Review Article

Inflammatory response of macrophages in infection

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BACKGROUND: **Macrophages are widely-distributed innate immune cells playing diverse roles in various physiological and pathological processes. The primary function of macrophages is to phagocytize and clear invading pathogens.**

DATA SOURCES: **A systematic search of PubMed was performed to identify relevant studies in English language literature using the key words such as macrophage and inflammation. A total of 122 articles related to inflammatory response of macrophages in infection were systematically reviewed.**

RESULTS: **The inflammatory responses of macrophages triggered by infection comprise four interrelated phases: recognition of pathogen-associated molecular patterns by pattern-recognition receptors expressed on/in macrophages; enrichment of quantity of macrophages in local infected tissue by recruitment of circulating monocytes and/or *in situ* proliferation; macrophage-mediation of microbicidal activity and conversion to anti-inflammatory phenotype to terminate anti-infectious response and to promote tissue repair. Complicated regulation of macrophage activation at molecular level recognized in the past decade is also reviewed, including intracellular multiple signaling molecules, membrane molecules, microRNAs and even epigenetic-associated molecules.**

CONCLUSION: **The inflammatory response of macrophages in infection is an orderly and complicated process under elaborate regulation at molecular level.**

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KEY WORDS: **macrophage; inflammation; infection; Toll-like receptor**

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Introduction

Macrophage is an important component of innate cellular immunity with versatile functions prominently involved in host defense and immunity against foreign microorganisms, including bacteria, viruses, fungi and parasites.[1-3] Macrophages possess a broad array of cell surface receptors, intracellular mediators and essential secretory molecules for recognition, engulfment and destruction of invading pathogens and also regulation of other kinds of immune cells.[4] Although more than a century has passed since Elie Metchnikoff first identified macrophages and described their phagocytosis of harmful microbes,[5] the crucial and diverse functions of macrophages and the underlying mechanisms and the regulation of their functions need to be updated. In addition to their well-known functions of immune defense against various infections, macrophages also have been found to play essential roles in diverse physiological and pathological processes, for example, tumor-associated macrophages (TAMs) facilitate angiogenesis and extracellular matrix degradation, and directly inhibit anti-tumor T cell response, thus promoting tumor cell progression and motility;[6, 7] adipose-infiltrating macrophage-mediated inflammation is responsible for insulin resistance and subsequent type 2 diabetes;[8] the accumulation of cholesterol-laden macrophages (foam cells) in the artery wall is closely related to atherosclerosis by driving the imbalance of lipid metabolism and adaptive immune response;[9] $CD169^+$ bone marrow macrophages support erythropoiesis under pathological conditions;[10, 11] and muscle-associated macrophages support the regeneration of skeletal muscle following injury.[12] In this review, we focus on the updating progression on the functions and underlying mechanisms of macrophages in inflammatory responses mainly induced by invading pathogens, as well as the regulation of their function at the molecular level.

Macrophage polarization and subsets

In terms of their anatomical location as well as phenotype and function, macrophages possess remarkable heterogeneity, mainly including microglial cells in the brain, bone-resorbing osteoclasts in the skeletal system, Kupffer cells in the liver, alveolar macrophages in the lung, histiocytes in interstitial connective tissue and foam cells in plague of atherosclerosis, reflecting the specialization of tissue-resident macrophages in different microenvironments of various organs and tissues, all of which mainly differentiate from circulating monocytes.[13] These tissue-specific macrophages can ingest foreign microbes and recruit other macrophages from circulation during an infection. Furthermore, depending on different settings, inflammatory macrophages can be polarized into two well-established functional subsets, referring to classically activated macrophages (M1) and alternatively activated macrophages (M2).[14, 15]

M1 macrophages

The typical characteristic of M1 macrophages is their ability to participate in and promote type 1 immune response, accompanied with increased synthesis of proinflammatory cytokines (TNF-α, IL-1β, IL-12, IL-18, CCL15, CCL20, CXCL8-11 and CXCL13), reactive oxygen and nitrogen species, increased complement-mediated phagocytosis and antigen presenting function.[14] IFN-γ and/or bacterial lipopolysaccharide (LPS) usually induce M1-type activation *in vitro*. The main function of M1 macrophages is to kill intracellular pathogens. In mice, M1-associated markers include IL-12, MHC class II molecules and nitric oxide synthase 2 (NOS2), while in humans, M1 macrophages do not induce NOS2.[13]

M2 macrophages

The typical characteristic of M2 macrophages is their ability to participate in and promote type 2 immune response such as parasitic infection, asthma and allergic disorders.[15] M2 macrophages can be further subdivided into M2a that induced by IL-4 or IL-13, M2b that induced by immune complexes in combination with LPS or IL-1β, and M2c that induced by IL-10, transforming growth factor-β (TGF-β) or glucocorticoids.[16, 17] In addition, IL-33 and thymic stromal lymphopoietin (TSLP) have been proved to amplify the differentiation of M2 macrophages in an IL-13-dependent manner.[18, 19] In mice, M2-associated markers include arginase 1, mannose receptor (MR, CD206, Mrc1), resistin-like molecule α (Relmα) and chitinase 3-like 3 (also known as Ym1), while in humans, M2 macrophages express indoleamine 2, 3-dioxygenase (IDO).[13, 15] M2 macrophages are also associated with anti-inflammatory functions and homeostatic functions such as tissue repair and wound healing by expressing profibrotic factors including fibronectin, matrix metalloproteinases (MMPs), IL-1β and TGF-β. Unexpectedly, M2 macrophages also produce catecholamines to sustain adaptive thermogenesis in response to cold.[20] TAM is another polarized macrophage phenotype that has been extensively studied, and is often considered to belong to M2 macrophage. However, transcriptional profile of TAMs is quite different from that of M1 and M2 macrophages, although they share some other characteristics.[21]

The flexibility of macrophage phenotype

Unlike T helper subsets, such as Th1 and Th2, which are definite and discrete subpopulations, it is well accepted that the activated phenotype of macrophages is flexible and continually changeable, and macrophage can change from one functional phenotype to another in response to the variable microenvironment.[22] Numerous reports have supported this viewpoint. Macrophages sequentially change their functional phenotype *in vitro* in response to changes in cytokine stimulation.[23] M2 macrophages elicited by helminth infection *in vivo* can be reprogrammed *in vitro* by LPS and IFN-γ stimulation to M1-like macrophages with the microbicidal ability via NO.[24] After injury, the transition of muscle-associated macrophages from proinflammatory (M1) to anti-inflammatory (M2) phenotype is critical for skeletal muscle regeneration, and AMP-activated protein kinase α1 (AMPKα1) regulates this macrophage skewing.[25, 26] TAMs can be re-educated by targeting NF-κB to M1 phenotype with the ability to kill tumor cells.[27] This ability of macrophages can help the host adapt variable environments but also can be used by microbes to attack against the host.

Otherwise, as to M2 macrophages, it seems that these cells act as both proinflammatory potential, such as in helminth infection, and anti-inflammatory potential to eliminate inflammation after infection. Although it is possible that different M2 macrophage subsets are responsible for the two opposite roles of these cells, considering the flexibility of these cells, it seems more probable that the different status of M2 macrophages is the key. At the early stage of infection, M2 macrophages show the proinflammatory potential, and at the late stage, some certain characteristics of these cells change according to the changed environment, thus showing the anti-inflammatory potential. Of course, which one is correct needs further examination in the future.