Clinical Immunology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Review Article

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

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ARTICLE INFO

Article history:
Received 15 June 2016
Received in revised form 4 September 2016
accepted with revision 7 September 2016
Available online xxxx

Keywords:
Macrophages
Monocytes
Autoimmune disease
Intestine

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.

Contents

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

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http://dx.doi.org/10.1016/j.clim.2016.09.005
1521-6616/

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

Please cite this article as: Z. Zhou, et al., Clin. Immunol. (2016), http://dx.doi.org/10.1016/j.clim.2016.09.005