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# Are M1 and M2 macrophages Effectual Players in Pathological Conditions?

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**Abstract:** Pathologic inflammatory conditions are frequently correlated with dynamic alterations through macrophage activation, with classically activated M1 cells associated with promoting and sustaining inflammation and M2 cells implicated in resolving or smoldering chronic inflammation. Inflammation is a common feature of various chronic diseases, and it has direct involvement in the emergence and progression of these conditions. Macrophages participate in an autoregulatory loop characterizing inflammatory process, as they produce a wide range of biologically active mediators that exert either deleterious or beneficial effects during inflammation. Therefore, balancing the ratio of M1/M2 macrophages can help to ameliorate the inflammatory landscape of pathological conditions. This review will explore the role of macrophage polarization in distant pathological inflammatory conditions, such as cancer, autoimmunity, renal inflammation, stroke, and atherosclerosis, while sharing macrophage-driven pathogenesis.

**Keywords:** M1; M2; Macrophages; Inflammation; Polarization

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## 1. Introduction

Inflammation acts as a double-edged sword. Inflammatory processes offer a life-preserving and protective response to protect the body against external and internal injuries; however, an unbridled or aberrant inflammation has a negative impact and must be firmly tuned to prevent undue tissue injury [1]. Notably, macrophages, an essential component of non-specific defense (innate immunity) and specific defense (adaptive immunity), have a central role in inflammatory processes [2]. They are found in all tissues and activate in response to various stimuli, such as activated lymphocytes, injured or dead cells, and microbial products. Macrophages engulf and digest foreign substances, cellular debris, and tumor cells, thereby promoting anti-infective immunity, maintaining tissue homeostasis, and protecting the body. Besides, macrophages can modulate immune responses by secreting a wide spectrum of inflammatory cytokines, which may result in inflammation [3].

Macrophages have high plasticity. Their activation leads to differentiation into various subsets with distinct functional phenotypes [1]. Based on environment composition, such as the presence of chemokines, cytokines, and other factors secreted by immune cells, mesenchymal cells, and tumor cells, macrophages polarize into two major phenotypes that play opposite roles in immune defense and immune surveillance. These are called classically (M1) and alternatively (M2) activated macrophages with pro-inflammatory and anti-inflammatory activities, respectively [4]. Pathological inflammatory conditions are frequently

correlated with dynamic alterations through the activation of macrophages. M1 cells are mainly associated with promoting and sustaining inflammation, while M2 cells implicate in resolving or smoldering chronic inflammation [1]. During inflammation, macrophages drive in the autoregulatory loop characterizing this process, as they produce numerous bioactive mediators that incorporate in both harmful and beneficial aspects of inflammation. Therefore, inflammation serves the typical environmental setting, where macrophages possess dual behavior [5-7].

M1 and M2 subtypes have been defined based on the type-1/type-2 helper-T(h) cell polarization scenario [1,8]. Macrophages promote polarization into M1 by Th1 cytokines, such as interleukin-12 (IL-12), IL-18, and interferon-gamma (IFNγ) or by granulocyte-macrophage colony-stimulating factor (GM-CSF), activated toll-like receptors (TLRs), and lipopolysaccharides (LPS) [8,9]. On the other hand, Th2 cytokines, such as IL-4, IL-10, and IL-13, stimulate M2 phenotype [10] (**Table 1**).

Inflammation is a common feature of various chronic disorders, and it directly incorporates in the emergence and progression of these conditions [1]. M1 and M2 macrophages exert distinct roles in the course of different inflammatory diseases [1]. For example, M2 macrophages safeguard adjacent cells via eliminating cellular debris and secreting trophic substances for brain repair, whereas when M1 macrophages are over-activated for a long period of time, they produce neurotoxic substances that can worsen brain damage [1,9]. On the contrary, in the tumor environment, M1 macrophages act as protective killer cells, while M2 macrophages have a major role in driving tumor progression. In response to alterations in the microenvironment, macrophages can reversibly and progressively switch their phenotype [11]. Therefore, balancing a favorable ratio of M1/M2 macrophages can help to ameliorate the inflammatory landscape of pathological conditions.

### 1.1. M1 macrophages

M1 macrophages participate in Th1 responses to pathogenic microorganisms and tumor cells [12]. These cells produce pro-inflammatory mediators that destroy tumor cells and microorganisms that harm the body. M1 macrophages can also cause tissue destruction, resulting in various clinical complications, such as autoimmunity, renal disease, stroke, and atherosclerosis.

M1 macrophages secrete inflammatory cytokines, including tumor necrosis factor-α (TNF-α), type I IFNs, IL-12, IL-6, IL-1, CCL2, which is also known as monocyte chemoattractant protein-1 (MCP-1), CXCL1-3, CXCL5, and CXCL8-10 (**Table 1**), as well as a large amount of reactive oxygen species (ROS) and inducible nitric oxide synthase (iNOS, an enzyme that converts arginine into the “killer” substance nitric oxide), which all contribute to the induction of inflammatory responses [12,13].

Hypoxia-inducible factors, HIF-1α and HIF-2α, are differentially produced in M1 and M2 macrophages, and they control iNOS2 (M1) and arginase 1 (M2), respectively [14]. Nitric oxide (NO) mediates the elimination of tumor cells by directly inducing apoptosis and cell cycle arrest through the activation of caspases and the downregulation of cyclin D1 [15]. M1 macrophages upregulate interferon regulatory factor 5 (IRF5), which is important for the promotion of cytokines (IL-12, IL-23, and TNF) involved in inducing Th1 and Th17 responses. M1 macrophages are also characterized by the secretion of low levels of IL-10 and high levels of IL-12, as well as their capacity for antigen presentation [16]. IL-12 is one of the most important anti-tumor cytokines [17], and it activates the signal transducer and activator of transcription 4 (STAT4) via stimulating tyrosine phosphorylation of Janus kinases [18].

### 1.2. M2 macrophages

M2 macrophages play an important role in Th2 immune responses, including humoral immunity, tissue remodeling, wound healing, and angiogenesis, in the absence of any infection. Furthermore, M2 macrophages release inflammatory cytokines, such as IL-10, IL-13, and TGF-β, which can promote tumor

progression. Peroxisome proliferator-activated receptor-gamma (PPARγ), a ligand-activated nuclear receptor known as an established marker of M2 macrophages, can regulate M1-related inflammatory responses by suppressing mediators of various signaling pathways, including activating protein-1 (AP-1), STAT, and nuclear factor kβ (NF-kβ) involved in the regulation of genes encoding inflammatory cytokines [19-21]. Moreover, M2 macrophages generate ornithine and polyamines through arginase pathway instead of producing ROS or NO [22-24]. Of note, NO and ornithine are associated with functions such as destruction (M1) and repair (M2), respectively, and have been regarded as the most characteristic molecules associated with macrophages [25].

M2 macrophages present four sub-phenotypes, which include M2a, M2b, M2c, and M2-like [24,26]. M2a macrophages are activated by IL-13 and IL-4, along with Th2 immune response. M2b macrophages, possessing immunoregulatory roles, are activated by immune complex plus TLR or IL-1 receptor ligands. M2c macrophages are induced by IL-10 and transforming growth factor (TGF)-β, and they participate in extracellular matrix (ECM) and tissue remodeling. M2-like macrophages activated by growth factors and cytokines in TME are termed as M2d subtype, which has an immunosuppressive role and pro-tumor property [27].

### 1.3. Mechanisms underlying macrophage polarization

Polarization and function of macrophages are finely regulated through the activation of a network of transcription factors and signaling molecules, in which the balance between activation of STAT1 and STAT3/STAT6 shows a central impact. Several studies have shown that cytokines play a major role in macrophage polarization [27-32]. M1 polarization usually involves IFN-γ with a TLR agonist, such as LPS, whereas M2 polarization usually involves stimulation with IL-4 or IL-13. This approach is meant to simulate what happens when macrophages are exposed to polarized $CD_4^+$ T cells in producing their distinctive cytokine combinations (for example, IFN-γ from Th1, or IL-4 and IL-13 from Th2) [33,34]. A predominant activation of NF-κB and STAT1 by IFN-γ and TLR signaling stimulates M1 macrophage polarization, leading to inflammatory and cytotoxic functions. Oppositely, a predominant activation of STAT3 and STAT6 by IL-10 and IL-4/IL-13 signaling skews the function of macrophage towards M2 phenotype, correlated with tissue repairing or immune suppression and tumor progression [35]. When IL-4 engages its type I or type II receptor, STAT6 is activated and promotes expression of typical genes for M2 polarization, such as chitinase 3-like 3 (Chi3l3, Ym1), resistin-like molecule α (Retnla, FIZZ1), and mannose receptor (MRC1) [36]. Moreover, STAT3 is activated by IL-10 and mediates expression of genes (MRC1, TGF-β1, IL-10) involved in the polarization of M2-like phenotype [27,34]. STAT-mediated macrophage activation is controlled by members of the suppressor of cytokine signaling (SOCS) family of proteins. SOCS1 and SOCS3, which are upregulated by IL-4 and IFN-γ, inhibit the function of STAT1 and STAT3, respectively [38,39].

In coordination with or the downstream of STAT/SOCS pathway, several transcription factors direct the polarization of macrophages. The nuclear receptors PPARγ [40] and PPARδ [40,41] regulate a panel of genes mediating the activation of M2 macrophages. Moreover, Krüppel-like factor (KLF)2 and KLF4 are members of a protein family involved in macrophage activity. Notably, STAT6 attunes and synergizes with both KLF4 [42-43] and PPARγ [44]. The collaboration of KLF4 and STAT6 as well as the sequestrating co-stimulators of NF-κB lead to the activation of M2-related genes (ARG1, MRC1, FIZZ1, and PPARγ) and the inhibition of M1-related genes (TNFα, Cox-2, CCL5, and iNOS). KLF2 activates M2 macrophages by suppressing transcriptions regulated by NF-κB/HIF-1α [45].

IL-4 activates c-Myc transcription factor, which controls the expression of M2-associated genes (SCARB1, ALOX15, and MRC1) as well as the activation of PPARγ and STAT6 [46]. IL-4 also activates M2-polarizing IRF4 axis to suppress IRF5-assocated M1 polarization. IL-10 induces M2 polarization by

promoting the activities of STAT3, c-Maf, and p50 NF-κB homodimer. Although p50 NF-κB homodimer is an important mediator for M2 polarization [47], TLR engagement results in the activation of NF-κB and the generation of inflammatory cytokines correlated with M1 macrophages [48]. However, NF-κB also directs a genetic program involved in the resolution of inflammation [49] and polarization of tumor-associated macrophages (TAMs) towards M2 phenotype [50].

## 2. Conclusion

Balancing the favorable ratio of M1/M2 macrophages can help to ameliorate the inflammatory landscape of pathological conditions. Therefore, it is strongly recommended that future clinical trials should focus on evaluating therapeutic interventions in relation to the polarization of M1 and M2 macrophages in inflammatory conditions.

**Table 1.** Characteristic future of various subclasses of macrophages

| Macrophage subclasses | Stimulators | Surface markers | Metabolic enzymes | Transcription factors | Released cytokines and chemokines | Functions | Ref |
|---|---|---|---|---|---|---|---|
| M1 | LPS<br>PAMPS<br>IFN-γ<br>Modified lipoproteins | CD80<br>CD86<br>CIITA<br>CD32<br>CD16<br>CD11b<br>CD11c<br>MHC-II | iNOS<br>PFKFB3<br>PKM2<br>ACOD1 | NF-kB<br>STAT4<br>IRF-4<br>HIF1a<br>AP1<br>STAT6<br>GATA3<br>SOCS1<br>PPAR-γ | TNF-α<br>IL-1β<br>IL-6<br>IL-12<br>IL-23<br>CCL10<br>CCL11<br>CCL5<br>CCL8<br>CCL9<br>CCL2<br>CCL3<br>CCL4 | Bacterial killing<br>Tumor resistance<br>Th1 response | [19,21,51-54] |
| M2a | L-4/IL-13 | CD206<br>CD36<br>IL1Ra<br>CD163 | ARG1<br>CARKL | STAT3<br>IRF4<br>NF-kβ | IL-10<br>TGF-β<br>CCL17<br>CCL22<br>CCL24 | Anti-inflammatory response<br>Tissue remodeling<br>Wound healing | [55] |
| M2b | TLR ligands<br>IL-1Ra | CD86<br>MHC II | ARG1<br>CARKL | STAT3<br>STAT6<br>IRF4<br>NF-kB | IL-10<br>IL-1b<br>IL-6<br>TNF-α<br>CCL1 | Tumor progression<br>Immunoregulation<br>Th2 response | [55] |
| M2c | IL-10 | CD163<br>TLR1<br>TLR8 | ARG1<br>GS | STAT1<br>IRF3<br>NF-kB | IL-10<br>TGF- β<br>CCR-2 | Phagocytosis of apoptotic bodies<br>Tissue remodeling<br>Immunosuppression | [55] |

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| Macrophage subclasses | Stimulators | Surface markers | Metabolic enzymes | Transcription factors | Released cytokines and chemokines | Functions | Ref |
|---|---|---|---|---|---|---|---|
| | | | | | IL-10 | | [55] |
| M2d | TLR ligands | CD206 | ARG1 | | VEGF | Angiogenesis | |
| | A2R/IL-6 | CD204 | IDO | | CCL5 | Tumor progression | |
| | | CD163 | | | CXCL10 | | |
| | | | | | CXCL16 | | |

## Disclosure statement

The authors declare no conflict of interest.

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