**Biologia Serbica,** 2023, 45: 38-43

DOI: 10.5281/zenodo.10402369

Mini review

# Macrophage polarization and infectious diseases

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Accepted: 8 September 2023 / Published online: 21 September 2023

**Summary.** Macrophages are a heterogeneous cell population present in most mammalian tissues with a wide range of functions. They are an essential component of optimal tissue homeostasis and an essential first line of defense against pathogens. Activated macrophages are typically divided into two phenotypes, M1 macrophages and M2 macrophages, which are influenced by microorganisms, the tissue microenvironment, and cytokine signals from physiological conditions to infections. The management of macrophage polarity is crucial for the prevention and treatment of infections and inflammatory disorders. In this review, we will evaluate the current state of knowledge regarding macrophage polarity and discuss how pathogens exploit macrophage phenotypes for efficient replication and disease progression.

**Keywords:** macrophage polarization, M1 macrophages, M2 macrophages, pathogens.

## INTRODUCTION

Macrophages are specialized, tissue-resident phagocytic cells of the innate immune system. They were first observed in 1892 by a Russian zoologist, Ilya Metchnikov, in an experiment where he introduced a rose torn into the body of a starfish larvae and observed the accumulation of phagocytes attempting to devour the foreign material (Yona and Gordon 2015). For his work in immunology, Metchnikov was awarded in 1908 the Nobel Prize for Physiology or Medicine together with Paul Ehrlich, both of whom are considered pioneers of cellular and humoral immunology (Gordon 2008). Pathogen sensing is a key feature of macrophages. Infectious agents are recognized through pathogen recognition receptors (PRRs) that are activated by pathogen-associated molecular patterns (PAMPS). This activation leads to a signaling cascade that allows for the production and release of cytokines and chemokines which in turn recruit and activate a range of additional immune cells (Grigoryeva and Cianciotto 2021). PRRs include Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), Nod-like receptors (NLRs), AIM2-like receptors (ALRs), C-type lectin receptors (CLRs), and intracellular DNA sensors such as cGAS (Kawasaki and Kawai 2014).

Macrophages are present in almost all tissues, but their origin is mainly linked to monocytes, which migrate to peripheral tissues and differentiate into macrophages as needed. Interestingly, there have been reports and evidence that support the hypothesis that some macrophages originate from the yolk sack during embryogenesis and are maintained independently of monocytes (Yona and Gordon 2015). In addition, some tissues have macrophages with unique tissue-specific functions, such as microglia, bone osteoclasts, alveolar mac-

Invited lecture presented at the XII Conference of The Serbian Biochemical Society, entitled "Biochemistry in Biotechnology", September 21-23, 2023, Belgrade, Serbia

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rophages, and Kupffer cells, that could be considered separate classes of macrophages (Ross et al. 2021). More than a century after the discovery of macrophages, there are still some uncertainties regarding their origin, phenotype, and functions, which are due to the cells' great plasticity to accommodate their many functions under both physiological and pathological conditions. This article provides an overview of the different phenotypes macrophages can adopt in response to different stimuli and pathogens.

## MACROPHAGES: THE CONCEPT OF CELL POLARIZATION

The concept of macrophage polarity is still controversial. Macrophage classification is adapted mainly for *in vitro* research and an easier understanding of different macrophage activation states in response to various factors. *In vivo,* macrophages adopt and modify their functional phenotypes in response to continuous changes in the tissue microenvironment (Strizova et al. 2023). Therefore, although not ideal, macrophage taxonomy is useful in systematically classifying and describing the complexity and adaptability of mononuclear phagocytes. According to their basic functions, macrophages are divided into two populations – M1, pro-inflammatory or classically activated macrophages, and M2, immunoregulatory and wound healing, or alternatively activated macrophages (Mantovani et al. 2004; Martinez et al. 2008; Mosser and Edwards 2008). The M1/M2 classification of macrophages mirrors Th1/2 nomenclature, and it might lead us to believe that T cells are instructing macrophage polarization, but on the contrary, macrophages are the cells that can initiate and direct T-cell responses as the adaptive immune response is triggered by innate immunity (Viola et al. 2019). The M1/M2 classification of macrophages can be viewed as a framework representing a continuum of different functional states, of which M1 and M2 activation states represent the extremes (Martinez and Gordon 2014).

## M1/M2 MACROPHAGES: *IN VITRO* MODELS AND PHENOTYPING

*In vitro* models of human macrophages can be generated from CD14+ monocytes isolated from human peripheral blood mononuclear cells (PBMCs) after a 7-day stimulation with colony-stimulating factors (CSF). M1 primed macrophages are generated with granulocyte macrophage colony-stimulating factor (GM-CSF) in a complete RPMI medium and the M2 phenotype is promoted with macrophage colony-stimulating factor (M-CSF) (Lukic, Larssen et al. 2017). General M1/M2 stimuli and phenotyping markers for human M1/M2 monocyte-derived macrophages are included in Figure 1 and Table 1. As both cell types originate from the same cell precursor, substantial overlap between molecular markers is expected, and one must include surface, cellular, and secretory molecular targets in a phenotyping panel.

Primed macrophages are activated towards the full M1 pro-inflammatory phenotype by subsequent incubation with LPS or inflammation-related cytokines TNF-α or IFN-γ, alone or in combination (Mantovani et al. 2004). These cells are detected as IL-12high, IL-23high and IL-10low secreting cells with high surface expression of MHC class II molecules, positive for CD68 (monocyte and macrophage marker), CD80 and CD86 (both are ligands to the costimulatory molecule CD28 on the surface of all naïve T cells). To kill pathogens and initiate an inflammatory immune response, these cells produce reactive oxygen species (ROS) and nitric oxide (NO) as toxic effector molecules and inflammatory cytokines IL-12, IL-23, IL-6, TNFα, and IL-1. Expression of genes responsible for M1 differentiation and function is under the tight control of transcription factors and post-translational regulators activated by IFNs and TLR signaling, including STAT1, STAT5, IRF3, IRF5 and NF-κB (Italiani and Boraschi 2014; Labonte et al. 2014). M1 macrophages also secrete large amounts of functional activin A, a growth and differentiation factor that promotes the expression of M1 markers and down-regulates IL-10 (Sierra-Filardi et al. 2011).

Contrarily to the M1 phenotype, the M2 phenotype has quickly expanded to three subtypes: M2a, M2b and M2c (Table 1). There is also a fourth class of M2s, labeled

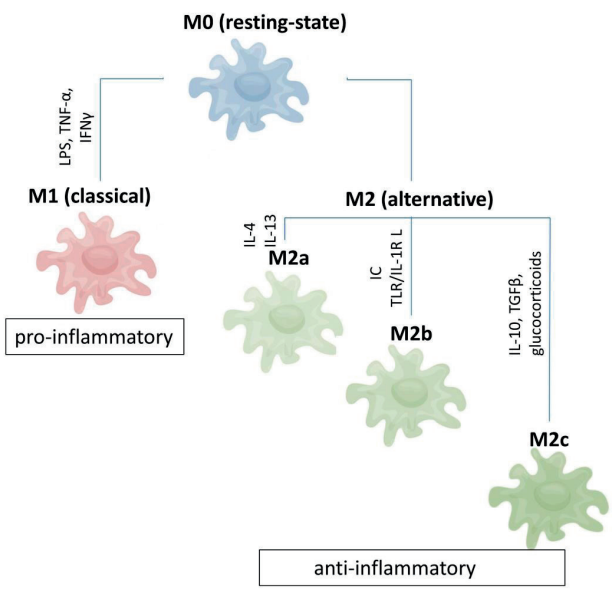


**Fig. 1.** Activation of resting-state macrophages, M0, towards M1 or M2 phenotype (M2a-M2c sub-phenotypes) is governed by different stimuli. IC- immune complexes; TLR/IL-1R L- TLR/IL-1R ligands.

**Table 1**. M1/M2 stimuli and phenotyping markers for human M1/M2 monocyte-derived macrophages.

| Macrophage type | *In vitro* stimuli | Surface markers | Cellular markers | Secreted cytokines and other reactive molecules | Function |
|---|---|---|---|---|---|
| **M1 (classical)** | LPS, TNF-α, IFNγ, GM-CSF | CD80, CD86, TLR2&4, MHC $II^{high}$, IFNγR | CD68, NF-κB, STAT1&5, IRF3&5, iNOS | IL-12, IL-23, IL-6, TNFα, IL-1, ROS, NO | Th1 responses, killing pathogens, tumor resistance |
| **M2 (alternative):** | | | | | |
| **M2a** | IL-4 and IL-13 | CD163, CD200, Dectin-1, MHC $II^{low}$, mannose receptor (MR, CD206), SRs (scavenger receptors A & B1) | IRF4, PPARγ, STAT6, Arginase-1 | IL-10, IL-1Rα, TGFβ, IL-12, polyamines | Th2 responses, allergy, killing pathogens |
| **M2b** | Immune complexes and TLR/IL-1R ligands | CD86, MHC $II^{low}$ | IRF4, SOCS3 | IL-1β, IL-6, $IL\text{-}10^{high}$, $IL\text{-}^{12low}$, TNFα | Th 2 activation, immunoregulation |
| **M2c** | IL-10, TGFβ, glucocorticoids | CD163, CD206, TLR1 | IRF4, SOCS3 | IL-10, TGFβ, extracellular matrix proteoglycan- versican | Immunoregulation, tissue remodeling |

Sources: Mantovani et al. 2004; Gordon and Taylor 2005; Labonte et al. 2014; Martinez and Gordon 2014; Lukic et al. 2017.

M2d, which represents tumor-associated macrophages, or TAMs which are known to promote cancer invasion (Wu et al. 2012). M2a is activated by IL-4 or IL-13, M2b by immune complexes and TLR ligands or IL-1R agonists, and M2c by glucocorticoids or IL-10. In general, alternatively activated macrophages are regarded as IL-10 secreting macrophages with an anti-inflammatory profile, allowing for inflammation resolution and tissue repair. They express high levels of the mannose receptor and C-type lectin receptors (CD206, CD209, and Dectin-1 to name a few) and scavenger receptors (CD163) and produce pro-fibrotic factors such as TGFβ (Mantovani et al. 2013). Furthermore, the intracellular markers and effectors linked to M2 polarization encompass STAT6, SOCS3 (suppressor of cytokine signaling 3), PPARγ (peroxisome proliferator-activated receptor gamma), and arginase-1 (Italiani and Boraschi 2014).

Polarized macrophages have differential metabolic features that are closely related to their function. M1 stimuli shift glucose metabolism towards the anaerobic glycolytic pathway as they need a quick energy supply and performance under a hypoxic tissue microenvironment. On the contrary, M2 polarization-related tissue remodeling actions require a continuous energy supply as achieved via oxidative glucose metabolism (Rodríguez-Prados et al. 2010). Investigations in mouse and human macrophages show that iron metabolism differs significantly between M1- and M2-polarized cells (Corna et al. 2010; Recalcati et al. 2010). M1 macrophages display large levels of iron storage proteins such as ferritin, whereas M2 macrophages express low levels of ferritin but high levels of ferroportin (iron exporter). This differential iron metabolism has been linked to their functional outcomes. Interestingly, the major metabolic difference between the two cell phenotypes is in the conversion of arginine. In M2 macrophages, it results in the production of ornithine and polyamines, but in M1 cells, it leads to the generation of citrulline and NO (Qualls et al. 2012). Production of ornithine can enhance cellular proliferation and promote wound healing by facilitating the biosynthesis of polyamines and collagen. Moreover, previous studies have established a correlation between ornithine and fibrosis, as well as other processes related to tissue remodeling (Pesce et al. 2009). It is noteworthy to add that the synthesis of polyamines has been discovered to autonomously induce M2 polarization (Van den Bossche et al. 2012). Overall, metabolic adaptability plays an important role in macrophage polarization and functional diversity.

## MACROPHAGE POLARIZATION IN INFECTIOUS DISEASES

Following stimulation with microbiological products, macrophages can acquire enhanced microbicidal capabilities. M1 macrophages are often linked to disease protection and help the body get rid of bacteria including *Listeria monocytogenes*, *Salmonella typhimurium*, *Mycobacterium tuberculosis*, *Mycobacterium ulcerans*, and *Chlamydia* (Benoit et al. 2008).

However, some pathogenic bacteria, particularly intracellular species, have evolved strategies to redirect and modify macrophage activation to increase their survival. Paciello and colleagues (2013), found that the intracellular form of *Shigella flexneri* produces an altered, hypoacetylated form of LPS that evades recognition by TLR4 and induces decreased production of proinflammatory cytokines from murine bone marrow-derived macrophages. Bacteria *Mycobacterium tuberculosis* subverted the inflammatory response in infected mice by stimulating Wnt6 signaling in lung macrophages, thereby promoting M2-like polarization (Schaale et al. 2013). Biofilms of *Staphylococcus aureus* were resistant to macrophage invasion in a mouse model of catheter-associated biofilm infections; however, some macrophages that effectively invaded the biofilm exhibited decreased IL-1, TNFα, and iNOS expression but robust arginase-1 expression, indicative of an M2 profile (Thurlow et al. 2011). *Salmonella* strains have an interesting mechanism of infection. They shift the macrophage phenotype to M2 by driving noncanonical activation of STAT3 and by upregulating PPARδ, a transcription factor that forces a lipid oxidation metabolism in the cell leaving more glucose available for the bacteria (Eisele et al. 2013; Taylor and Winter 2020).

In contrast to bacterial pathogens, which typically flourish within and promote the production of M2 macrophages, viral pathogens tend to have a more complex relationship with macrophages. Some viruses induce macrophage polarization toward the M1 phenotype (Avian influenza A H5N1 (Zhang et al. 2018), Foot and mouth disease virus (FMDV) (Sebastian et al. 2020)), while others promote M2 polarization (SARS-CoV-2 (Boumaza et al. 2021)). Moreover, several viruses induce complex macrophage phenotypes depending on viral strains, infection stages, and even the gender of the host (Yu et al. 2022). For example, the relationship between human cytomegalovirus (HCMV) and macrophage polarization. HCMV encodes a homolog of human IL-10 (product of the viral gene UL111A), so the virus is capable of polarizing monocytes towards the M2 phenotype to repress the host immune response required for replication (Avdic et al. 2013). Despite this, it has been shown that HCMV-activated macrophages acquire an M1 transcriptome profile (Chan et al. 2008). It seems that upon infection in monocytes, HCMV drives their acquisition of a unique mixed-mode macrophage phenotype by upregulating selected M1 and M2 differentiation markers, via a non-canonical activation of the Akt signaling network (Cojohari et al. 2020).

The human immunodeficiency virus, HIV, appears to gain an advantage from the M2 polarization. HIV-1 exhibits impaired or delayed infection of M1 macrophages with multiple issues in the entry and post-entry steps (Cassetta et al. 2013), but M2 macrophages express a surface receptor DC-SIGN which facilitates HIV-1 entry, DNA synthesis, and transmission from infected macrophages to CD4+ T cells (Cassol et al. 2013). Notably, it was also reported that HIV-1 clathrin-mediated endocytosis is increased in M1 and decreased in M2 macrophages (Gobeil et al. 2012). However, this type of endocytosis results in increased viral degradation rather than productive infection. Like HCMV, HIV-1 can induce macrophage polarization. HIV-1 drives macrophages toward M1 polarization and stimulates an M2-to-M1 transition (Lugo-Villarino et al. 2011). These contradictions are quite useful for the virus, M2 macrophages are used as a reservoir of replication and M1 macrophages recruit new immune cells and disseminate the infection.

## CONCLUSION AND FUTURE PERSPECTIVES

The involvement of M1 and M2 macrophages is evident in several stages of infection, including early, late, and chronic phases, as well as in the pathogenesis of other conditions not mentioned here, such as allergies, diabetes, and malignancies. In the fight against the immune-system invaders, the host seeks to eradicate the invading pathogens by activating the M1 macrophages, which induce an inflammatory response. Subsequently, the host aims to promote tissue repair and mitigate the immunological response by engaging M2 macrophages among other cells. As the functional phenotype of macrophages can be influenced by both innate and adaptive immune signals, a lack of adequate regulation can lead to potentially harmful outcomes. For example, uncontrolled actions of the M1 macrophages can induce tissue damage and affect glucose metabolism. Conversely, M2 macrophages can be utilized by pathogens as a means of facilitating intracellular survival. In the long competitive history between viruses and hosts, viruses have evolved various immune evasion strategies that interfere with the M1/M2 resolution of infections. Therefore, studying the biology of these intriguing cells presents a promising prospect for the future development of therapeutics. In addition, recent trends in immunology (Wu et al. 2022; Kloc et al. 2023) suggest that following the elimination of infectious agents, the macrophage genome retains the immunological memory from the initial encounter which allows for faster and stronger pro-inflammatory response upon a second encounter with the same or different pathogens. Hence, it is most likely that future treatment strategies against some pathogens will be directed towards macrophages, either by inhibiting their migration to areas of inflammation or by modulating their phenotypes from M1 to M2, or conversely.

## ACKNOWLEDGEMENTS

This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia Contract number: 451-03-68/2022-14/200168.

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