chemically induced colitis in wild-type SPF mice [42, 43].

Importantly, the detrimental effect of fungal species has been demonstrated in models where intestinal homeostasis was strongly compromised or where the fungal load was greatly increased. In the clinics, these conditions are present in subsets of IBD patients and include prolonged epithelial damage [43], intestinal dysbiosis [41, 42] or compromised anti-fungal immunity [3, 47] (Fig. 1). We have recently shown that *Candida albicans* and *Candida tropicalis* do not exacerbate the outcome of DSS intestinal inflammation in immune-competent mice [3]. Interestingly, immune-deficient hosts with an impaired anti-fungal immunity failed to control *Candida* spp. outgrowth and experience an exacerbated colitis [3, 47]. In mice deficient in the anti-fungal receptor Dectin-1 (*Clec7a*) opportunistic fungi can invade the intestinal mucosa and be detrimental during chemically induced colitis [47, 51]. We have recently shown that intestinal CX3CR1⁺ MNPs express high amount of Dectin-1 and other C-type lectin receptors, can intake various fungal commensals and initiate anti-fungal adaptive immune responses via the Syk signaling pathway [3]. Impaired CX3CR1⁺ MNP function predisposed mice to intestinal disease caused by intestinal *Candida* spp. [3]. Altogether these recent studies suggest that similar to commensal bacteria, gut mycobiota might be beneficial to host immunity and health, and can contribute to intestinal disease only under specific conditions. CX3CR1⁺ MNPs appear as a key subset of phagocyte not only interacting with intestinal bacteria, but also with intestinal fungi. It remains to be investigated whether other cell types in the phagocyte network lining the intestines might also play a role in the “transmission” of immunological signals generated upon fungal interactions with CX3CR1⁺ MNPs.

Role of mononuclear phagocytes in anti-fungal antibody responses in IBD

Antibodies against *Saccharomyces cerevisiae*'s mannan (ASCA) are known to be increased in Crohn's disease patients even before the clinical diagnosis of CD and are elevated in 20–25% of their first degree relatives [52][46]. Interestingly, their production is induced by both *C. albicans* and *S. cerevisiae* [46][53]. However, the mechanisms behind ASCA generation are poorly understood. CD patients with defects in the mannan-binding lectin (MBL) that binds to component of the fungal cell wall, have increased level of circulating mannan and enhanced levels of circulating ASCA [54].

Upon depletion of CX3CR1⁺ MNPs, mice fail to control fungal burden and to mount the systemic humoral IgG responses observed in wild type mice after colonization with *Candida albicans* [3]. CX3CR1⁺ MNPs appear important for the proliferation and differentiation of B cells into antibody secreting. Plasma and memory B cells. CX3CR1⁺ MNPs have been shown to promote follicular helper T (Tfh) cells differentiation and germinal center formation in response to systemic live bacteria [55]. In vitro, sorted intestinal CX3CR1⁺ MNPs can directly stimulate B cells to produce both IgG and IgA. In vivo, the induction of mucosal IgA and IgG upon systemic delivery of the model antigen OVA appears mediated by CX3CR1⁺ MNPs in a Peyer's patches (PP) independent manner and requires the proliferation inducing ligands, such as BAFF and TNF- α [56]. The exact mechanisms by which CX3CR1⁺ MNPs mediate the induction of humoral responses to fungi in the gut still remains unclear.

In CD patients, a dysfunctional CX3CR1 variant is associated with the development of intestinal stenosis and ileocolonic involvement. This mutation has been previously associated with increased risk and worse outcome of human systemic candidiasis [57] and interferes with the fractalkine-mediated survival of blood monocytes [58]. Moreover, CD patients carrying this mutation have reduced serum levels of ASCA IgG and present reduced IgG titers against a variety of fungal commensals [3]. These finding suggest that in these individuals a reduced number of CX3CR1⁺ MNPs results in impaired anti-fungal humoral responses. Whether antibody responses against fungi play any role in disease outcome or/and control of mycobiota, remains to be elucidated.

Conclusion

Intestinal resident macrophages are increasingly recognized as key cellular sensors that integrate signals from the luminal microbiota to regulate intestinal homeostasis. Recent evidences suggest that they actively promote an anti-inflammatory environment in the healthy gut and can shift to a pro-inflammatory state in response to deviations in the intestinal microbiota. It is crucial to better understand the cellular networks between intestinal resident macrophages, lymphocytes and gut epithelium in response to acute and chronic microbiota dysbiosis. Next steps should develop tools to precisely identify patients with compromised resident-intestinal macrophages function and asses the clinical advantage of targeting both fungal and bacterial microbiota and immune dysfunctions within this subset of IBD patients.

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Key Points:

- At steady state, gut resident macrophages are required for the establishment of an immunoregulatory response.
- In Inflammatory Bowel Disease patients, intestinal inflammation affects the maturation of infiltrating monocytes into tolerogenic macrophages and results in the accumulation of pro-inflammatory monocytes.
- Gut resident macrophages are required to control intestinal fungi and bacteria
- Defects in CX3CR1⁺ mononuclear phagocyte function worsens gut intestinal inflammation.
- Loss of function mutation in CX3CR1 affects the induction of humoral responses against intestinal fungi in Crohn's Disease patients.

Figure 1:

Dual role of intestinal resident macrophages (MΦ and monocytes in the intestine. Left: Intestinal phagocytes orchestrate the maintenance of intestinal homeostasis in response to microbial stimuli and food antigens. Right: during inflammation and dysbiosis, infiltrating monocytes and pro-inflammatory resident macrophages promote inflammatory responses. Among others, expansion of adherent-invasive *Escherichia coli* (AIEC) and *Candida* spp. occurs in IBD patients.