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Toll-like receptor-mediated immune responses in intestinal macrophages; implications for mucosal immunity and autoimmune diseases

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Abstract

Monocytes are precursors of macrophages and key players during inflammation and pathogen challenge in the periphery, whereas intestinal resident macrophages act as innate effector cells to engulf and clear bacteria, secrete cytokines, and maintain intestinal immunity and homeostasis. However, perturbation of toll-like receptor signaling pathway in intestinal macrophages has been associated with tolerance breakdown in autoimmune diseases. In the present review, we have summarized and discussed the role of toll-like receptor signals in human intestinal macrophages, and the role of human intestinal macrophages in keeping human intestinal immunity, homeostasis, and autoimmune diseases.

Keywords

macrophages; monocytes; autoimmune disease; intestine

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1. Introduction

The human intestinal tract harbors 10^{12} microorganisms per gram of luminal content, representing ten times more than that of human cells in the body [1, 2]. It is exposed constantly to massive foreign antigens and must discriminate between harmful and harmless antigens to ensure the normal function and homeostasis [3, 4]. The intestinal cells rapidly respond to different stimuli including microorganisms [4–6]. Meanwhile, the mucous barrier provides perfect protection against the diversity of bacteria residing in the lumen [7, 8]. Therefore, the interaction and conjunction between intestinal cells and luminal bacteria in the gut are identified to be crucial in maintaining intestinal homeostasis and are believed as “firewalls” for protection from the pathogens [1]. In the gut, mononuclear phagocyte system (MPS) maintains a delicate equilibrium between the induction of immune responses to potential pathogens and the tolerance to innocuous antigens [9]. Macrophages are major mononuclear phagocytes that play a crucial role in intestinal homeostasis and immunity [10, 11]. Monocytes in both human and mice are key players during inflammation and pathogen challenge in the periphery, whereas intestinal resident macrophages act as innate effector cells to engulf and clear bacteria or their products, secrete cytokines, and maintain intestinal homeostasis [10, 11]. However, perturbations between immunity and tolerance in the intestinal system have been shown to be associated with autoimmune diseases [12], including inflammatory bowel disease (IBD) [13, 14], systemic lupus erythematous (SLE) [15–17], type 1 diabetes (T1D) [18, 19], rheumatoid arthritis (RA) [20], and multiple sclerosis (MS) [21]. In this review, we have discussed the phenotypic characterization and function of intestinal macrophages, their subpopulations, and involvement in autoimmune diseases.

2. The origin and function of monocytes and macrophages in the intestine

Monocytes are a conserved population of leukocytes and play a central role in immune system [22, 23]. The homeostasis of tissue resident macrophages relies on the constant recruitment of blood monocytes [10, 11]. Recent studies showed that resident macrophages in mice are part of the MPS that arise from the hematopoietic system, which are constituted by self-renewal hematopoietic stem cells and progenitor cells in primary lymphoid organs [10, 11]. In human, monocytes express multiple molecules, including CD14 and CD16 [24]. Consequently, monocytes are regrouped into three main subsets based on their CD14 and CD16 expression, the classical subset (CD14++CD16−), the intermediate subset (CD14++CD16+) and the non-classical subset (CD14+CD16++) [25–27]. In humans, the classical monocytes are rapidly recruited to the sites of inflammation and produce IL-10 in response to the toll-like receptor (TLR) 4 ligand LPS [28]; while the classical monocytes in mice are most likely acting as the precursors of peripheral DCs and macrophages [29]. The non-classical monocytes have differential capacities to secrete key inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α and sCD14) in response to TLR stimulation [30, 31]. Furthermore, monocytes are involved in innate immunity against pathogens and toxins [23, 32, 33]. Notably, monocytes in human and mice are very preponderant phagocytic cells responding to specific signals through surface molecules, including scavenger receptors (SR-A and CD36), low-density lipoprotein receptors (LRP1), TLRs (TLR1, TLR2 and TLR4), chemokine receptors (CCR2 and CX3CR1), cytokine receptors (M-CSFR), Fcγ receptors

(FcγRs) and adhesion molecules (LFA-1) [33, 34]. Moreover, monocytes are important in antigen processing and presentation because of their large number in the periphery and their roles as DC progenitors [23, 35].

Recent opinions suggested that tissue macrophages in mice are derived from embryonic precursors that seed the developing tissues before birth [9–11]. However, a notable exception is the gastrointestinal tract, which contains large populations of resident macrophages, derived from blood monocytes in the steady state [10, 11]. A reasonable explanation is that intestinal macrophages are relatively short-lived compared to most other tissue macrophages and have very poor proliferative capacities, requiring a robust and rapid replacement from blood monocytes [28, 29, 36, 37]. Interestingly, human gut-resident macrophages do not fit into the classical “M1–M2” classification [28]. For instance, they express high levels of MHC-II and produce TNF-α constitutively that are normally associated with M1 or “classically activated” macrophages [38–40]; Whereas they also express CD206, CD163, and IL-10 that are associated with M2 or M2-like macrophages [41].

Macrophages are the most abundant mononuclear phagocytes in the healthy tissues and have emerged as crucial sentinels for the maintenance of tissue homeostasis [42]. Macrophages are further defined to equip with a broad range of pathogen recognition receptors that make them efficient at phagocytosis and produce inflammatory cytokines to maintain tissue homeostasis [43]. They are characterized by surface expression of CD14, CD68, HLA-DR, as well as human epidermal growth factor module-containing mucin-like receptor 1 (EMR1) in human tissues [9, 42]. However, resident gut macrophages in murine models are identified to express high levels of CD64, Fc-g receptor 1 (FcgRI), chemokine receptors CX3CR1 and CCR2 [1, 12, 43]. In addition, macrophages in human gut are identified to closely associate with the epithelial monolayer coupled with high phagocytic and actively bactericidal, which means they are ideally located to capture and destroy any material breaching the epithelial barrier [44]. Importantly however, this is not necessary to result in the release of pro-inflammatory mediators or respiratory burst [44, 45]. Intestinal macrophages in mice also serve as antigen-presenting cells due to their high expression of MHC-II and their ability to take up antigens [12, 29, 43]. And as one of the most abundant leucocytes living in the intestinal mucosa, macrophages in mice can be activated and regulated by the prototypical Th1, Th2 cytokines, microbial or endogenous danger signals, such as IL-4, IL-13, IL-10 and TGF-β [9, 12, 46]. Recent studies have also proposed macrophage-induced IL-1β but not IL-6 in mice is critical for the development of steady-state Th17 cells, critical cells against infection, in the intestine [47, 48].

3. TLRs expression and stimulation on macrophages in gut

TLRs are key initiators of innate immune responses and promote adaptive immunity [49]. The most important cell types expressing TLRs are APCs, including macrophages, DCs, and B lymphocytes, which directly recognize various microbial pathogens through PAMPs [49, 50]. TLR engagement triggers downstream signaling pathways and ultimately results in antimicrobial responses [49, 51]. Intestinal macrophages, which represent a unique population of cells that exist in the gut, express most TLRs in humans [52]. However, hyporesponsiveness to activation via TLRs is a key feature of the resident intestinal

macrophages in mice [28, 38, 47]. Intestinal macrophages contact with a biomass of bacteria, it is necessary to regulate the TLR signaling pathways because prolonged and excessive activation of TLRs can lead to uncontrolled inflammation detrimental to the host [53–55]. Previous studies showed that human intestinal macrophages expressed several anti-inflammatory molecules, including IL-10, but little or no pro-inflammatory cytokines, even after stimulation with TLRs ligands [28, 44]. Intestinal macrophages have reduced CD14 surface expression and inhibit DC potential to drive Th17 T cells [56]. During the maturation from monocytes, human intestinal macrophages also down-regulate key TLR signaling molecules such as MyD88 and TRAF6, and up-regulate negative regulators such as IRAK-M and A20 [44, 52]. Moreover, intestinal macrophages in mice also continuously produce IL-10 to maintain their hyporesponsiveness to TLR ligands [12, 38]. Consistently, intestinal macrophages isolated from IL-$10^{-/-}$ mice robustly respond to gut bacteria, whereas wild-type intestinal macrophages are hyporesponsive [47, 48, 57–59]. These data suggest the possibility that the TLR signaling pathway in macrophages in the gut may contribute to intestinal homeostasis and prevent inflammation. Interestingly, human intestinal macrophages do not produce pro-inflammatory cytokines in response to TLR ligation, but retain fully phagocytic and bactericidal activities [44].

4. The role of intestinal macrophage in autoimmune diseases

4.1 IBD

There is increasing evidence that mice knock out individual TLRs or MyD88 can trigger an abnormal inflammatory response of resident intestinal macrophages and thereby facilitate the development of IBD [58–61]. As we know, to keep human intestinal homeostasis, intestinal macrophages have reduced CD14 expression and do not produce inflammatory cytokines through TLRs, although they remain phagocytic and bactericidal activities in the healthy human gut [44, 58, 62]. Moreover, mice intestinal macrophages express anti-inflammatory molecules, such as IL-10, and contribute to the differentiation of Treg cells, while suppressing DC-derived Th1 and Th17 immunities [47, 57, 63]. However, intestinal macrophages in patients with IBD robustly respond to microbial products and the resident bacteria, which results in the production of large amounts of pro-inflammatory cytokines such as TNF-α and IL-23 [64]. Consistently, colonic macrophages from mice with defective IL-10R signaling or global IL-10 cannot respond robustly to TLR stimulation, and these animals develop spontaneous colitis [65–67]. On the other hand, in patients with Crohn’s disease (CD), a unique type of inflammatory macrophage population is present in the intestine, which is characterized by expressing both macrophage and DC markers (CD14, CD33, CD68, CD205, CD209), and by producing large amounts of pro-inflammatory cytokines, such as IL-23, TNF-α and IL-6 [68–71]. However, these CD14-expressing lamina propria macrophages appear to contribute to IFN-γ, rather than IL-17 production, depending on IL-23 and TNF-α [72, 73].

Furthermore, administration of TLR4 ligand (LPS) or TLR9 ligand (CpG) can protect mice from colitis by increasing cyto-protective heat shock proteins or by promoting the type I IFN production, respectively [74]. In contrast, deficiencies in TLR2, TLR4, TLR5, TLR9, or MyD88 are all associated with enhanced susceptibility to colitis in mice [5, 61, 75–77].

However, the precise mechanisms by which the intestinal macrophages mediate resistance against the development of colitis through TLR signaling remain unclear.

It has further been reported that the intestinal macrophages in mice also protect against colitis through TLR-independent mechanisms [78]. Besides TLRs, other PRRs expressed in intestinal macrophages such as NOD-like receptor (NLR) family of proteins are also associated with IBD [79–81]. For instance, Nlrp6$^{-/-}$ and Nod2$^{-/-}$ mice have an increased susceptibility to dextran sulphate sodium (DSS)-induced colitis [82, 83]. These results suggested that the impaired recognition of microbial products by intestinal macrophages may contribute to the IBD development.

4.2 SLE

SLE is an autoimmune disease characterized by autoantibody production and chronic inflammation targeting multiple organs [15–17]. Aberrant monocyte/macrophage surface markers were expressed in cells from SLE patients, including Fcγ receptors (FcγRs), ICAM-1 (intercellular adhesion molecule-1, CD54), CD40, MHC II, type-1 interferon-stimulated genes (ISGs), and sialoadhesin (Siglec-1, CD169) [84–91]. In line with the deregulations of monocyte/macrophage surface markers, abnormalities in cytokine production were also exhibited in patients with SLE [92–94]. Studies from ours and others found that plasma levels of sCD14, secreted by monocytes in response to LPS stimulation, are elevated, whereas the expression of membrane CD14 on monocytes are reduced in patients with SLE compared to healthy controls [95, 96]. Previous studies from our group and others showed that patients with SLE have increased monocyte number, CD16 expression, and IL-6 expression compared to healthy controls [97–102], suggesting that TLR4 responses may play an important role in SLE disease pathogenesis. Notably, TLR7, TLR8 and TLR9 signaling pathways in SLE have been extensively studied [84, 95, 103, 104]. Studies in mice showed that autoantibodies against DNA and RNA-associated antigens promote the formation of nucleic acid-containing immune complexes, resulting in the activation via TLR7/8 and TLR9, thereby may be responsible for the excess production of inflammatory cytokines in patients with SLE [105, 106]. In addition, the production of two regulators of inflammatory responses (IL-10 and TNF-α) is dysregulated in SLE patients, suggesting that these cytokines may be involved in SLE disease pathogenesis [107–109].

Besides the dysfunction of cytokine production, macrophages in SLE patients also have a defect in phagocytosis [110–112]. Ineffective clearance of dying cells and debris by macrophages may provide a source of autoantigens for the development of autoantibodies in SLE disease [113, 114]. For instance, Denny et al. found that macrophages from lupus-prone SNF_1 mice developed increases in autoantibodies against dsDNA, nucleosomes, and nephritic antibody IdLNF1 compared to untreated SNF_1 mice [115]. Interestingly, a recent study showed that drinking acidic pH water promotes SNF_1 mice to develop nephritis but not those on neutral pH water [116]. However, whether intestinal macrophages play a role in the induction of nephritis in response to acidic pH water is unknown.

The complement pathway was also implicated in SLE pathogenesis [117, 118]. Previous studies showed that blood monocytes express C1q receptors (cC1qR and gC1qR) as well as synthesize and secrete the classical pathway proteins C1q, C1r, C1s and C1-INH [119].

However, reduced serum levels of C1q, C3, and C4 were found in SLE, suggesting that there are maybe a direct or indirect link between complement pathway and SLE pathogenesis [119–121]. It is reported that macrophages from SLE patients showed a significant defect in the internalization of apoptotic cells compared with those from healthy controls [119, 120, 122]. One reason maybe that C1q is associated with the recognition and removal of apoptotic cells; this relative C1q deficiency observed in SLE is likely to contribute to the inhibitory effect of lupus sera on the uptake of apoptotic cells by macrophages [121, 123, 124]. However, the mechanism underlying this phenomenon is largely unknown.

4.3 Type 1 diabetes

Type 1 diabetes (T1D) is an autoimmune disorder that results in the destruction of insulin-producing cells in the pancreas [3]. Aberrant PRR signaling activation through macrophages can lead to chronic inflammation and autoimmunity in the gut [125–127]. On one hand, macrophages activated through a variety of PRRs signaling may play a pathogenic role in both the initiation and destruction phases of T1D [128–130]. For instance, macrophages have been shown to produce IL-12 and to promote efficient differentiation of diabetogenic CD8+ cytotoxic T lymphocytes (CTLs) leading to T1D onset [131, 132]. *In vitro* and *in vivo* studies in mice and rats showed that the deleterious effect of macrophages on β-cells was mediated through the production of TNF-α and IL-1β [133, 134]. On the other hand, the dynamic adjustment of commensal bacteria in the gut may interfere with the recognition of intestinal macrophages and contribute to the development of T1D [135, 136]. For instance, pathogen-free MyD88$^{-/-}$ non-obese diabetic (NOD) mice that lack the ability to recognize microbial stimuli do not develop to T1D; and this effect is dependent on commensal microbes because germ-free MyD88-negative NOD mice develop to diabetes [137].

The commensal microbial community may also play an important role against T1D disease through sex hormones and preventing TLR recognition by intestinal macrophages [58, 137–139]. It has been shown that the commensal microbial communities in mouse gut increased serum testosterone and protected NOD males from T1D; In contrast, transfer of gut microbiota from adult males to immature females altered the recipient's microbiota, resulting in elevated testosterone and metabolic changes, reduced islet inflammation and autoantibody production, and protection from T1D [138]. However, much work remains to be done to understand the involvement of intestinal macrophages and sex hormones in this disease.

4.4 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by inflammation of the synovial lining (synovitis), eventually resulting in the damage of cartilage and underlying bone [140]. The RA joint harbors a large amount of immune cell types, including monocytes, macrophages and CD4+ T cells [141]. TLR activation has been widely studied in RA [142–145]. Notably, the expression of TLR2 in CD16+ blood monocytes, and that of TLR2 and TLR4 in CD14+ synovial fluid macrophages, is higher in patients with RA than those in healthy controls [146, 147]. In addition to directly promoting local inflammation by secreting pro-inflammatory mediators (TNF-α, IFNγ, IL-1β, IL-6, and IL-17), synovial monocytes/macrophages secrete chemokines that attract and maintain CD4+ T cells in the

joint [145, 148]. After that, activated mouse monocytes promote CD4+ T helper cell polarization toward Th1/Th17 cells [148, 149]. Furthermore, mouse intestine macrophage-induced IL-1β is essential for Th17 cell differentiation [150], and the enhanced Th17 cell responses might be essential for progression to arthritis [151]. However, the mechanism that intestine macrophages contribute to the development of autoimmune arthritis remains unknown.

4.5 Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that is characterized by peripheral inflammatory processes, blood-brain barrier (BBB) breakdown, and immune cell infiltration into the CNS, leading to both axonal damage and demyelination, and ultimately resulting in disability in MS patients [152–154]. Previous studies showed that high salt not only potentiates LPS-induced macrophage activation, including enhanced IL-1α, TNF-α and IL-1β production, but also enhances the development of MS partly through changing the gut microbiome [153, 155–160]. Conversely, inhibition of salt-inducible kinases induces an anti-inflammatory phenotype on mice macrophages, and produces increased amount of IL-10 and decreased amount of pro-inflammatory cytokines [161]. Besides cytokines, macrophages also produce enhanced level of chemokines, defined as macrophage inflammatory protein-2 and CCL2, which are strongly depend on the salty condition [155, 162, 163]. CCL2 in particular plays an important role in the recruitment of monocytes to the CNS during experimental autoimmune encephalomyelitis (EAE) [156, 163].

5. Conclusion

To inform future research, refining the phenotypic characterization of human intestinal monocyte/macrophage subpopulations would facilitate further investigation of their involvement in autoimmune diseases. Further investigation into the direct interactions between gut microbiota and intestinal macrophages in autoimmune diseases may elucidate how macrophage responses are generated and regulated by the dynamic adjustment of microorganisms. In conclusion, an increased understanding on these fields may contribute to the understanding of autoimmune disease pathogenesis and will benefit the development of new therapeutic strategies.

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