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Macrophage Polarization in Infectious Diseases

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Abstract

Macrophages are present in almost all tissues of the body and are endowed with alternative differentiation programs resulting in a variety of terminal differentiated cells. They have role in the innate responses as well as in development and maintenance of adaptive immunity against invading pathogens. These cells have phagocytic activity and can sense the microenvironmental stimuli including microbial components that result in differentiation of distinct marker expression patterns and functions that clearly define macrophage subsets. Here we review the functional plasticity of macrophages in response to infections and their integration into adaptive immunity.

Keywords: Macrophages; Infections; Adaptive immunity; Homeostasis; Polarization

Introduction

One of the first descriptions of the immune system function was evidenced by the characterization of macrophages as cells with phagocytic activity by Metchnikoff [1]. These cells are present in different tissues from the organism as resident macrophages, encompassing the mononuclear phagocytic system. As these cells have a wide tissue distribution, they play a role not only in the immune responses but also during development, homeostasis and repair of the different tissues [2,3].

Recent studies are beginning to uncover the transcriptional regulation of the tissue-specific macrophages [4-6]. The cellular heterogeneity of these cells has also raised questions regarding their origin. A long-held dogma in the field has been assumed that all tissue-resident macrophages could be derived from local differentiation of circulating monocytes [7]. In this line of thinking, the tissue resident macrophages were thought to be exclusively derived from circulating monocytes found in the blood. These precursor cells are differentiated from bone marrow progenitors and have such plasticity to differentiate in a wide range of macrophage subsets with distinct phenotype and function profiles.

However, recent studies have provided conclusive evidences for the existence of a monocyte-independent differentiation pathway of resident macrophages, leading to a shift a in the paradigm of this model [8,9]. Although the term macrophage refers to multiple differentiation states in the ontogeny of these cells, when stimulated in polarizing conditions the macrophages can present dichotomous profiles between two states of the classical inflammatory responses [8,9]. The polarized categories are referred to as M1 and M2, which are both, defined in the context of cytokines and innate receptors present during the activation of macrophages, such as Toll-like receptors (TLRs), and the cytokines interferon-γ (IFN-γ), interleukin-4 (IL-4) and IL-13. In extreme polarizing conditions, the M1 phenotype is induced by Th1-derived interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α) or toll-like receptor ligands (TLR), showing a cytokine expression profile for inflammatory mediators (IL-12, TNF-α and IL-23) [10,11]. M1 macrophages produce high amounts of microbicide products such as nitric oxide (NO) and/or reactive oxygen intermediators (ROS) and mediate cell-mediated immunity in intracellular infection responses [10]. Beside its role on innate responses, the M1 cytokines are critical to promote increased phagocytic activity of macrophages, augmented MHC class II expression and co-stimulatory receptors that collectively have a role on the activation of the antigen processing and presentation to T cells [10,11].

The differentiation of M2 macrophages, however, is dependent of Th2-derived IL-4 responses found in the context of extracellular parasitic infection, allergies or healing-type circumstance without infections. The M2 phenotype can also be amplified in a feedback loop mechanism by IL-4, IL-10 and/or IL-13. These anti-inflammatory macrophage subsets are well characterized by the up-regulation of Dectin-1, DC-SIGN, mannose receptor, scavenger receptor A, scavenger receptor B-1, CD163, CCR2, CXCR1, CXCR2 and LIGHT [11]. Alternatively activated macrophages are permissive to parasites due to its inhibitory effect on the IL-12 expression, which is determinant for the induction of pro-inflammatory IFN-γ dependent responses [11].

The range between these two categories of macrophage is in fact represented by a wide variation in the transition state of the cellular differentiation program as a result of a complex sort of numerous other cytokines and innate receptor stimulation present in the inflammatory sites of infection whose influence are determinant for the final activation state of these cells. In fact, tissue-resident macrophages show high transcriptional diversity with slightest overlap that reinforce their different categories of cells acting as sentinels and

promptly responding to disturbances in the physiological homeostasis of the tissues as well as to threats from invading microorganisms. This review will focus on macrophage responses to pathogens taking into account the diversity of their different lineages and its functional adaptation to different battle scenario requested in every type of immune response in infectious diseases.

Signaling Pathways Governing the Macrophage Polarization

Recent studies have characterized several signaling pathways implicated in the regulation of macrophage polarization. The JAK-STAT signaling pathway consist an important via mediating responses to the cytokine-induced macrophage polarization. The signaling pathway mediated by IFN-γ during M1 polarization activates the receptor-associated STAT1 necessary to induce the transcription of pro-inflammatory cytokines [12-14]. The Interferon-regulatory factor 5 (IRF5) is one of the proteins induced by IFN-γ that endorse the development of Th1 responses by promoting the transcription of IL-12-encoded genes responsible for induction of Th1 responses while inhibiting those that promote development of Th2 cells [15,16].

The polarization towards the M1 phenotype is also accompanied by the expression of Th1-attracting chemokines such as CXCL9 and CXCL10 [17,18]. It has been shown that the granulocyte-macrophage colony-stimulating factor (GM-CSF) controls the polarization of macrophages by leading to downstream activation of IRF5 during M1 development [16-19] . Moreover, the activation of IFN-γ-induced genes increases production of reactive oxygen species that culminates in the intracellular pathogen elimination by M1 macrophages [20]. In contrast, the polarization of M2 phenotype depends on the IL-4 and IL-13-induced STAT6 pathway and is repressed by the effects of SHIP (SH2-containingInositol 5′-Phosphatase), a component of growth factor receptor signaling that is shown to inhibit the IL-4 production from basophils [21].

Unlike to the M1 pathway, the peroxisome proliferator-activated receptors (PPARs) are activated to promote the polarization of differentiating macrophages toward the anti-inflammatory M2 phenotype [22,23]. PPARs are nuclear receptors that induce signaling and transcription of different pathways [24]. Overall, they participate in the regulation of lipid metabolism and glucose homeostasis, and are also activated by specific ligands [24,25]. The family of PPARs is mostly composed of three known isoforms: PPARα, PPARβ/δ, and PPARγ. These receptors share a structural homology that consists of four functional units (A,B,C, and D) [24-26].

The unit A/B of PPARs are located in N-terminal region of the receptor and controls the activation domain by AF-1 ligand. The units C and D represent a DNA binding domain that includes two zinc fingers motives and a docking domain [24-26]. The C-terminal region contains a specific binding domain and a transactivation domain for AF-2 [25]. This region is very important for nuclear localization of PPARs and other interactions with activator factors in the signaling pathway of these receptors [24-26]. The binding of specific-PPAR receptor agonists leads to association between PPARs and retinoic acid receptor (RXR). This receptor-associated heterodimers bind to specific PPRE regions of DNA to activate different target genes [27]. In addition, these receptor heterodimers can interact with other co-activator proteins such as CBP/p300, SRC1, PBP, and PGC-1α to induce a specific gene expression [26,27].

PPARγ play an important role in modulating macrophage M2 polarization induced by IL-4 or IL-13 [28]. Studies using PPARγ-deficient macrophages have shown the role of this nuclear receptor in promoting M2 activation to protect mice from insulin resistance [22]. A similar role was also found for PPARδ in determination of macrophage polarization [29]. Using the myeloid specific transcription factor (KLF-4) knockout mice [30], demonstrated the role of KLF-4 during M2 polarization in a protection model from obesity-induced insulin resistance. Similarly, IRF4 is also involved in regulating the expression of genes associated with M2 polarization [30].

Another signaling pathway involved in M2 differentiation relies on the activation of the phosphoinositol-3-kinase (PI3K) signaling pathway. PI3K activates multiple cascades through phosphorylation of the hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns) to generate the second messenger phosphatidylinositol (3,4,5)-trisphosphate (PIP3) [11,31]. This pathway controls the activation of mTOR pathway, which is determinant for differentiation of M2 macrophages expressing anti-inflammatory cytokines. Importantly, the suppressor of cytokine signaling 1 (SOCS1), a member of the STAT-induced STAT inhibitor (SSI), is upregulated by IL-4 and mediates inhibition of IFN-gamma-induced STAT1 and is essential in sustaining the enhanced PI3K signaling pathway activity that promotes the M2 polarization responses [21].

Role of Macrophage Polarization in Infectious Diseases

The macrophages have an important role in both innate and adaptive immune responses as these cells acquire different ways to sense the presence of pathogens in every tissue of the organism [32]. The Toll-like receptors (TLRs) and other pattern recognition receptors (PRRs) are determinant to discriminate the presence of Pathogen-associated molecular patterns (PAMPs), which are molecules associated with groups of pathogens [33]. These components can be referred to as molecular motifs conserved within a class of microbes and recognized by the innate TLR and PRR receptors present in the macrophage and other cells of the immune system as well. Once engaged by their ligands, the innate receptors promote the acquisition of macrophage`s microbicidal activity against the pathogens [34-36].

Given the critical role of macrophages in the host defense, several pathogens evolved strategies to subvert the macrophage differentiation program by altering the M1 and M2 phenotype commitment in their favor. Bacteria that infect the host intracellular compartment such as *Salmonella typhimurium* and *Mycobacterium turbeculosis* are adapted to avoid the classically activated M1 cells by subverting the pro-inflammatory differentiation program of macrophages in order to enhance their own survival [37,38]. The outcome of this interference in the host phagocytic system has been well studied during murine pulmonary infection with Staphylococcus aureus. These pathogenic bacteria activate the PI3K pathway to promote SOCS1 signaling thus avoiding the differentiation of an anti-inflammatory M1 phenotype [39].

The M1 macrophage differentiation program is overall correlated with protection against intracellular pathogens. This is the case of typhoid fever which is caused by infection with the bacteria *Salmonella typhi*. This microbe induces M1 polarization during protective-mediated response against the infection. The production of reactive nitrogen species such as nitric oxide (NO) in M1 cells is also known to play a critical role in the intracellular killing mediated-responses

against *Salmonella* infection [40]. Further studies have also demonstrated a critical role of IFNγ depended-M1 polarization responses on the host protective immune responses against *mycobacteria* and *chlamydial* infections [41-44].

Other pathogens such as viruses can employ different strategies exerted by bacteria species to increase the disease severity by promoting the inflammatory activity of M1 macrophages. Chronic viruses such as Hepatitis C virus stablish persistent infections with sustained inflammatory responses along the disease. The mechanism underlined in this event partially depends on the expression of the viral protein NS3 along with recombinant GP96 that increases IL-12 and TNF-α secretion profile of differentiating M1 macrophage [45]. In addition, this polarization effect can be seen in avian H5N1 influenza virus infection in which augmented levels of the pro-inflammatory cytokines IL-1β, IL-6, TNFα and IFNγ are implicated in M1 polarization and exacerbation of the infection [46-48].

Notably, viruses such as HIV-1 and Human cytomegalovirus (HCMV) take advantage from the M2 macrophage subset. These cells consist of an important reservoir of replication for both viruses as they have weak microbial activity thus enhancing the viral burden. Moreover, the HCMV infection is able to polarize the macrophage differentiation towards the M2 phenotype through activation of mTOR pathway [49]. The use of M2 cells as a reservoir is an evasion strategy also shared by the intracellular protozoan parasites. It has been shown that the uptake of apoptotic cells by *T. cruzi* infected macrophages promotes an anti-inflammatory state of these host phagocyte cells that are permissive to parasite replication [50-54].

The modulation of the mononuclear phagocytic system by *T. cruzi* parasites depends on the induction of prostaglandins, transforming growth factor-beta (TGF-β), arginase and polyamine biosynthesis to reduce the inflammation and microbicidal functions of macrophages [51,53,54]. It is possible that these mechanisms exert a regulatory role in the primary site of infection by jeopardizing the phagocytic responses of tissue resident macrophages thus increasing the parasite spread through host tissues. This adaptation is also seen in infection with the trypanosomatids protozoan Leishmania in which efferocytosis of apoptotic neutrophils modulate the macrophage activation and microbicidal activity therefore favoring the parasite growth inside the phagocytic cells [55-59]. Macrophage responses to microbial and immunological stimuli lead to discrete, stereotyped phenotypes [57]. Classically activated, or M1, macrophages are microbicidal, while alternatively activated (M2) macrophages are permissive to parasites [57-59]. These polarized states of activation represent a conceptual model for understanding the extremes of the cellular differentiation program capabilities of macrophages. It is therefore possible to conceive a range of potential intermediate phenotypes although their phenotypic characterizations are not well demonstrated. Importantly, the stereotypic M1/M2 macrophage profiles provide insights into the role of these cells in the physiologic and pathologic responses of the immune system.

Conclusions

The immunity is equalized between the strength of inflammatory responses and the regulatory counterparts that limit the side effects of the host defense system. The M1 and M2 activities are the essence of this balance, as these cells are able to participate in all the instances of immune responses. The macrophages are endowed with the capacity of sensing microbial components and host-derived factors during the first steps of pathogen–host cell invasion interactions that play a determinant role in the phagocyte differentiation pathways. The different macrophage commitments might be important to the role of these cells in reshaping the subsequent responses to microbial encounters during acquisition of adaptive immunity and its homeostasis. Understanding the paradigm of alternative activation pathways of macrophage differentiation will help us to clarify the role of these cells in the disease pathogenesis making them ideal for therapeutic targets.

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