

# Functional aspects, phenotypic heterogeneity, and tissue immune response of macrophages in infectious diseases

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**Abstract:** Macrophages are a functionally heterogeneous group of cells with specialized functions depending not only on their subgroup but also on the function of the organ or tissue in which the cells are located. The concept of macrophage phenotypic heterogeneity has been investigated since the 1980s, and more recent studies have identified a diverse spectrum of phenotypic subpopulations. Several types of macrophages play a central role in the response to infectious agents and, along with other components of the immune system, determine the clinical outcome of major infectious diseases. Here, we review the functions of various macrophage phenotypic subpopulations, the concept of macrophage polarization, and the influence of these cells on the evolution of infections. In addition, we emphasize their role in the immune response in vivo and in situ, as well as the molecular effectors and signaling mechanisms used by these cells. Furthermore, we highlight the mechanisms of immune evasion triggered by infectious agents to counter the actions of macrophages and their consequences. Our aim here is to provide an overview of the role of macrophages in the pathogenesis of critical transmissible diseases and discuss how elucidation of this relationship could enhance our understanding of the host–pathogen association in organ-specific immune responses.

**Keywords:** macrophage, macrophage phenotype, macrophage activation, infections, infectious diseases

## Introduction

The primary function of the immune system has traditionally been defined as protection against microorganisms, although it plays an equally crucial role in protecting the host against invasion by foreign agents and eliminating affected cells that might compromise organic homeostasis.<sup>1-5</sup> The immune system functions through mechanisms involving both humoral and cellular immunity, which generally act in the early and late inborn phases of the response to antigens, respectively.<sup>2-5</sup> In this context, the concept of organ-specific tissue immunity, which is related to the functional specificity of each organ mostly arose from the research of Engwerda and Kaye.<sup>1</sup> Particularly, in their study in 2000, the authors discussed the immunological mechanisms triggered in response to hepatic infection by parasites of the genus *Leishmania*.<sup>1</sup> This work helped focus attention on the concept of tissue immunity and prompted investigations into its mechanisms in various organs because of the close relationship between the induction routes of the cellular lesions involved in distinct organs in infectious, inflammatory, metabolic, and neoplastic diseases.<sup>1</sup>

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According to the concept of tissue immunity, responses can be categorized into three major groups: immunity of epithelial barriers, complex organ immunity, and organ immunity with immunological privilege.<sup>6</sup> In this context, the cells of the immune system acquire functional specializations that are related to the characteristics of the organs where these cells are.<sup>7–12</sup> Consequently, investigating local immune responses is crucial to understanding the host–pathogen relationship in infectious diseases.<sup>7–12</sup> Among the various cells of the immune system, macrophages constitute a functionally heterogeneous group that act in various stages of the immune response. In addition, they are also involved in the maintenance of homeostasis because they release growth factors and enzymes for tissue renewal and remodeling. Similar to lymphocytes, macrophages display considerable functional heterogeneity and are classified according to both their ability to release cytokines and chemokines and their expression of specific receptors. This heterogeneity probably reflects the plasticity and versatility of macrophages in their response to signals from the microenvironment.<sup>13,14</sup>

The process of macrophage formation is initiated in the bone marrow, where the differentiation of hematopoietic stem cells generates precursor cells. Subsequently, pre-monocytic lines in the blood produce monocytes, which enter various tissues from the bloodstream to form resident macrophages that perform multiple functions.<sup>13–15</sup>

Both under normal or pathological conditions, macrophages perform diverse functions in an organism dependent on their location.<sup>13</sup> In the liver, macrophages named Kupffer cells are responsible for removing various substances, toxins, and aggressive pathogens.<sup>10,16–18</sup> The lung contains alveolar macrophages, which eliminate microorganisms, allergens, and microparticles.<sup>19,20</sup> In the brain, macrophages known as microglia provide the main cellular defense of the central nervous system and modulate proliferation, responses, morphological transformation, motility, migration, intracellular communication, and phagocytosis.<sup>13,21–25</sup>

Macrophages in the lymph nodes are classified as spinal or subcapsular sinusoidal, which capture antigens and present them to B cells.<sup>23</sup> In the intestine, macrophages recognize and remove enteric pathogens and maintain the balance necessary for the operation of the microbiota.<sup>23,26–28</sup> The spleen contains macrophage lines derived to perform diverse functions. Splenic macrophages are responsible for phagocytizing senescent or altered erythrocytes, capturing antigens, and processing and presenting them to T lymphocytes.<sup>23,29,30</sup> Lastly, in

the skin, macrophages might be present as Langerhans cells or histiocytes, which primarily function in phagocytosis as well as antigen capture, processing, and presentation.<sup>13,21–23,31–33</sup>

## Macrophage phenotypes

Emerging new concepts have recently highlighted the need for a novel approach to our understanding of macrophage response.<sup>34–36</sup> Similar to T lymphocytes, which feature numerous cellular subtypes, macrophages also differentiate into several phenotypes.<sup>37,38</sup> Cells belonging to distinct phenotypes are distinguished by expression of groups of markers that define each phenotype. Thorough elucidation of these groups of markers, or panels, has revealed that these phenotypes are distinguished by expression differences in chemokines, chemokine receptors, enzymes, costimulatory molecules, Toll receptors, cytokines, and cytokine receptors.<sup>39–43</sup>

M1 macrophages express inducible nitric oxide synthase (iNOS), the primary marker that confirms the response of these cells in a specific disease (Table 1).<sup>44–46</sup> However, a surface marker that defines the identity of M1 macrophages has not yet been identified.

Among the phenotypes of M2 macrophages, M2a, M2b, and M2c macrophages are characterized by the presence of arginase (Arg).<sup>47–49</sup> These subpopulations express a cell-surface scavenger receptor that recognizes haptoglobin–hemoglobin complexes used to identify M2 macrophages and is labeled with CD163. Moreover, a previously unrecognized subpopulation of M2 macrophages, M2d, has been described, but the molecules responsible for the differentiation of M0 macrophages into M2d macrophages remain unknown. However, this population participates in the angiogenesis response, producing interleukin (IL)-10 and vascular endothelial growth factor (Table 1).<sup>50–52</sup>

Macrophages are capable of differentiating into six additional subpopulations: regulatory (Mreg), hematophage-associated (Mha), oxidative (Mox), M3, M4, and M17 macrophages (Table 1).<sup>53–56</sup>

Mreg macrophages respond to the stimulation of Treg cells and are responsible for inducing the repair response and inhibiting triggering of mechanisms that produce pro-inflammatory cytokines in tissue lesions.<sup>57–59</sup> Mox macrophages differ from the other cell types in expressing oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine and producing HO-1 and sulfiredoxin-1.<sup>60–62</sup> Mox macrophages are also associated with triggering of oxidative responses (Table 1).<sup>60–62</sup>

**Table 1** Macrophage phenotypes, stimulating factors, genes, primary markers, and functions described in the scientific literature

Phenotype	Mains stimulus	Gene	Mains markers	Function	Reference
M1	IFN- $\gamma$ , TNF- $\alpha$ , LPS	<i>pSTAT1</i> , <i>pSTAT6</i> , <i>Socs1</i> , <i>Nfkbiz</i> , <i>Irf5</i> , <i>Irf1</i> , <i>Tnf</i> , <i>Il6</i> , <i>Il27</i> , <i>Il23a</i> , <i>Il12a</i> , <i>CCL5</i> , <i>CXCL9</i> , <i>CXCL10</i> , <i>CXCL11</i> , <i>Nos2</i> , <i>Gbp1</i> , <i>CCR7</i> , <i>CD40</i>	IFN- $\gamma$ , TNF- $\alpha$ , IFN- $\beta$ , iNOS, IL-1 $\beta$ , IL-6, IL-12, IL-23, B7, B7.1, MCP3, IP-10, CD16, CD32, CD62, CD127, CTLA8 e $\alpha$ -chain, CD38, Gpr18, Fpr2, WNITA 5A, GPD2, CD120b, TLR2, SLAMF7, CXCL8, CCL5, CCL2	Pro-inflammatory Response, bacterial killing	48-50, 72-76, 81, 85-88
M2	LPS, IL-4, IL-10, IL-13	<i>pSTAT6</i> , <i>pSTAT1</i> , <i>ifn4</i> , <i>Socs2</i> , <i>ccl17</i> , <i>Ccl22</i> , <i>Ccl24</i> , <i>Arg1</i> , <i>Irf4</i> , <i>SOCS1</i> , <i>GATA3</i> , <i>CCL4</i> , <i>CCL13</i> , <i>CCL17</i> , <i>CCL18</i> , <i>MRC1</i> , <i>STAB1</i> , <i>MARCO</i> , <i>CD163</i> , <i>FN</i> , <i>TGFB1</i> , <i>MMPI1</i> , <i>MMP12</i> , <i>TG</i> , <i>F13A1</i> , <i>TGM2</i> , <i>ADORA3</i> , <i>TGFBR2</i> , <i>IL17RB</i> , <i>ALOX15</i> , <i>CD200R</i>	M130, CD163, CD206, MRC1, Mannose receptor, Ym1, FZZ1, CCR7, MCP-3, Fc $\epsilon$ RII, CD23, GPR86, GPR105, TLR-2, P2Y8, P2Y11, P2Y12, C-type lectin-like receptor, dectin-1, DC-SIGN, CD209, DCIR, CLECSF6, CLACSF13, FIZZI, ST2, SR-A, M60, Arginase1, CD184, TRAIL, IL-4, IL-5, IL-10, TGF- $\beta$ , IL-13, FGF b, zinc finger TFs, Egr2, c-Myc	Anti-inflammatory response, tissue repair	48-50, 72-76, 81, 85-88
M2a	IL-4, IL-13	<i>CCL26</i> , <i>PP1R14A</i> , <i>IRF4</i> , <i>BCL7A</i> , <i>EMBPI</i> , <i>RAMP1</i> , <i>CLEC4G</i> , <i>CCL26</i> , <i>ESPNL</i> , <i>SOCS1</i> , <i>GALNTL4</i> , <i>BEM1</i> , <i>PLCB1</i> , <i>DNASE1L3</i> , <i>BATF3</i> , <i>CHN2</i> , <i>ALOX15</i> , <i>DACT1</i>	Ym1, FZZ1, CD163, CD206, MHC II, TGM2, IL-10, TGF- $\beta$ , IL-4, IL-13, COX5a, WNT5b	Inflammation type II allergy, parasite killing, tissue repair	48-50, 73, 91
M2b	Immune complex, TLR, IL-IR	UNKNOWN	CD86, MHCI IL-1, IL-6, IL-10, TNF- $\alpha$	Stress oxidative, efferocytosis	48-50
M2c	IL-10, Glucocorticoids, TGF- $\beta$	<i>CD163</i> , <i>MMP8</i> , <i>TIMP1</i> , <i>VCAN</i> , <i>SERPINA1</i> , <i>MARCO</i> , <i>PLOD2</i> , <i>PCOLE2</i> , <i>F5</i> , <i>FCRLA</i> , <i>FPRI</i> , <i>CD300E</i>	CD163, CD206, IL-10, TGF- $\beta$ , MERTK, ECM	Anti-inflammatory response remodeling tissue, matrix deposition	48-50, 93
M2d	Adenosine, TLR, A2R ligands, Fra1	UNKNOWN	VEGF-A, IL-10, IL-12, TNF- $\alpha$ , TGF- $\beta$	Angiogenesis, anti- and pro-inflammatory response	48-51
Mreg	TLR agonists, immune complexes, apoptotic cells, and prostaglandins, M-CSF, CSF1, CD14	<i>ALDH1A1</i> , <i>ALDH1A2</i> , <i>BCO2</i> , <i>Ccl200</i> , <i>Arg1</i> , <i>Sdc1</i> , <i>CD138</i> , <i>Cav1</i> , <i>Cx3cl1</i> , <i>Ccl22</i> , <i>CD1D</i> , <i>FOXP3</i> , <i>IL2RA</i> , <i>EBI3</i> , <i>LRRC32</i> , <i>GARP</i> , <i>TBET</i> , <i>GATA3</i> , <i>RORC</i> , <i>BTNL8</i> , <i>CYS1</i> , <i>OXCT2</i> , <i>RET</i> , <i>GNG4</i>	DHRS9, IL-10, TGF- $\beta$ 1, CD11a, CD11b, CD68, F4/80, CD14, CD16, CD32, CD64, CD169, CD204, CD11c, Dectin-1, CD200, CD138, CD38, TGIT, FoxP3, D64, CD163, CD169, CD204, CD206, CD209, CD301 (MGL1), LYVE-1, Factor XIIIa, MER, PPI4, glycodelin, SEC14L6, C11orf96	Treg and anti-inflammatory response Regulation	57-59
M3	UNKNOWN	UNKNOWN	UNKNOWN	Switch between M1 and M2 response	54, 63

(Continued)

Table 1 (Continued).

Phenotype	Mains stimulus	Gene	Mains markers	Function	Reference
M4	CXCL4	GM-CSF, CCL18, CD86, TNFSF10, ALOX5, IL1RN, AIF1, HLA-DRB1, HLA-DRB3, HLA-DRB4 e HLA-DQA1, CCL3, CCL7, CCRI, ITGAV, ITGA6, ITGB8B	MMP7, MMP12, IL-6, MRP8, MRP14, TNF- $\alpha$ , CD68, TRAIL, CCL17, CCL22	Pro-inflammatory response, oxidative stress, low phagocytosis, tissue repair	49,56, 64-71, 72-76, 96-98
M17	IL-17	UNKNOWN	IL-17/IL-23	Pro-inflammatory	55
Mox	Ox-PL-PPC	Srxn1, Cebpb, Gclc, Gefl5, Gclm, Pde3b, Txnrd1, Pim1, Hmox1, Gadd45a, Dgat1, Gsr, Dusp1, Tgfr1	HMOX-1, Nr1f2, Srxn1, Txnrd1, IL-1 $\beta$ , IL-10	Weak phagocytosis, proatherogenic	49,53, 60-63

The recently discovered M3 macrophages are known as commuting macrophages. The first study discussing the emergence of this previously unknown lineage showed that their appearance depended on the switching response between M1 and M2 macrophage pathways (Table 1).<sup>63</sup>

M4 macrophages, similar to M3 macrophages, represent a group of newly identified cells that have attracted much attention in research because of the response mechanisms they can develop.<sup>48,64</sup> M4 macrophages differentiate in the presence of colony-stimulating factor (CSF) and (CXCL4). The markers of these cells are CD206, CD68, metalloproteinase 7 (MMP7), MMP12, and calcium-binding protein A8 (S100A8); the cells produce IL-6, TNF- $\alpha$ , and CCL18 and CCL20.<sup>65,66</sup> M4 macrophages highly express the low-density lipoprotein (LDL) receptor, and in chronic lesions, these cells form a large contingent of foam cells that in the inflammatory process (Table 1).<sup>67-69</sup>

Lastly, the concept of cell emergence in the case of M17 macrophages is new. One of the earliest studies supporting this hypothesis showed that cell formation can be induced by corticosteroids, granulocyte-macrophage (GM)-CSF, or IL-10, and a key feature is the cells that respond to IL-17 become resistant to apoptosis (Table 1).<sup>70</sup>

## Markers of M1, M2, and M4 macrophages

With advances in technology, discovery of the transcriptome has allowed for identification of several genes related to the phenotypic modulation of macrophages.<sup>71,72</sup>

This transcriptomic characterization of the phenotypes M1, M2, and M4 is a topic that needs to be addressed.<sup>73,74</sup> For instance, the integrated network established by a combination of factors typically characterizes a complex phenomenon where real-time polymerase chain reaction (PCR) validation, for example, shows that the expression of CD38, Gpr18, and Fpr2 is exclusive to the M1 phenotype.<sup>75</sup> The importance of this relationship is the fact that these newly identified markers are essential to cell activation and the oxidative stress mechanism.<sup>76</sup>

Without disregarding findings previously confirmed by other techniques, the transcriptome study reaffirmed the expression of classical markers that affect not only cell activation but also differentiation and development of the pro-inflammatory response. Therefore, IFN- $\gamma$ , TNF- $\alpha$ , LPS, IFN- $\beta$ , iNOS, IL-1 $\beta$ , IL-6, IL-12, B7, B7.1, MCP3, IP-10 or CXCL10, CD16, CD32, CD62, CTLA8, and  $\alpha$ -chain still

represent a set of fundamental markers that characterize activation of the classical pathway (M1).<sup>77–79</sup> In situations where the stimulus is mediated by LPS + IFN- $\gamma$ , there is an increase in expression of pSTAT1, pSTAT6, Socs1, NF-kB Nfkbiz, IRF5, IRF1, TNF, Ii6, Ii27, IL23a, Ii12a, CCL5, CXCL9, CXCL10, CXCL11, NOS2, GBPI, CCR7, and CD40 on M1 macrophages (Table 1).<sup>80</sup>

In humans, a very peculiar phenomenon occurs by polarization of the response between M1 and M2 macrophages, attributable to the M1 phenotype expression of Wnt family member 5A (WNTA5A) and glycerol-3-phosphate dehydrogenase 2 (GPD2) and modulation of oncogenesis and mitochondrial stress. In addition, another important discovery made using transcriptome analysis and in vitro experimental models is that CD120b, Toll-like receptor 2 (TLR2), SLAM family member 7 (SLAMF7), and chemotactic factors, such as CXCL8, CCL5, CCL2, and IL-6, regulate the M1 phenotype matrix.<sup>81</sup> Considerable data support that polarization via the M1 phenotype classically conjugates the result, such as stimulation mainly by IFN- $\gamma$ , LPS, and TNF- $\alpha$ .<sup>82</sup> However, an interesting approach has shown that the M1 phenotype is dependent on transient receptor potential cation channel subfamily C member 3 (TRPC3) to activate calcium/calmodulin-dependent protein kinase II alpha (CAMK2) and STAT1, and activation of intracellular signaling mechanisms that influence the production of apoptotic markers.<sup>83</sup>

As for the M2 phenotype, regulation of the alternative pathway results in interaction of different stimuli that modulate gene expression in different cellular environments. For example, in mice, the M (IL-4) regulates expression of pStat6, pStat1, ifr4, Socs2, ccl17, Ccl22, Ccl24, and Arg1. In humans, modulation of IRF4, SOCS1, GATA3, CCL13, CCL17, CCL17, CCL18, MRC1, STAB1, MARCO, CD163, FN, TGFB1, MMP1, MMP12, TG, F13A1, TGM2, ADORA3, TGFB2, IL17RB, ALOX15, and CD200R occurs (Table 1).<sup>80,84</sup>

Expression of Arg1 is classical evidence of the presence of the repair phenotype. In addition, cytokines such as IL-4 and IL-13 are required to establish cell differentiation. The transcriptome can aggregate a standard of analysis for the M2 phenotype characterized mainly by the expression of M130, CD163, CD206, MRC1, CCR7, MCP-3, Fc $\epsilon$ R2, CD23, GPR86, GPR105, TLR-2, P2Y8, P2Y11, P2Y12, dectin-1, DC-SIGN, CD209, DCIR (CLECSF6), CLACSF13, FIZZ1, ST2 (SR-A, M60), CD184, TRAIL, STAT6, IL-27Ra, Chil3,

Retnla, Ppar- $\gamma$ , ARG1, TGF- $\beta$ , IL-4, IL-5, IL-10, and IL-13 (Table 1).<sup>85,86</sup>

It is noteworthy that transcriptome analysis has enabled elucidation of mechanisms underlying the modulation of IL-4 intracellular signaling by the induction of zinc finger TFs, Egr2, and c-Myc expression. As a final outcome, ingenuity pathway analysis shows that expression of these markers is directly involved in cell cycle progression in tumorigenesis.<sup>34</sup>

How the M2 phenotype converts to M2a, M2b, or M2c depends highly on the stimuli provided.<sup>87,88</sup> The M2a phenotype is generally observed after exposure to IL-4/IL-13, which induces this phenotype during the process of immunoregulation, tissue repair, and tumor progression.<sup>34</sup> Transcriptome analysis reveals modulation of M2a, which shows that the response triggered by this cell is quite ambiguous and mainly involves polarization of the response between M1 and M2 macrophages. This is because the M2a phenotype can activate genes that regulate pro- and anti-inflammatory responses. Confirmation of such a situation is centered on the exacerbated expression of cytochrome c oxidase subunit 5A (COX5a) and WNT5b.<sup>89</sup> In contrast, previous reports have documented that the M2a phenotype cannot process an adequate response to produce pro-inflammatory cytokines and mediate an efficient microbicidal effect.

The response mediated by the M2c phenotype is basically induced by the stimulus provided by IL-10/transforming growth factor (TGF)- $\beta$ , where post-differentiation transcriptome analysis indicates that this phenotype strongly regulates the expression of genes, such as *CD163*, *MMP8*, *TIMP1*, *VCAM*, *SERPINA1*, *MARCO*, *PLOD2*, *PCOCLE2*, and *F5*. Furthermore, the results of responses triggered by the production of these markers are directly associated with angiogenesis, remodeling of the extracellular matrix, and phagocytosis (Table 1).<sup>90</sup>

Regarding the M4 phenotype, the modulatory effect correlates strongly with the CXCL-4-mediated response that directly influences cell differentiation.<sup>48,91,92</sup> This was confirmed mainly by approaches investigating the development of atherosclerosis where the appearance of foamy macrophages with overexpressed genes, such as *GM-CSF*, *CCL18*, *CD86*, *TNFSF10*, *ALOX5*, *IL1RN*, and *AIF1*, induced production of pro-inflammatory mediators. In addition, development of the immune response in the processing and presentation of antigens by this cell triggers a regulatory phenomenon leading to overexpression of CD86, HLA-DRB1, HLA-DRB3, HLA-DRB4, and



HLA-DQA1.<sup>93</sup> Interestingly, in the activation of an intracellular cascade that aims to regulate metabolism by accumulation of lipids, the cell overexpresses APOC2, APOE, and SORL1.<sup>93</sup> The purpose of the M4 phenotype study expanded to a set of interpretations, including the overexpression of chemotaxis-inducing genes (*CCL3*, *CCL7*, and *CCR1*) and cell adhesion where the cell overexpresses *ITGAV*, *ITGA6*, and *ITGB8B*.<sup>93</sup>

The importance and relevance of the M4 phenotype in understanding atherogenesis indicate that M4 macrophages strongly express genes responsible for inducing proteases that degrade the extracellular matrix such as *MMP7*, *MMP8*, and *MMP12*. The results of the pathophysiological analysis of atherosclerosis investigated using transcriptome analysis shows that these cells express genes that facilitate the formation of foam cells such as *CD36*, *MSR1*, and *ABCG1* by accumulation of LDL, which when metabolized, causes oxidative reactions that impair not only phagocytosis but also the destruction of microorganisms (Table 1).<sup>93,94</sup>

## Transduction signal and polarization of macrophage M1, M2, and M4 macrophages

Investigation of the spectral role of macrophages began at the end of the 19th century, more precisely in 1883 with elaboration of the phagocytosis theory.<sup>95</sup> In 1905, Metchnikoff showed that phagocytic cells are able to destroy bacteria in infection persistent.<sup>96</sup> From that moment, the concept of macrophage activation began to be constructed. In 1964, the idea was further expounded, and between 1966 and 1971, lymphocytes were identified as the major antigen-specific cells responsible for macrophage microbicidal activation.<sup>96–98</sup> The discovery of IFN- $\gamma$  in 1983 was the determinant for the proposal of the classical pathway of macrophage activation.<sup>99</sup> It is important to note that in 1986, the identification of the two subpopulations of T lymphocytes (Th1 and Th2) represented further advances underlying the emergence of the spectral macrophage concept.<sup>100</sup> In 1992, the concept of M2 macrophages began to be constructed, and in 2000, Mills et al<sup>101,102</sup> proposed the classification of M1 and M2 macrophages based on the response mediated by Th1 and Th2 lymphocytes. Between 2002 and 2006, the concepts of activation, heterogeneity, and plasticity of M1 and M2 macrophages were amplified given the diversity of a set of experimental models, which heralded the appearance of M2 subtypes

M2a, M2b, and others.<sup>103–106</sup> However, the theoretical basis of the response behavior of macrophages indicates a complex relationship, mainly with polarization. In 2010, Biswas and Mantovani<sup>107,108</sup> showed a response paradigm between M1 and M2 macrophages. Finally, during the last few years, technological advances have led to deeper discussions on the polarization of response of M1 and M2 macrophages. In 2014, Murray et al<sup>80</sup> attempted to standardize terminology regarding macrophage polarization concepts from the responses obtained in several experimental models. However, problems still exist at the conceptual level, particularly regarding the stabilization of macrophage subpopulations through their participation in pathophysiological, pathological, and immunological mechanisms (Figure 1).<sup>109–111</sup>

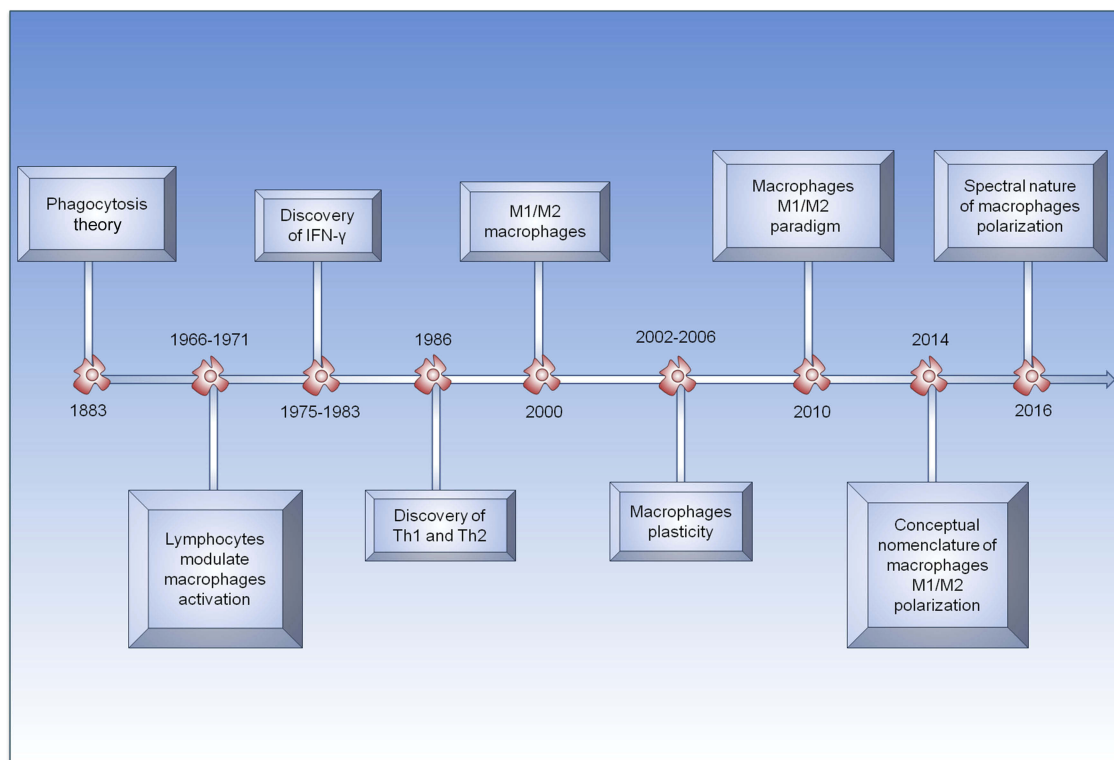
Following the identification of the M2 phenotype, studies began to emerge demonstrating that two distinct types of macrophages were present, which were each associated with a distinct activation pathway. In the classical pathway, the main cells are M1 macrophages, also known as inflammatory macrophages and microbicides. In the alternative pathway, also known as the reparative pathway, cells responsible for the repair response are the M2 macrophages.<sup>112–114</sup>

Considering the versatility of macrophages, their response mechanisms in destroying microorganisms appear to include aspects of the immune response that remain incompletely elucidated. However, current evidence further strengthens their relationship with components of the innate and adaptive immune systems.<sup>115,116</sup>

In the innate immune response, when macrophages exposed to certain stimuli, such as LPS-peptide complexes, are recognized by TLRs and CD14, signaling cascades might be initiated that generate reactive oxygen and nitrogen species and inflammatory cytokines such as IFN- $\alpha$  and IFN- $\beta$ .<sup>117–119</sup>

During the humoral response, phagocytosis of certain microorganisms might be mediated by recognition of the Fc portion.<sup>120</sup> Specific costimulatory molecules act as a key step in enhancing phagocytosis, antigen presentation, and endocytosis. These molecules belong to the family of receptors known as scavenger and mannose receptors.<sup>121</sup>

During the innate response, certain components of the complement system regulate polarization of the macrophage response. In the inflammatory pathway, some complements, such as C3a, C5a, C5b, and C9, might induce production of inflammatory mediators. In the regenerative pathway, the presence of opsonized apoptotic bodies with



**Figure 1** Timeline of main events marking development of concept of polarization of macrophages.

fragments of complement C1q or C3b might stimulate M2 macrophages to produce Arg and anti-inflammatory cytokines.<sup>122</sup>

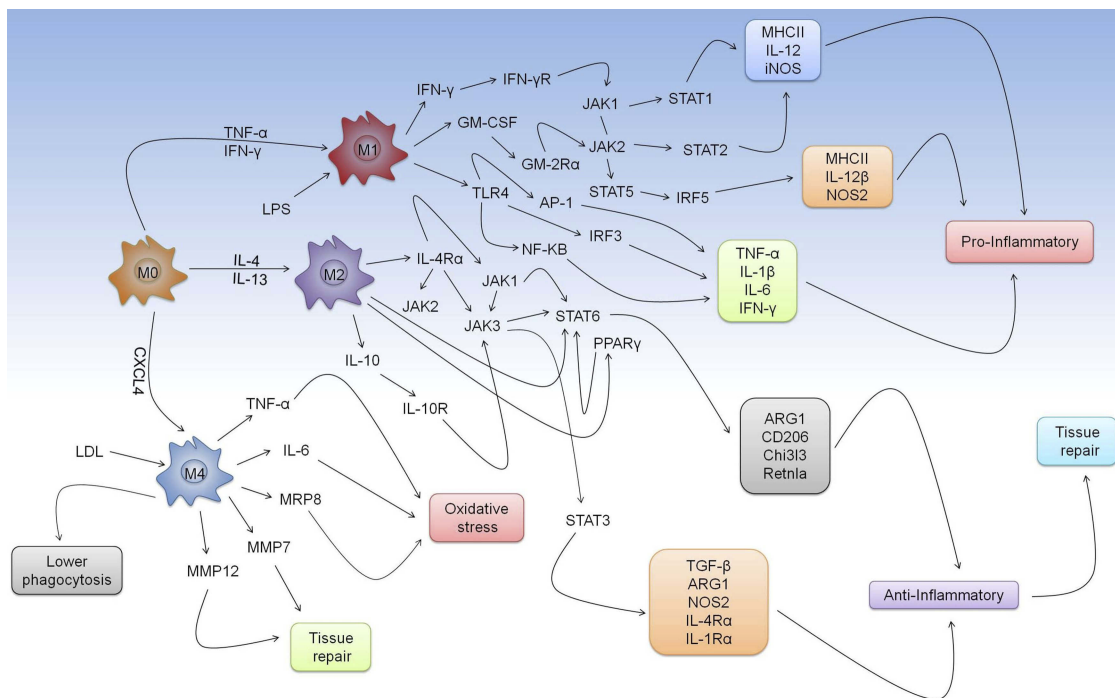
The classical signal-transduction response scheme described for both M1 and M2 macrophages follows a pathway starting from the binding of a protein or some other component to a receptor, which initiates a signaling cascade involving signal transduction through phosphorylation of transcription factors, migration of the factors to the nucleus, activation of genes, and production of molecules such as cytokines, enzymes, and costimulatory molecules.<sup>21,123–125</sup>

In the classical pathway, we highlight three routes that are essential to the modulation of the microbicidal activity of M1 macrophages. The first is the binding of IFN- $\gamma$  or TNF- $\alpha$  to their respective receptors (IFN- $\gamma$ R or TNF- $\alpha$ R), whose main event is the development of intracellular cascade based on the activation of JAK1 and JAK2 and STAT1 or STAT2 responsible for inducing the production of MHCII, IL-12, and iNOS.<sup>126–128</sup> We cannot fail to mention the importance of GM-CSF in mediating NOS2 production. MHC class II, IL-12b, which is dependent on the activation of JAK2 and STAT5 and phosphorylation of IRF5.<sup>129,130</sup> In addition to a set of immunological strategies mediated by

response of M1 macrophages, TLR4 recognizes LPS, one of the major components produced by gram-negative bacteria, which activates NF- $\kappa$ B, AP1, and the production of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IFN- $\gamma$  (Figure 2).<sup>131–133</sup>

As an alternative pathway, M2 macrophages respond to stimulation by IL-4, IL-10, or IL-13 to mediate the development of the repair phenotype. By binding to their respective receptors, these cytokines can trigger activation of repair signaling cascades that modulate the activation and phosphorylation of JAK1-3, STAT3, STAT6, peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) or phosphoinositide 3-K (PI3K) in order to induce production of Arg1, CD206, chitinase-like 3 (Chi313), reticulon-like A (Rtnla), TGF- $\beta$ , NOS2, IL-4R $\alpha$ , and IL-1R $\alpha$  (Figure 2).<sup>134,135</sup>

M4 macrophages have attracted attention in the research community due to their relationship to M0 macrophages. Specifically, their exposure to CXCL4 was shown to lead to the production of CD68, IL-6, TNF- $\alpha$ , S100A8, MMP7, and MMP12.<sup>136,137</sup> M4 macrophages are highly enriched in atherosclerotic lesions, where the cells exhibit increased expression of LDL receptors.<sup>138–140</sup> This phenomenon causes accumulation of fat inside phagocytes, leading to the development of atheroma plaques and, consequently, oxidative lesions.<sup>138–140</sup> Although more comprehensive studies



**Figure 2** Mechanism of response mediated by M1, M2, and M4 macrophages. Macrophage differentiation spectrum includes markers that modulate development of certain phenotypes. Depending on the stimulus, cytokines, such as TNF- $\alpha$  and IFN- $\gamma$ , may influence the process of shifting the M0 macrophage to M1. In this scenario, we highlight the performance of IFN- $\gamma$ , GM-CSF, and TLR4 that influence development of intracellular cascade, which aims to produce of a series of markers to enhance the pro-inflammatory response in several aspects of classical pathway. In contrast, the antagonistic relationship between the duality of M1/M2 macrophages shows that IL-4 and IL-13 cytokines are mainly responsible for inducing differentiation of macrophages from M0 to M2. In the alternative pathway, activation of IL-4R $\alpha$  or IL-10R shows that IL-4, IL-13, or IL-10 directly modulate development of anti-inflammatory responses and tissue repair. Through pathways of polarization, we emphasized the significance of M4 macrophages in the modulation of oxidative stress response as well as tissue repair. This relationship is particularly important in pathophysiology of atherosclerosis, where formation of foam cells due to LDL accumulation and low phagocytosis implies a regulatory phenomenon that triggers the production of TNF- $\alpha$ , IL-6, MRP8, MMP7, and MMP12.

must be conducted to further elucidate the roles of M4 macrophages in the pathogenesis of diseases, the functions are probably related to an immunosuppressive environment targeting infectious pathogens (Figure 2).<sup>141–143</sup>

## Antagonistic phenomena and duality of response between iNOS and arg1 and its relationship with M1 and M2 phenotype in infectious diseases

Macrophages are one of the primary cell types that exert microbicidal activity against several groups microorganisms via polarization and duality of the response between the M1 and M2 phenotypes.<sup>144–146</sup> Therefore, an intriguing relationship is established in infectious diseases due to what happens intracellularly.<sup>144–146</sup> Classically, iNOS and Arg1 are characteristic and determinant markers for modulating the response of either M1 (iNOS) or M2 (Arg1) macrophages.<sup>147–149</sup> The resulting effects of these enzymes demonstrate that both compete for the same substrate (arginine) in order to induce the production of NO

(M1) or proliamines and proline (M2). This antagonistic relation causes a phenomenon of duality that facilitates the destruction or survival of microorganisms.<sup>149–151</sup> In light of this phenomenon, we highlight the evolution of the understanding of this ambiguous relationship mainly in leprosy, tuberculosis, and leishmaniasis.

In the case of bacteria, this relationship shows that contradictory events are associated with the response mechanism triggered by both enzymes. In leprosy, the in situ expression of iNOS is curiously predominant in the lepromatous form of the disease, whereas the immune response is directed more toward an immunosuppressive profile. Interestingly, in lepromatous leprosy, iNOS correlates positively with the expression of natural resistance-associated macrophage protein 1 (NRAMP1), IL-22, and STAT3, indicating that the M1 phenotype is present in the tissue environment, generating reactive metabolites an attempt to eliminate the infection. Given that in this clinical form the anti-inflammatory response is more incisive, the development of the M2 phenotype fundamentally participates in inactivating the microbicidal response linked to



the M1 phenotype. It is precisely because of this that the tissue damage is much more obvious, and the associated response includes the exacerbated expression of Arg1, IL-4, IL-10, TGF- $\beta$ , and FGF $\beta$ .<sup>152–154</sup>

With regard to *Mycobacterium tuberculosis*, the response mediated by iNOS is more complex. Several seminal studies have shown that, as in leprosy, in tuberculosis iNOS exerts microbicidal activity.<sup>155,156</sup> However, one of the final products generated in the metabolic cascade of iNOS favors the development of an intracellular signaling mechanism that controls inflammation. In this context, NO is able to inhibit the expression of NF- $\kappa$ B, one of the major transcription factors responsible for inducing the production of pro-inflammatory cytokines such as IFN- $\gamma$  and TNF- $\alpha$ .<sup>157</sup> Controversial events in the immunopathogenesis of *M. tuberculosis* infection are crucial in the interpretation of iNOS and Arg1 responses when the tissue microenvironment in tuberculoid granulomas are analyzed. The duality of the polarization of the relationship between M1 and M2 macrophages in both human and monkey granulomas, the anti-inflammatory phenotype (CD163+iNOS+Arg1<sup>high</sup>) is located in more external areas, whereas in the internal portion, the pro-inflammatory phenotype (CD11C+CD68+CD163<sup>dim</sup>iNOS+eNOS+Arg1<sup>low</sup>) is predominant. Therefore, in the same tissue environment, the presence of the M1 and M2 phenotype is crucial to maintaining the balance of the immune response and tissue damage.<sup>158</sup>

A study focused on the hypoxic granuloma regions in tuberculosis demonstrated that Arg1 expression seems to control *M. tuberculosis* growth when NOS2 is ineffective. In this case, enzyme expression correlates negatively with the proliferation of T cells.<sup>149</sup>

Against leishmaniasis, stimuli presented to the same cells may or may not trigger the microbicidal response.<sup>159,160</sup> Therefore, what is pertinent to the performance of TNF- $\alpha$  or IL-4 directly influences the formation of the M1/M2 phenotype. In vitro, for example, TNF- $\alpha$  inhibits IL-4-induced Arg1 expression in bone marrow-derived macrophages. The consequences of this inactivation directly affect the phosphorylation and translocation of STAT6 to mediate production of Arg1.<sup>161</sup> In vivo *Leishmania* infections mainly show that in C57BL/6WT, the control of the cellular and microbicidal stress response is regulated by NOS2 and Arg1 with a predominance of NOS2 and NO. In the case of C57BL/6WT TNF<sup>-/-</sup> BALB/c, this change favors pathogen survival as well as non-phenotype change and a balanced expression of NOS2 and Arg1.<sup>161</sup> In Tie2Cre<sup>±</sup>Arg<sup>fl/fl</sup> mice,

the amastigote forms of *Leishmania major* are destroyed in activated macrophages where the inflammatory response is accentuated. In light of this, we conclude that the expression of TNF- $\alpha$  influences change in the cellular phenotype and potentiates the response of M1 macrophages in situ by Arg1 deletion, histone acetylation, and NOS2 and NO production. Interestingly, deletion of Arg1 can restore control of parasite proliferation in animals that evolved resistance.<sup>161</sup>

## Mechanisms of immune evasion used by intracellular pathogens against macrophage responses

Macrophages have failed to develop an effective response against certain intracellular pathogens.<sup>162,163</sup> The reason for this failure has been a long-standing question in this field. Thus, numerous studies have sought to elucidate the pathway through which the behavior of an infected cell is altered. Regardless of whether a cell is infected by viruses, bacteria, protozoa, or fungi, the pathogen in each case uses the immune system to modulate the response and, thereby, survive inside the cell.<sup>163–165</sup>

## Bacteria and protozoa

One of the key issues arising from the discussion of this subject is understanding the response that PRRs can induce through the recognition of PAMPs of certain microorganisms. Classically, receptors such as those in the Toll family agglutinate a variable range from TLR1 to TLR13.<sup>166–168</sup> Therefore, in the case of mycobacteria, the importance of TLR2, TLR4, and TLR9 in the development of the microbicidal response is paramount since the regulation of the intracellular cascade involves the binding of MyD88 and Mal, also known as TIRAP, which recruits IRAK1/4, TRAF6, and TRICA1 to induce the production of mitogen-activated protein kinase (MAPK) and NF- $\kappa$ B.<sup>169–171</sup> As a final outcome, NF- $\kappa$ B is responsible for inducing the production of pro-inflammatory cytokines such as TNF- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , and IL-6 that participate in the activation of macrophages and enzymes such as iNOS, which is responsible the generation of ROS and destruction of the microorganism.<sup>126,172,173</sup> However, the immune evasion strategies adopted by mycobacteria include a series of events aimed at inactivating this mechanism. With regard to *M. tuberculosis*, TLR2 is the main receptor by which mycobacteria modulate immune escape. Therefore, the interaction between TLR2, ESAT-6, and CFP-10 drastically suppresses the immune response of macrophages by

inhibiting NF- $\kappa$ B activation, iNOS, and NO production.<sup>174</sup> Nevertheless, recognition events of PAMPs show that *M. tuberculosis* mutants produce sulfoglycolipids that antagonize the activation of both TLR2 and NF- $\kappa$ B.<sup>175</sup> Interestingly, in this same dynamic, the bacterium can subvert the TLR2-MyD88 pathway and facilitate its translocation into the cytosol. The consequences of this modulation include the direct involvement of H37Rv strains and the escape of the phagosome or phagolysosome.<sup>176</sup> It is worth mentioning that immune evasion via modulation of TLR2 by the recombinant lipoprotein Rv1016c, induces apoptosis of macrophages by increasing annexin expression.<sup>177</sup> Consequently, this relationship becomes beneficial because in addition to Rv1016c inhibition of MHC-II expression, TLR2-dependent apoptosis may promote the release of residual bacilli into apoptotic cells and, thereby, decrease the recognition of CD4<sup>+</sup> T cells, impairing surveillance in chronic disease conditions (Figure 3).<sup>177</sup>

Concerning protozoa, one of the main parasites that compromise macrophage activity is *Leishmania*.<sup>163</sup> *L. major* negatively modulates TLR2 receptor activity to increase the recruitment of SOCS1 and SOCS3, which inhibit the production of NF- $\kappa$ B, IFN- $\gamma$ , and TNF- $\alpha$  in order to establish pathogen survival.<sup>178</sup> In *Leishmania donovani*, the amastigote forms and TLR2 suppress the inhibitor of NF- $\kappa$ B kinase (IKK)-NF- $\kappa$ B complex and the positive regulation of the enzyme deubiquitinating A20.<sup>15,179</sup> As a result, this process facilitates the degradation of TRAF6 and inhibition of the TNF- $\alpha$  and IL-12 response. As a survival strategy, *L. donovani* also prevents apoptosis triggered by oxidative stress, inducing SOCS1 and SOCS3 production.<sup>180</sup> Interestingly, that in *Leishmania amazonensis*, the intracellular regulatory effect anchored in the action of protein kinase triggers production of IFN- $\beta$ , which in turn, increases expression of superoxide dismutase 1 (SOD1), inhibiting destruction of the parasite and facilitating its proliferation (Figure 3).<sup>181</sup>

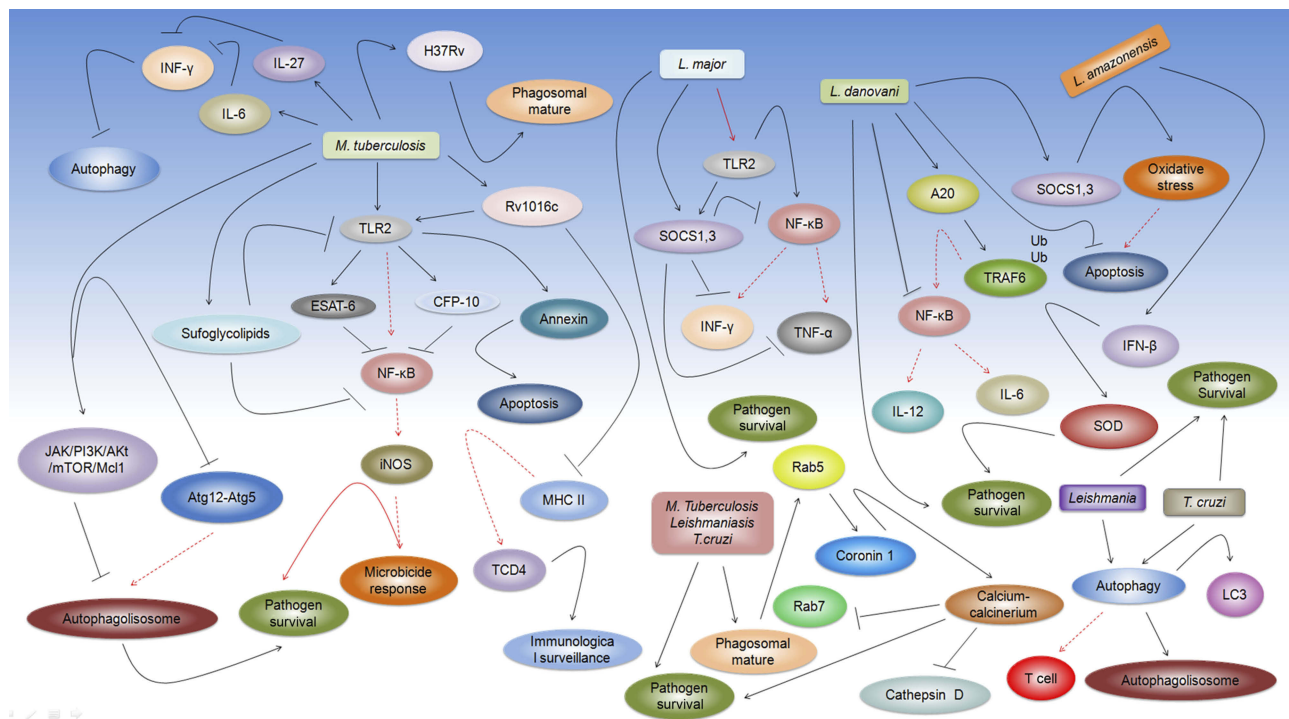
Regarding *Trypanosomiasis cruzi*, TLRs play a crucial role in resistance to the protozoan infection in macrophages, where GPIs and mucins modulate the behavioral difference among TLR2, TLR4, TLR7, and TLR9. In fact, this relationship mainly affects the production of Th1 cytokines. Notably, in TLR2-deficient mice, a potent pro-inflammatory response was observed, mainly induced by IFN- $\gamma$ .<sup>181,182</sup>

One of the central questions surrounding the strategies of immune evasion by *M. tuberculosis*, *Leishmania*, or *T. cruzi* is the mechanism underlying phagosome maturation

modulation.<sup>183–185</sup> This has direct implications on the biogenesis of the phagolysosome. To survive in a hostile environment, these microorganisms have developed a series of mechanisms aimed at neutralizing one of the cell's primary lines of defense. It starts at the point of inhibition of the inflammatory cytokine response (IFN- $\gamma$  or TNF- $\alpha$ ), where this relationship influences the endosome immaturity.<sup>186–188</sup> Incidentally, Rab family proteins are actively involved in this process. In this context, Rab5 and 7 are directly related to the early and late fusion of the endosome and lysosome, respectively. The stage of immaturity of the phagosome is organized in this duality of interaction between early and late fusion.<sup>189–191</sup> Therefore, microorganisms initially maintain Rab5 expression in order to facilitate recruitment of coronin 1a protein and the development of the calcium-calcineurin signaling pathway whose final outcome is the loss of fusion of the phagosome with the lysosome (Figure 3).<sup>192–194</sup> The implications of this catastrophic cellular effect include the inhibition of late markers such as Rab7 and the loss of various hydrolases such as cathepsin D. Another final point that dramatically impacts the immune escape of pathogens is inhibition of PI3K, which deregulates the gallbladder traffic in the Golgi apparatus (Figure 3).<sup>195–197</sup>

## Virus

Currently, the action of macrophages has not been shown to be directly related to the antiviral response. This is attributed to the fact that TLR3, TLR7, TLR8, RIG-I, and MDA5 are largely produced by the cell. In this context, the modulation of viral replication starts from information that is passed to the cytoplasm where RIG-I and MDA5 recognize single-stranded RNA viruses to facilitate the formation of the IKK complex ( $\alpha$ ,  $\beta$ , and  $\gamma$ ). Consequently, the phosphorylation and migration of NF- $\kappa$ B and IRF3 and 7 to the nucleus activate genes responsible for inducing the production of IFN- $\alpha$  and  $\beta$  (Figure 4).<sup>198–200</sup> However, the strategies used by the virus modulate the immune evasion mechanism, whereas non-structural NSs of DENV, WNV, ZIKV, and HCV flaviviruses inhibit activation of RIG-I and MDA5 as well as a series of intracellular markers during the inactivation of molecules such as STING, MAVS, and NF- $\kappa$ B. This mechanism directly affects the inhibition of ISGs, Mx, OS, PKR, and the production of IFN- $\alpha$  and  $\beta$ . In the case of type 1 IFN, intracellular signaling triggered by receptor-cytokine binding influences concomitant activation and phosphorylation of JAK1, JAK2, STAT1, and STAT2, as well as the



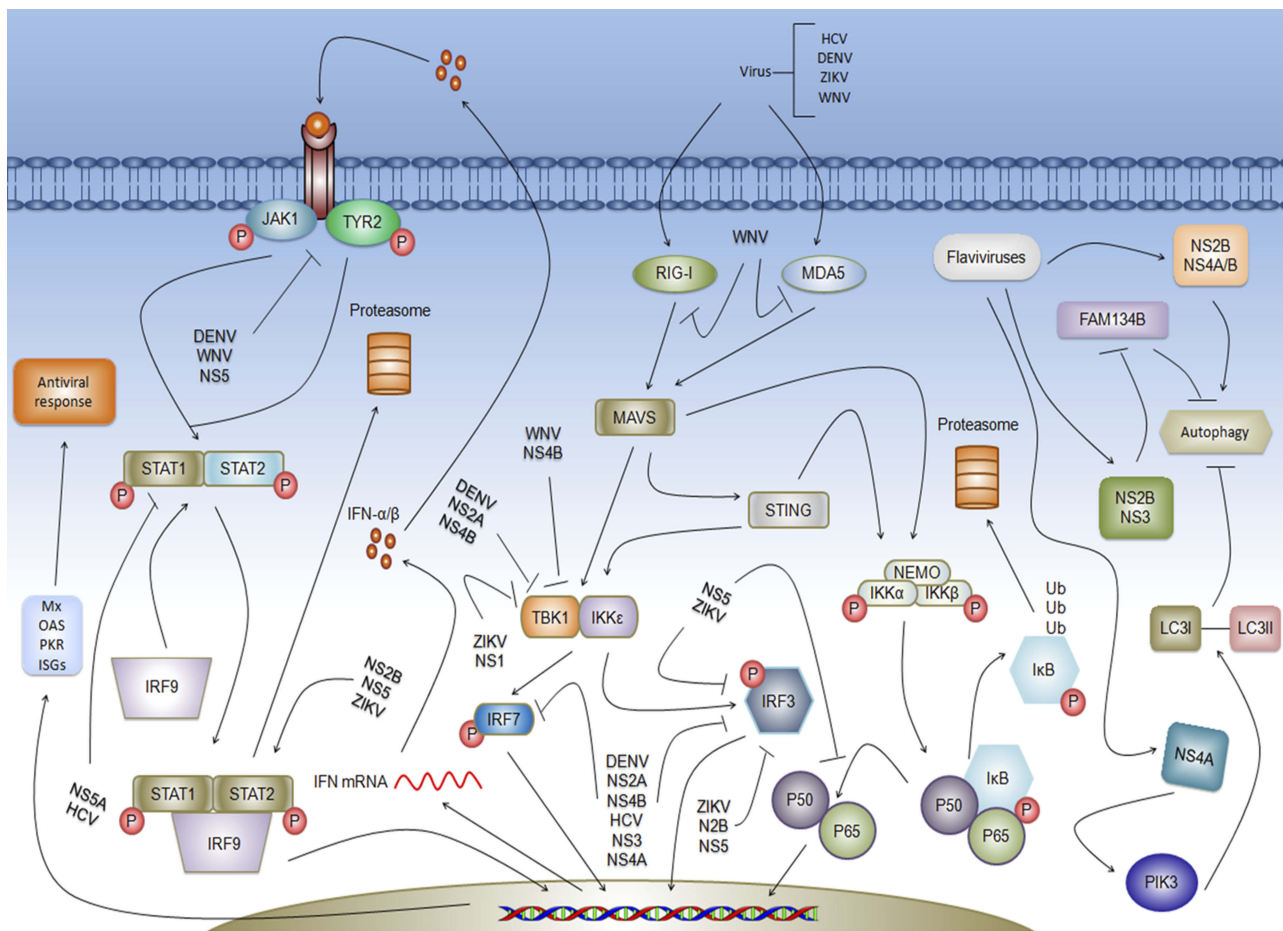
**Figure 3** Immune evasion and strategies adopted by *Mycobacterium tuberculosis*, *Leishmania*, and *Trypanosoma cruzi* to evade microbicidal response of macrophages. Because it is a sequence of events that trigger destruction of microorganisms, immune escape strategies that inhibit microbicidal responses are as varied as possible. However, we seek to centralize an understanding of the crucial points that facilitate a pathogen's survival in the environment. For *M. tuberculosis*, it is noteworthy that TLR2 is the main receptor by which the immune escape correlates with ESAT-6 and CFP-10 response, whereas inhibitory modulation mainly affects the inflammatory cascade associated with NF- $\kappa$ B and to iNOS. Since sufglycolipids inhibit activation of TLR2 and NF- $\kappa$ B, this not only compromises the microbicidal response but also facilitates the survival and proliferation of the bacillus. Through evolution of mycobacterial destruction mechanisms, adaptation of pathogens to evade the immune system has generated certain strains such as H37Rv that modulate phagosome maturation and facilitate translocation of bacillus to the cytosol. In addition, a recombinant lipoprotein derived from *M. tuberculosis*, such as Rv1016c, regulates the mechanism of apoptosis through the annexins. This is crucial to facilitating proliferation of the bacillus in the tissue environment because Rv1016c inhibits MHC II expression, compromising the CD4 T cell response and immune surveillance. Considering that the cytokine response is fundamental to induce the activation of macrophages, as well as the microbicidal response, *M. tuberculosis* inhibits the action of IFN- $\gamma$  by inhibiting autophagy through responses of IL-6 and IL-27. Expansion of this scenario negatively regulates Atg12-atg5 and positive intracellular cascade involving JAK/PIK3/Akt/mTOR/Mcl1. Implications of such events are inhibitive of phagolysosome maturation and, consequently, the microbicidal response of the cell, which favors pathogen survival in phagocytes. With regard to protozoa, we highlight *Leishmania*, which, in addition to using the cells of the phagocytic system as a reservoir, also uses innumerable strategies of immune evasion to survive. Therefore, *Leishmania major* modulates TLR2 responses to induce SOCS1 and 3 to inhibit not only intracellular cascades of NF- $\kappa$ B but also the response of IFN- $\gamma$  and TNF- $\alpha$ . For *Leishmania donovani*, by ubiquitination of TRAF 6 through A20, the response of NF- $\kappa$ B is compromised as well as the production of IL-6 and IL-12. Interestingly, *L. major* modulates immunosuppressive responses to facilitate its survival, and *L. donovani* follows the same path by mainly regulating expression of SOCS1 and 3 to avoid oxidative stress and catastrophic effects that may occur with apoptosis. Despite this dynamic, *Leishmania amazonensis* can induce macrophages to produce IFN- $\beta$  to generate SOD in order to create an environment conducive for the parasite to evade the immune system, survive, and multiply. Considering that vesicular traffic is fundamental for phagosome maturation, either protozoa or *M. tuberculosis* manipulates macrophages to maintain Rab5 expression increased to establish early phagosome fusion with lysosome, as well as formation of the calcium-calcienerin complex to inhibit the production of cathepsin D and Rab7 and to facilitate the survival of the pathogens. The effect of evasion of *Leishmania* with *T. cruzi* is very peculiar in the case of leishmaniasis, autophagy is explored to eliminate promastigotes forms and reduce responses of T cells. In contrast, *T. cruzi* uses autophagy as a central point to invade phagocytic cells and multiplies whether at basal levels or not. Interestingly, LC3 protein serves as the gateway to mediate this process.

formation of STAT/IRF complexes that primarily activate genes associated with the production of inflammatory mediators responsible for inhibiting viral replication (Figure 4).<sup>201–203</sup> Assuming that negative regulation coupled to non-structural proteins of flavivirus or HCV is crucial for viral survival, the immune leakage, in this case, mainly inhibits intracellular signaling pathways (Figure 4).

## Autophagy

Just as the cell death process directly impacts the immune evasion strategies triggered by microorganisms, autophagy

is used to mediate pathogen replication at various stages of development.<sup>204–206</sup> Interestingly, the apoptotic-like *Leishmania* uses autophagy to reduce the elimination of the promastigote forms in macrophages and diminish the response of T cells. It is worth noting that Annexin V, light chain 3 (LC3), beclin 1, and mechanistic target of rapamycin (mTOR) participate actively in this mechanism.<sup>207</sup> On the other hand, *T. cruzi* uses autophagy to subvert the lysosomal exocytic process and invade host cells under basal conditions. This occurs frequently because of recruitment of the LC3 protein.<sup>208</sup> Interestingly, when the process



**Figure 4** Antiviral response and immune escape mechanism triggered by hepatitis C virus (HCV) and flaviviruses DENV, ZIKV, and WNV. Among PRRs, RLRs are extremely important in development of antiviral responses mainly associated with actions of IFN- $\alpha$  and  $\beta$ . Among the receptors, we highlight RIG-I and MDA5 that recognize PAMPs either HCV or flaviviruses to activate MAVS and STING, which in turn, provoke the formation of TBK1/IKK $\epsilon$  and NEMO/IKK- $\alpha$ / $\beta$  complex. This mechanism has the final product for both phosphorylation of IRF7 and IRF3 and the release of NF- $\kappa$ B p50/p65 subunit that migrates to the nucleus to activate genes responsible for production of inflammatory cytokines and IFN-type 1. In the case of IFN- $\alpha$  and  $\beta$ , IFN $\alpha$ R recruits JAK1 and TYR2, which when phosphorylated, trigger formation of an intracellular cascade that culminates in formation of the STAT1/STAT2/IRF9 complex, which migrates to the nucleus, activating genes associated with the antiviral response such as *Mx*, *OAS*, *PKR*, and *ISGs*. To evade the immune response, HCV or flaviviruses induce the production of non-structural proteins that inhibit response of several markers at points considered essential for the development of the intracellular cascade, facilitating the viral replication process. A priori WNV can establish primordial control of antiviral responses at the level of inhibition of RIG-I and MDA5. In another follow-up, ZIKV, DENV, WNV, or HCV through NS1, NS2A, NS2B, NS3, NS4A, NS4B, or NS5 inhibit TBK1/IKK $\epsilon$  complex formation, IRF3 and 7 phosphorylation, and NF- $\kappa$ B activation. In the response by IFN-type 1, NS5N of DENV and WNV inhibited activation of JAK1/TYR2. HCV NS5A inhibits activation of STAT1 and 2. Among various immune escape mechanisms, autophagy is critical for flavivirus to mediate biogenesis of viral replication, mainly because of changes in pH and endocytosis. In this sequence, it is worth noting that NS2B and NS4A/B proteins can manipulate autophagy to alter membrane curvature in the Golgi apparatus to facilitate viral replication. However, in another follow-up, NS2B/3 cleaves FAM134B into endoplasmic reticulum (ER) to suppress autophagolysosome formation and reticulophagy, a form of selective autophagy, to facilitate viral replication. As a result, NS4A induces cells to produce PIK3, which impair the conversion of LC3I to LC3II and inhibit autophagy.

is induced by starvation or rapamycin, autophagolysosome formation and LC3 expression is increased. This also results in large-scale formation of the parasitoid vacuole. As a form of escape, the trypomastigote form resides in the autophagolysosome and escapes into the cytosol, increasing the autophagic cell response (Figure 3).<sup>209</sup>

For *M. tuberculosis*, the suppression of autophagy to increase the survival of mycobacteria serves as a potential regulatory effect. In this context, cytokines such as IL-6 and IL-27 inhibit IFN- $\gamma$ -induced autophagy. In this process, expression of IL-6 or IL-27 considerably reduces the

maturation of the autophagolysosome from the negative regulation of Atg12-Atg5 and positive effects of complex JAK/PI3K/Akt/mTOR and Mcl-1 (Figure 3).<sup>210,211</sup>

Concerning the modulation of the autophagic cascade for flavivirus, autophagy seems to be a crucial factor in mediating the biogenesis of viral replication.<sup>212–214</sup> This relationship overlaps in a dynamic where the internalization of viruses at endocytosis facilitates the change in pH and, consequently, the release of viral RNA (vRNA) into the cytoplasm. The events of autophagy manipulation are mainly modulated by non-structural proteins, such as



NS2B, NS4A, and NS4B.<sup>215–217</sup> Interestingly, at the beginning of the infection, both NS4A and NS4B manipulate the cell to mediate membrane curvature and induce autophagy. This process mobilizes the membranes and lipids to establish a proviral event that facilitates viral replication. This directly impacts regulation of the Golgi apparatus because NS2B/3 induces the production of proteases that trigger the cleavage of FAM134B, one of the main receptors involved in endoplasmic reticulum (ER)-phagy.<sup>218</sup> Finally, it is worth mentioning that in this dynamic, NS4A can deregulate the PI3K pathway, which, in turn, impairs the conversion of the LC3-I protein to LC3-II (Figure 4).<sup>215,219</sup>

## Tissue response of macrophages to infectious agents

Macrophages are a population of cells that play critical roles in maintaining homeostasis and in the pathogenesis of inflammatory, infectious, and neoplastic diseases.<sup>220</sup> Macrophages are found in both blood and tissues, and despite their common origin in the bone marrow, tissue macrophages appear to exhibit an embryogenic development that is independent of that of blood macrophages or even of macrophages that migrate from the blood into tissues.<sup>221–223</sup>

Macrophages perform a wide spectrum of functions in various tissues, including the removal of dead cells, as well as tissue remodeling and repair, which are associated with an elaborate response to foreign agents and infectious or non-infectious aggressors.<sup>224–226</sup> Given this, macrophages are crucial for the development of the organ-specific immune response, which acts on innate and adaptive immunity, frequently serving as a bridge between these two types of responses.<sup>2,227,228</sup>

During an immune response, macrophages can function to maintain tissue homeostasis as well as contribute to the development of tissue lesions that are ultimately the result of a lack of control of the tissue immune response against aggressors. These aggressors concurrently trigger mechanisms to escape the action of macrophages, thus leading to a lack of control of the cellular response associated with tissue injury.<sup>229–234</sup> This phenomenon is observed both in non-infectious and infectious diseases caused by viruses, bacteria, fungi, protozoa, and helminths.

Macrophages can acquire microbicidal properties after stimulation by microbial products, acting in both innate and adaptive immunity mechanisms. One of the main strategies used by microorganisms to escape this

macrophage activity involves altering the response profile of macrophages.<sup>185,235–252</sup> The activation of a response profile mediated by M1 macrophages is commonly associated with a protective tissue environment and has been described for infections by pathogens such as *Helicobacter pylori*, *M. tuberculosis*, *Mycobacterium leprae*, *Salmonella typhi*, and *Chlamydia*.<sup>253–258</sup> M1 macrophages elicit an effective immune response against *S. typhi* and *H. pylori*, and in the response against *H. pylori*, the induction of iNOS associated with the M1 profile is closely related to the occurrence of gastric cancer.<sup>259–264</sup> Early and acute stages of *M. tuberculosis* infections are mediated by M1 macrophages. In the later stages and chronic disease, the infection is associated with responses mediated by M2 macrophages, whose weak microbicidal activity and ability to eliminate bacteria are linked to the occurrence of the lesions observed during disease evolution.<sup>265–269</sup> In leprosy, macrophages are the primary cells that exert microbicidal activity. Thus, the role of macrophages in the response to *M. leprae* has been widely described and is correlated with the expression of certain cytokines that are classical representatives of the cellular immune response, such as TNF- $\alpha$  and IFN- $\gamma$ .<sup>270–272</sup>

In leprosy, when TNF- $\alpha$  and IFN- $\gamma$  bind to their specific receptors, the behavior of M0 macrophages is altered. Furthermore, after undergoing phenotypic modification, the M0 macrophages become inflammatory, producing inflammatory cytokines and enzymes such as iNOS, which produces NO and, consequently, reactive oxygen radicals, leading to the destruction of the bacteria.<sup>273–275</sup> In contrast, M2 and M4 macrophages are observed mainly in lepromatous lesions, and both cell types present expression profiles associated with immunosuppressive cytokines. Therefore, these cells are likely to be related to more diffuse and severe aspects of the disease. These features are also observed in tegumentary leishmaniasis, where M2 macrophages are related mainly to diffuse and anergic aspects of the disease.<sup>276–278</sup>

In viral diseases, the macrophage response might be subverted to a certain extent by the numerous escape mechanisms that viral agents use to resist the host immune response.<sup>279–289</sup> Nevertheless, viruses generally trigger a response mediated by M1 macrophages that might contribute to the severity of the disease. In hepatitis C, chronic infection can lead to cell damage and cirrhosis, and the virus can induce an immune response, targeting the viral protein NS3, mediated by IL-12 and TNF- $\alpha$  produced by M1



macrophages. This process creates a pro-inflammatory environment that contributes to the induction of cell injury. A similar process occurs in the liver of patients infected with dengue virus and yellow fever, where cytokines, such as TNF- $\alpha$  and TGF- $\beta$  released by Kupffer cells, contribute to the development of a pro-inflammatory and proapoptotic environment in tissue hepatic necrosis, which leads to massive apoptosis of hepatocytes because of the proapoptotic action of TGF- $\beta$ .<sup>290,291</sup> Viral influenza infections have been linked to lung injury induced by M1 macrophage-associated cytokines, including TNF- $\alpha$ , IFN- $\gamma$ , and IL-6. Furthermore, these lung lesions might be attenuated in coinfection by *Staphylococcus aureus*, which is normally present in the airway mucosal microbiota, because of the bacterium's ability to stimulate the expression of M2 macrophages.<sup>292–294</sup> Conversely, in the pathogenesis of coronavirus and cytomegalovirus infections, the lesions that develop are related to the induction of an inflammatory environment mediated by M2 macrophages, which indicates that viral agents can still benefit from the induction of specific tissue environments related to the Th2 response and, consequently, tissue repair and induction of tissue fibrosis.<sup>287,295–299</sup>

In mice experimentally infected with *Schistosoma japonica*, liver fibrosis was associated with the presence of M2 macrophages, which exhibited increased regulation of Notch1/Jagged1 signals, and the blockade of this expression reversed the M2 phenotype and, subsequently, the associated fibrosis.<sup>300</sup> In another study, induction of the M2 phenotype in *Schistosoma mansoni* infections elicited a low-grade chronic inflammatory response that was associated with insulin resistance in obese patients.<sup>301</sup>

*Leishmania* infection development depends on both the immune response pattern and the *Leishmania* species. Thus, as described for leprosy, the clinical evolution of leishmaniasis depends on the interaction of the infectious agent and M1 or M2 macrophages, with the M2 subpopulation related to the process of disease progression.<sup>302,303</sup> Lastly, in rats experimentally infected with *Toxoplasma gondii*, peritoneal macrophages in the pre-gestational phase were primarily composed of M1 macrophages, whereas in the intra-gestational phase, the M2 phenotype dominated. This is related to the immune response patterns mediated by Th2 lymphocytes, which are predominant during gestation.<sup>304</sup>

## Conclusion and perspective

The immune mechanisms inherent to the macrophage response in various organs and tissues are distinct to the

pathogen–host interaction. Furthermore, these mechanisms are strongly influenced by both the infectious agents that induce a specific phenotype and the tissue characteristics of the organs where the cells are located. This phenomenon clearly demonstrates the diverse nature and importance of the response in the evolution of specific tissue lesions. Elucidation of the involvement of each phenotypic macrophage subpopulations in infections in various organs and tissues would undoubtedly enhance our understanding of the complex mechanisms of interactions between pathogens and the immune system and their consequence in the genesis of tissue lesions in infectious diseases.

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## Disclosure

The authors declare no conflicts of interest in this work.

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