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REVIEW

# M2b macrophage polarization and its roles in diseases

**Le-xun Wang** | **Sheng-xi Zhang** | **Hui-juan Wu** | **Xiang-lu Rong** | **Jiao Guo**

Guangdong Metabolic Disease Research Center of Integrated Chinese and Western Medicine, Joint Laboratory of Guangdong, Hong Kong and Macao on Glycolipid Metabolic Diseases, Guangdong Key Laboratory of Metabolic Disease Prevention and Treatment of Traditional Chinese Medicine, Institute of Chinese Medicine Sciences, Guangdong Pharmaceutical University, Guangzhou, China

**Correspondence**
Jiao Guo, Guangdong Pharmaceutical University, 280 Wai Huan Dong Road Guangzhou 510006, China.
Email: gyguooyz@163.com

## Abstract

Macrophages play an important role in a wide variety of physiologic and pathologic processes. Plasticity and functional polarization are hallmarks of macrophages. Macrophages commonly exist in two distinct subsets: classically activated macrophages (M1) and alternatively activated macrophages (M2). M2b, a subtype of M2 macrophages, has attracted increasing attention over the past decade due to its strong immune-regulated and anti-inflammatory effects. A wide variety of stimuli and multiple factors modulate M2b macrophage polarization in vitro and in vivo. M2b macrophages possess both protective and pathogenic roles in various diseases. Understanding the mechanisms of M2b macrophage activation and the modulation of their polarization might provide a great perspective for the design of novel therapeutic strategies. The purpose of this review is to discuss current knowledge of M2b macrophage polarization, the roles of M2b macrophages in a variety of diseases and the stimuli to modulate M2b macrophage polarization.

KEYWORDS

Autoimmunity, Chemokines, Disease pathogenesis, Inflammation, Manipulation of immune response, Monocyte/Macrophage

## 1 | INTRODUCTION

Macrophages are widely distributed innate immune cells that play an indispensable role in a variety of physiologic and pathologic processes, including organ development, host defense, acute and chronic inflammation, and tissue homeostasis and remodeling.[1,2] The sources of macrophages include tissue resident macrophages that originate from progenitor cells generated in the yolk sac and monocyte-derived macrophages that originate from bone marrow hematopoietic stem cells.[3] They can be phenotypically polarized by surrounding microenvironmental stimuli and signals to mount specific functional programs.[4] Several forms of macrophages have been described in mice and humans based on the production of specific factors, expression of cell surface markers, and biologic activities.[2,4,5] Polarized macrophages can be broadly classified in two main groups: classically activated macrophages (M1), which steer proinflammatory responses, and alternatively activated macrophages (M2), which drive immune regulation and tissue remodeling. M2 macrophages can be further subdivided in M2a, M2b, M2c and M2d based upon the applied stimuli and the resultant transcriptional changes.[1,2,4,6,7]

M1 macrophages, which are typically induced by TLR ligands (bacterial LPS) or by some cytokines, such as IFN-$\gamma$, TNF-$\alpha$, and GM-CSF, are characterized by a high capacity to present antigen, high proinflammatory cytokine production (IL-1$\beta$, IL-6, IL-12, and IL-23),

Abbreviations: A2R, A2 adenosine receptor; AD, Alzheimer's disease; ALD-DNA, activated lymphocyte-derived DNA; A$\beta$, amyloid-$\beta$; BCL6, B-cell lymphoma-6; BMDMs, bone marrow-derived macrophages; Cath, cathelicidin; CCL1-ODN, CCL1 antisense oligodeoxynucleotides; CD, cluster of differentiation; Chil3, chitinase-like 3; cTnI, cardiac troponin I; DCs, dendritic cells; DS, Down syndrome; DSS, dextran sodium sulfate; GAS5, growth arrest-specific transcript 5; H, human; HCC, hepatocellular carcinoma; HK-SA, heat-killed *S. aureus*; HMGB1, high-mobility group box 1; I/R, ischemia/reperfusion; IBD, inflammatory bowel disease; IC, immune complex; IGF, insulin-like growth factor; IRFs, interferon-regulatory factors; LIGHT, homologous to lymphotoxin, inducible expression, competes with herpes simplex virus (HSV) glycoprotein D for binding to HSV entry mediator, a receptor expressed on T lymphocytes; LN, lupus nephritis; M, mouse; M1, classically activated macrophages; M2, alternatively activated macrophages; MBL, mannose-binding lectin; MerTK, Mer receptor tyrosine kinase; MLNs, mesenteric lymph nodes; MRSA, methicillin-resistant S. aureus; MSK1/2, mitogen- and stress-activated protein kinase-1/2; NMD, nonsense-mediated RNA decay; ORM1, orosomucoid 1; oxLDL, oxidized low-density lipoprotein; PRC2, polycomb repressive complex 2; Q-PCR, quantitative real time polymerase chain reaction; SAA, serum amyloid a; SCI, spinal cord injury; SLE, systemic lupus erythematosus; SPHK1, sphingosine kinase 1; TAMs, tumor-associated macrophages; TBSA, total body surface area; TNFSF14, TNF superfamily member 14; Tregs, T-regulatory cells; UTR, untranslated region; VEGF, vascular endothelial growth factor



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high chemokine (C-X-C motif) ligand 9 (CXCL9) production, and low levels of IL-10.[1,2,4,7,8] Functionally, M1 macrophages can facilitate immunity to remove foreign pathogens and tumor cells, mediate tissue damage induced by ROS, and impair wound healing and tissue regeneration.[8–10]

M2 macrophages can be polarized by several stimulatory factors, which include cytokines (IL-4, IL-10, and IL-13), glucocorticoids, immune complexes (IC) and LPS. Different subtypes of M2 macrophages can be induced by different stimulatory factors. M2a macrophages, also named wound-healing macrophages, are induced by IL-4 and IL-13 and express high levels of mannose receptor (MR, also called CD206), decoy IL-1 receptor (IL-R) and CCL17, and they secrete pro-fibrotic factors such as TGF-$\beta$, insulin-like growth factor (IGF), and fibronectin to contribute to tissue repair.[4,11–13] M2c subtype of macrophages (acquired deactivation macrophages) are induced by IL-10 via activating signal transducer and activator of transcription 3 (STAT3) through IL-10R and strongly exhibit anti-inflammatory activities by releasing large amounts of IL-10 and pro-fibrotic activity by secreting high levels of TGF-$\beta$.[4,13–15] In addition, M2c macrophages exhibit high expression of Mer receptor tyrosine kinase (MerTK), thus resulting in their efficient phagocytosis of apoptotic cells.[8,16] M2d macrophages, representing a novel M2 subset that are also known as tumor-associated macrophages (TAMs), are induced by costimulation with TLR ligands and A2 adenosine receptor (A2R) agonists or by IL-6.[8,17,18] These cells are mainly characterized by high IL-10, TGF-$\beta$, and vascular endothelial growth factor (VEGF), and low IL-12, TNF-$\alpha$, and IL-1$\beta$ production.[1,8,17–20] They constitute the major inflammatory component in neoplastic tissue, contributing to angiogenesis and cancer metastasis.[17–22]

As an M2 subtype, M2b macrophages, also known as regulatory macrophages, can be induced upon combined exposure to IC and TLR agonists or by IL-1R agonists and express high levels of CCL1 and TNF superfamily member 14 (TNFSF14).[2,4,7,14,23,24] In addition to proinflammatory cytokines (IL-1$\beta$, IL-6, and TNF-$\alpha$), M2b cells also express and secrete substantial amounts of the anti-inflammatory cytokine IL-10 and low levels of IL-12, which is the functional converse of M1 cells.[2,4,24] Based on the expression profile of cytokines, chemokines, and other secreted factors, M2b macrophages regulate the breadth and depth of the immune response and the inflammatory reaction.[2] In cancer and infectious diseases, M2b macrophages promote tumor development and parasite, bacterial, and fungal infections by blunting the immune and inflammatory response.[25–31] Moreover, M2b macrophages can reduce spinal cord injury (SCI) and myocardial ischemia/reperfusion (IR) injury, and contribute to recovery from these injuries.[6,24,32] Despite various important roles in many diseases, the definite and specific molecular markers of M2b macrophage have not yet been unified and established to date.

In the current review, we will present and discuss the phenotypes and functions of M2b macrophages under normal conditions and during disease pathogenesis and the possible mechanisms underlying M2b activation. Then, we will introduce the stimulatory factors to alleviate diseases by targeting M2b macrophage polarization.

## 2 | PHENOTYPIC MARKERS OF M2B

In 2002, Mosser and Anderson reported a novel phenotype of activated macrophage which was induced by LPS plus anti-ovalbumin (OVA) IgG/OVA ICs or anti-sheep erythrocyte IgG/erythrocytes ICs that was clearly distinct from either M1 or M2 cells and termed these cells type II activated macrophage.[23] These cells were defined as M2b macrophages by Locati and his colleagues.[1,4] Since then, many markers of M2b have been reported, including IL-10, CCL1, LIGHT, CD86, SPHK1, TNF-$\alpha$, and IL-6.

### 2.1 | IL-10

IL-10 is a potent anti-inflammatory cytokine that is expressed and secreted by many types of cells, including monocytes/macrophages, dendritic cells (DCs), B cells, and T-regulatory cells (Tregs).[33] As the primary marker of M2b, IL-10 was reported by Mosser and his colleagues to distinguish M2b from M1 and M2a.[23,34] M2b cells express not only high levels of IL-10, but also low levels of IL-12.[23,24] High IL-10 or/and low IL-12/IL-10 ratio is/are widely accepted as the characteristic marker(s) of M2b macrophages.[1,2,4–12] IL-10 can be tested by quantitative real time polymerase chain reaction (Q-PCR) for mRNA or by Western blotting, ELISA, or flow cytometry assays for protein. However, IL-10 is not a useful marker to distinguish M2b from M2c and M2d because M2c and M2d macrophages also produce high levels of IL-10.[8,16] Some specific molecules are needed to more accurately distinguish M2b macrophages from other subpopulations of M2 macrophages.

### 2.2 | CCL1

CCL1 (formerly known as I-309 and TCA3 in humans and mice, respectively) was the first among a long succession of C-C motif chemokines to be discovered.[35,36] CCL1 attracts monocytes, natural killer (NK) cells, immature B cells and DCs by interacting with the cell surface CCR8.[37] In addition to monocytes/macrophages, human immune cells that produce CCL1 include T cells, mast cells and DCs.[38] Moreover, studies have shown that M2b, but not other subtypes of macrophages (M1, M2a, and M2c), express high levels of CCL1.[30,39,40] Interestingly, CCL1 released from M2b cells is essentially required for maintaining the properties of M2b monocytes/macrophages.[40] Growing evidences have shown that CCL1 is the specific molecular identifier of M2b and may serve as a marker for identifying M2b from the other subtypes of macrophages.[1,2,4,8,20,25–29,41–43]

### 2.3 | TNFSF14

TNFSF14, also known as LIGHT (homologous to lymphotoxin, inducible expression, competes with herpes simplex virus [HSV] glycoprotein D for binding to HSV entry mediator, a receptor expressed on T lymphocytes) or CD258, is mainly expressed on T lymphocytes and immature DCs and may function as a costimulatory factor for the activation of lymphoid cells and as a deterrent to infection by HSV.[44,45] In addition, LIGHT has been shown to induce strong anti-tumor immunity to

inhibit the growth of primary tumors and eradicate metastases.[46] In 2006, Mosser and his colleagues found that LIGHT was specifically expressed in M2b macrophages.[34] Over the last decade, in vitro and in vivo substantial studies have shown that LIGHT is a specific marker for mice M2b monocytes/macrophages.[24,40,43,47–50] Because LIGHT is expressed by other of cell types,[45,51] its combination with other markers is a better strategy to identify mice M2b macrophages.

### 2.4 | CD86

CD86, also known as B7-2, a type I membrane protein that is a member of the immunoglobulin superfamily, is expressed on antigen-presenting cells (including macrophages, B cells, and DCs) to provide the costimulatory signals necessary for T cell activation and survival by binding to CD28 or/and cytolytic T cell–associated sequence-4 (CTLA-4, also called CD152).[52,53] CD86 works in tandem with CD80 (known as B7-1) to prime T cells.[54] Among the subpopulations of macrophages, CD86 is expressed in M2b macrophages and considered as the marker for this subtype.[32] However, abundant studies have shown that CD86 is expressed in and used as a marker to identify M1 macrophages.[55–61] These studies indicate that CD86 should be expressed in both M1 and M2b macrophages. Although many review articles have shown that CD86 is the marker for M1 and M2b,[5,6,8,41,62,63] CD86 is a suitable marker for discriminating M2b from the other subtypes of M2 macrophages, but not from M1 macrophages.

### 2.5 | SPHK1

Sphingosine kinases (two isoforms, SPHK1 and SPHK2) catalyze the formation of sphingosine 1-phosphate (S1P), a lipid mediator that functions in mammalian cells as an intracellular second messenger, as well as a ligand for S1P-specific G-protein-coupled receptors.[64] SPHK1 can be expressed in many types of cells, including monocytes, macrophages, hepatic stellate cells, and smooth muscle cells.[34,65–68] Previous studies have shown that SPHK1 is mainly expressed in M2b and suggested that it can be used as a marker for M2b monocytes/macrophages.[1,34,47,48] However, Mantovani and his colleagues reported that SPHK1 is expressed at higher levels in M1 than M2 cells.[69] In addition, some researchers have found that SPHK1 is expressed in M2c.[6,70,71] The expression of SPHK1 is not restricted to M2b macrophages[66,67,69]; thus, it should not be used as a sole marker to identify M2b macrophages.

### 2.6 | TNF-$\alpha$

TNF-$\alpha$, a pleiotropic mediator, is central to host defense and inflammatory responses by binding its receptors (TNFR1 and TNFR2).[72] Initially, TNF-$\alpha$ was considered as a proinflammatory cytokine. However, later preclinical and clinical studies have shown that it also mediates a paradoxical anti-inflammatory and immune-modulatory effect.[72,73] Its pleiotropic effects often lead to opposing outcomes during the development of immune-mediated diseases.[74] Although it can be produced by many other cell types such as neutrophils, lymphocytes, NK cells, and mast cells, TNF-$\alpha$ is chiefly produced by activated macrophages.[72,73] In activated macrophages, M1 and M2b are the main cell types expressing and secreting TNF-$\alpha$.[75] Accumulating evidences have shown that TNF-$\alpha$, in combination with other markers, such as IL-10, LIGHT, CCL1, or/and IL-6, can discriminate M2b from the other subtypes of macrophages very well.[30,71,75–80] In addition, TNF-$\alpha$ is considered a marker of M2b macrophages in many review articles.[6,8,9,11,41,62,63]

### 2.7 | IL-6

IL-6 is a prototypic cytokine with redundant and pleiotropic activities on immune and nonimmune cells and often displays hormone-like characteristics that affect homeostatic processes.[81] IL-6 binds to its receptor IL-6R, and this complex then binds to a second membrane protein, glycoprotein 130 (gp130), which dimerizes and initiates intracellular signaling.[82,83] Promptly and transiently produced in response to infections and tissue injuries, IL-6 contributes to host defense through the stimulation of acute phase responses, immune reactions, and hematopoiesis.[84,85] Almost all stromal cells and immune cells are involved in the production of IL-6.[86,87] It is secreted by monocytes and macrophages after stimulation of TLR ligands.[83,86] In typical methods of inducing macrophage polarization, LPS is a component of the stimuli to induce M1 and M2b. IL-6 is highly expressed in M1 and M2b macrophages but not in M2a and M2c.[71,78] Growing data show that in combination with other markers (IL-10, LIGHT, CCL1, or/and TNF-$\alpha$), IL-6 can identify M2b from the other macrophage subsets.[30,71,77–80,88–90]

In addition to the above molecules, other molecules used to identify M2b macrophages include MHCII/HLA-DR, CD163, CD64, PD-L1 IL-1$\beta$, and CCL2.[26,27,30,75,91–93] However, these molecules are not specific markers of M2b, nor even specific markers of macrophages. Excluding CCL1 and LIGHT, none of the above markers are uniquely expressed in M2b and have been considered a sole marker to identify M2b among macrophage subtypes. Due to the expression of CCL1 and LIGHT in other cell types, it is necessary to combine with the above-mentioned molecules to more accurately distinguish M2b cells from other subtypes of macrophages and from different cell types. The different phenotypes, cell surface markers, and functions of monocytes/macrophages are summarized in Table 1.

## 3 | MODULATION OF M2B MACROPHAGE POLARIZATION

As mentioned earlier, macrophages can display a continuum of phenotypes illustrated by distinct gene expression profiles with the capacity to switch from one phenotype to another depending on the external stimuli. Several factors, such as posttranscriptional regulators, signaling molecules, transcriptional factors, and physical factors, have been found to play pivotal roles in the control of M2b macrophage polarization (Fig. 1).

### 3.1 | Modulation by microRNA (miRNA)

miRNAs are short noncoding RNAs of approximately 22 nucleotides (nt), which have been highly conserved during evolution and play

**TABLE 1** Comparative markers and biologic functions of monocyte/macrophage subtypes

| Phenotypes | Stimuli | Markers | Functions | References |
|---|---|---|---|---|
| Human monocytes/macrophages | | | | |
| M1 | IFN-$\gamma$, LPS, GM-CSF, TNF-$\alpha$ | CXCL9, IL-12 high/IL-10 low, iNOS, IL-6, CD80, CD86, TNF-$\alpha$ | Pro-inflammation, microbicidal effect, tumor resistance | 1,2,6–8,11,27,63,105 |
| M2a | IL-4, IL-13 | CCL17, IL-1R, CD206, Dectin-1, IL-10, DC-SIGN | Anti-inflammatory, wound healing | 1,2,6–8,63,105,141 |
| M2b | LPS+IC, IL-1$\beta$+IC | CCL1, IL-10 high/IL-12 low, TNF-$\alpha$, CD86, IL-6 | Immunoregulation, promoting infection, tumor progression | 1,2,6–8,11,27,39,41,63,75, 90,136,163,164 |
| M2c | IL-10, Glucocorticoids | CXCL13, CD206, CD163, IL-10, TGF-$\beta$, MerTK | Immunosuppression, phagocytosis, tissue remodeling | 1,6–8,63 |
| M2d | LPS+A2R ligands, IL-6 | VEGF, IL-10, TGF-$\beta$ | Tumor progression, angiogenesis | 1,8,17,19 |
| Mouse monocytes/macrophages | | | | |
| M1 | IFN-$\gamma$, LPS, GM-CSF, TNF-$\alpha$ | CXCL9, IL-12 high/IL-10 low, iNOS, IL-6, CD80, CD86, TNF-$\alpha$ | Pro-inflammation, microbicidal effect, tumor resistance, | 1,2,6,8,11,26,63 |
| M2a | IL-4, IL-13 | CCL17, IL-1R, Dectin-1, IL-10, Arg-1, Chil3, FIZZ1 | Anti-inflammatory, wound healing, | 1,2,6,8,31,63 |
| M2b | LPS+IC, IL-1$\beta$+IC | CCL1, IL-10 high/IL-12 low, TNF-$\alpha$, CD86, IL-6, LIGHT | Immunoregulation, promoting infection, tumor progression | 1,2,6,8,11,41,43,63,71,164 |
| M2c | IL-10, Glucocorticoids | CXCL13, CD206, CD163, IL-10, TGF-$\beta$, MerTK, Arg-1 | Immunosuppression, phagocytosis, tissue remodeling | 1,6,8,63 |
| M2d | LPS+A2R ligands, IL-6 | VEGF, IL-10, TGF-$\beta$, iNOS | Tumor progression, angiogenesis | 1,8,12,18,19,63 |

A2R, A2 adenosine receptor; Arg-1, arginase-1; CCL, chemokine (C-C motif) ligand; CD, cluster of differentiation; Chil3, chitinase-like 3; CXCL, chemokine (C-X-C motif) ligand; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; FIZZ1, found in inflammatory zone 1; IC, immune complex; LIGHT, homologous to lymphotoxin, inducible expression, competes with herpes simplex virus (HSV) glycoprotein D for binding to HSV entry mediator, a receptor expressed on T lymphocytes; iNOS, inducible nitric oxide synthase; MerTK, Mer receptor tyrosine kinase; VEGF, vascular endothelial growth factor.

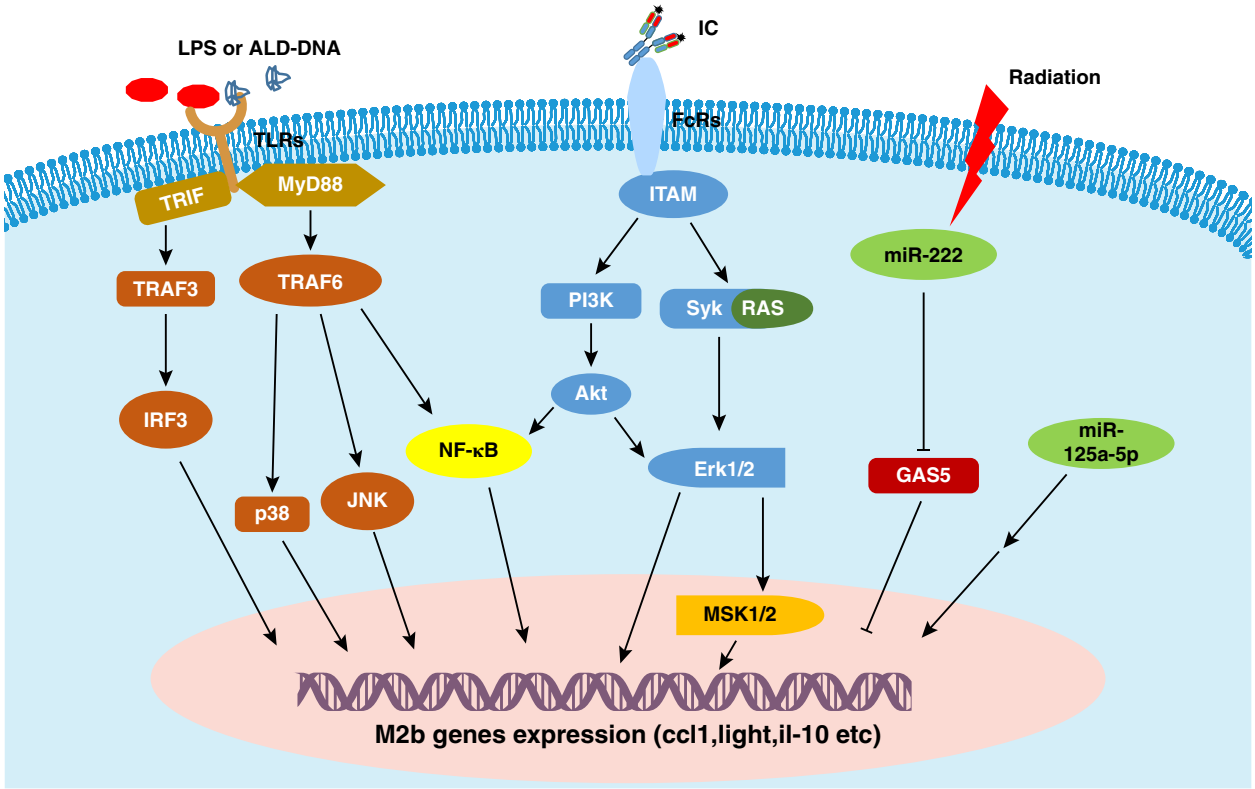


**FIGURE 1** **Regulation of macrophage M2b polarization.** LPS and IC are known to interact with specific receptors on macrophages, such as TLR4 and FcRs, and subsequently induce M2b polarization. Notably, NF-$\kappa$B, MAPK, PI3K/Akt, and IRF3 are activated in M2b macrophages. Moreover, radiation promotes M2b macrophage polarization by regulating the miR-222/GAS5 signaling pathway

crucial roles in immune and inflammatory responses.[94,95] Upon binding to the 3′-untranslated region (UTR) of target mRNAs, miRNAs negatively regulate gene expression by increasing mRNA degradation or/and by repressing the translation process.[96] miRNAs play pivotal roles in the regulation of macrophage development and functions. Recent studies have shown that miR-21, miR-125a-3p, miR-146a, miR-147, miR-214, and miR-455 are up-regulated in M1 macrophages, whereas miR-let7c, miR-143-3p, miR-145-5p, and miR-193 are more abundant in M2 macrophages.[7,97–99] The up-regulation of miR-155 in macrophages contributes to the increased production of CCL2 and TNF by directly repressing B-cell lymphoma-6 (BCL6) expression and the reduced expression of Arg-1 and Chil3.[100,101] By contrast, increased miR-223 promotes M2 polarization.[102]

miR-222 plays a crucial role in M2b polarization. miR-222 is up-regulated in M2b macrophages induced by radiation.[49] Moreover, up-regulation of miR-222 can promote M2b polarization by increasing the expression of CCL1.[49] The underlying mechanism is that miR-222 promotes the degradation of long noncoding RNA (lncRNA) growth arrest-specific transcript 5 (GAS5), which is a CCL1 gene silencer.[49,103] miR-125a-5p expression appears to be induced by LPS and inhibited by IFN-$\gamma$ and IL-4.[104,105] Interestingly, inhibition of miR-125a-5p contributes to the weak expression of M2b macrophage markers, whereas miR-125a-5p overexpression enhances M2b polarization.[104] In addition, miR-27a is increased but miR-26a-2 is decreased in M2b macrophages.[7] Further studies are needed to investigate the mechanisms of these miRNAs in M2b polarization.

## 3.2 | Modulation by lncRNA

The lncRNAs are a large class of nonprotein-coding transcripts that are more than 200 nt in length and are involved in various physiologic and pathologic processes.[106] lncRNA mediated transcriptional or post-transcriptional regulation is an important mechanism for epigenetic programming.[107] Studies have shown that lncRNAs play essential roles in macrophage activation and polarization. Lnc-MC regulates the differentiation of macrophages through the absorption of miR-199a-5p,[108] and overexpression of lncRNA E33 induces inflammatory gene expression, activates inflammatory signaling pathways, and increases foam cell formation in macrophages.[109] TCONS_00019715 expression is decreased when M1 is converted to M2 but increased when M2 is converted to M1.[110] This study indicated that TCONS_00019715 promotes macrophage polarization to the M1 phenotype. LncRNA COX-2 is more highly expressed in M1 macrophages and increases the expression levels of IL-12, iNOS, and TNF-$\alpha$.[111] A recent study has shown that lncRNA GAS5 suppresses IFN regulatory factor 4 (IRF4) transcription by binding polycomb repressive complex 2 (PRC2) to inhibit M2 polarization.[112]

Importantly, GAS5 is a negative regulator of M2b macrophage polarization. GAS5 is known as a silencer of CCL1, which is an essential chemokine for M2b polarization.[113] The RNA level of GAS5 is reduced in M2b macrophages.[43] The reduction of GAS5 RNA in M2b is mediated by activation of the nonsense-mediated RNA decay (NMD) pathway.[43] In contrast, overexpression GAS5 reduces the mRNA levels of CCL1 and LIGHT and inhibits M2b polarization in BMDMs under the stimulation with LPS plus IC.[43] Moreover, radiation also reduces the expression of GAS5 by up-regulating the level of miR-222 and then polarizes monocytes to M2b phenotype.[49]

## 3.3 | Modulation by signaling factors

After binding of receptors to their ligands, the ligand signals can be transferred into the cells via signaling pathways and regulate the physiologic functions of cells, including gene expression, cytokine secretion, cell proliferation, and differentiation. NF-$\kappa$B, MAPKs, PI3K/Akt, and IRFs are involved in M2b macrophage polarization.

### 3.3.1 | NF-$\kappa$B

NF-$\kappa$B family members, including p50, p52, p65, RelB, and c-Rel, can form homodimers or/and heterodimers, which regulate the expression of specific target genes. NF-$\kappa$Bs are the core regulators in the initiation and resolution of inflammation.[114] The activation of NF-$\kappa$B induced by TLR ligands produces proinflammatory factors, and the activation of NF-$\kappa$B p65 is a hallmark of M1 macrophage activation.[115,116] In contrast, the activation of NF-$\kappa$B p50 appears to be essential for M2 macrophage polarization in vitro and in vivo.[117] Indeed, the activation of NF-$\kappa$B plays a pivotal role in M2b macrophage polarization. In lupus nephritis (LN), activated lymphocyte-derived DNA (ALD-DNA) induces the macrophage activation and M2b polarization by activating the NF-$\kappa$B and the IRF3 signaling pathways via calcium signaling.[80] Moreover, the activation of NF-$\kappa$B as well as MAPK signaling in macrophages is inhibited by mannose-binding lectin (MBL), a recognition receptor with binding activity to DNA, resulting in a decrease in M2b macrophage polarization.[88] Furthermore, ALD-DNA-induced M2b polarization is dependent on the acceleration of NF-$\kappa$B p50 translocation into the nucleus mediated by the PI3K and MAPK pathways.[118] These observations suggest that NF-$\kappa$B p50 may be the crucial modulator for M2b macrophage polarization.

### 3.3.2 | MAPKs

MAPKs are a type of protein kinase specific to serine and threonine. MAPKs are involved in directing cellular responses to various stimuli and regulate many processes, such as proliferation, differentiation, cell survival, and apoptosis.[119] The activation of MAPKs (ERK1/2, p38, and JNK) is enhanced in M2b macrophages induced by granulin or ALD-DNA.[79,118] After dectin-1 binding to zymosan (a component derived from fungi), kinases ERK1/2 and p38 are activated and induce M2b macrophage polarization by provoking mitogen- and stress-activated protein kinase-1/2 (MSK1/2).[47] Moreover, MBL blunts macrophage M2b polarization by inhibiting MAPK and NF-$\kappa$B signaling.[88] These observations suggest that the MAPK signal is a crucial positive modulator of M2b macrophage polarization.

### 3.3.3 | PI3K/Akt

The PI3K/Akt pathway not only regulates macrophage survival, migration, and proliferation, but also orchestrates the response to different metabolic and inflammatory signals in macrophages.[120,121] PI3K/Akt signaling is activated by TLR4 and other pathogen recognition

receptors, as well as Fc receptors, modulating downstream signals that control cytokine production.[122,123] Activation of the PI3K/Akt pathway plays a critical role in restricting proinflammatory and promoting anti-inflammatory responses in LPS-stimulated macrophages.[124] A recent study has shown that the activation of Akt is enhanced in influenza virus-induced M2b cells from alveolar macrophages, and inhibition of PI3K/Akt signaling with LY294002 can cause a dramatic down-regulation of M2b polarization markers.[125] In addition, PI3K/Akt signaling is activated in ALD-DNA-induced M2b macrophages.[118] These data indicate that the PI3K/Akt pathway is involved in M2b macrophage polarization.

#### 3.3.4 | IRFs

IRFs, a family of transcription factors expressed in macrophages, play a pivotal role in the polarization of macrophages, depending on the IRF family member.[11] IRF5 acts as a mediator of M1 macrophage polarization in human and murine macrophages.[126,127] By contrast, IRF4 is a modulator of M2 macrophage polarization in response to parasite infection.[127,128] Additionally, IRF3 and NF-$\kappa$B are activated during M2b macrophage polarization by ALD-DNA.[80] This observation suggests that IRF3 may play a core role in M2b activation.

NF-$\kappa$B, MAPKs, PI3K/Akt, and IRFs are important signaling factors involved in cell survival, proliferation, biosynthesis, cell metabolism, and the inflammatory response. These signaling pathways interact with each other and regulate the macrophage switch toward M2b rather than M1 polarization.

### 3.4 | Modulation by radiation

Acute radiation exposure can cause lethal injuries to the hematopoietic and gastrointestinal systems.[129] After 5–9 Gy whole body radiation, the macrophages of mesenteric lymph nodes (MLNs) polarize toward the M2b phenotype.[49,50] This subtype of macrophages is not converted to M1 macrophages in response to stimulation by *E. faecalis* antigens and inhibits the conversion of macrophages from resident M0 to M1.[50] A further study has shown that miR-222, induced by whole body radiation, reduces the expression of GAS5, resulting in an increase in CCL1 levels and macrophage conversion to M2b.[49] Moreover, after treatment with CCL1 antisense oligodeoxynucleotides (CCL1-ODN, which can decrease the mRNA level of CCL1), M2b macrophages disappear in the MLNs of radiated mice, and M1 is generated in the MLNs of these mice following *E. faecalis* stimulation.[50] However, it is unclear how radiation induces the expression of miR-222.

In addition, some reports have shown that thoracic radiotherapy increases cardiovascular events and atherosclerosis development in patients with cancer.[11,130,131] Interestingly, local 14 Gy radiation in ApoE$^{-/-}$ mice results in a larger number of M1 and smaller number of M2 macrophages in atherosclerotic lesions.[132] Additionally, radiation reduces the phagocytic capacity of M2 macrophages, likely contributing to the increase in apoptotic cells and to the shift of macrophage polarization toward a proinflammatory M1 phenotype in vitro.[132] These observations indicate that during different diseases, different doses of radiation have various effects on the macrophages in different tissues. Due to the extensive application of radiotherapy in cancer patients, it will be important to investigate the effect of radiation on macrophage phenotype to improve the radiotherapy efficacy in further studies.

## 4 | M2B MACROPHAGES AND DISEASES

The immune system is the host's defense against infection, inflammation, tumors, and other diseases. Macrophages are multifunctional leukocytes that recognize and remove invading pathogens, toxins, cellular debris, and apoptotic cells in healthy or inflamed tissues. Due to their formidable immunoregulatory effects, M2b macrophages play various roles in infection, inflammation, tissue repair, and tumor progression. In this section, we focus on the roles of M2b in different diseases.

### 4.1 | M2b macrophages in infectious diseases

Under normal physiologic conditions, monocytes in the blood retain a quiescent state (M0: CCL1$^-$, CD163$^-$, CD14$^+$).[27,29] During infection, monocytes/macrophages acquire the M1 phenotype (IL-10$^-$, IL-12$^+$, iNOS$^+$, CXCL9$^+$), which is a major effector cells for the first line of host antibacterial defense.[20,26,133–135] Mild burn injury (5% of the total body surface area [TBSA] burn) induces M1 macrophage polarization.[26] However, moderate and severe burn injury (>15% TBSA) results in M2b monocyte polarization (CCL1$^+$, IL-12$^-$, IL-10$^+$, LIGHT$^+$, CD14$^+$, CD163$^+$) in humans and mice, promoting the infection.[26,27,40,136,137] The possible reason for this phenomenon is an inhibitory effect on the immune response by the substantial factors released after severe burn injury and induction of M2b polarization. In addition, chronic alcohol consumption also leads to the M2b macrophage polarization (CCL1$^+$, CD14$^+$, CD163$^+$, IL-10$^+$, LIGHT$^+$, CD11b$^+$), increasing opportunities for bacterial infection,[29,135,138] but the mechanism responsible for M2b polarization by alcohol consumption is unclear.

Bacteria and viruses directly induce M2b macrophage polarization (IL-10$^+$, IL-12$^-$, IL-6$^+$, TNF-$\alpha^+$, CD11b$^+$, MHCII$^+$).[77,91,125] Additionally, parasitic infections can increase the number and proportion of M2b macrophages (CCL1$^+$, IL-10$^+$, TNF-$\alpha^+$, IL-1$\beta^+$, IL-6$^+$, TGF-$\beta^+$, CCL17$^+$) in the peritoneal cavity,[30] and M2b polarization (IL-12$^{low}$, IL-10$^{high}$, LIGHT$^+$, TNF-$\alpha^+$) promotes the persistence of infection.[139] Despite a strong phagocytic capacity, M2b macrophages are not the main cells responsible for killing bacteria.[20,135,140] Moreover, M2b monocytes/macrophages not only have no antibacterial effect, but also they increase susceptibility to opportunistic pathogens such as *S. aureus*, methicillin-resistant *S. aureus* (MRSA) (M2b: CCL1$^+$, CD163$^+$, CD64$^-$, CD209$^-$), *E. faecalis*, *C. albicans* (M2b: IL-10$^+$, TNF-$\alpha^+$, MR$^+$, Dectin-1$^+$), and *K. pneumonia*.[26,27,31,40,50,135–138,141] Some studies have shown that M1 macrophages are not easily generated in immunosuppressed hosts (such as severely burned patients) with a predominance of M2b.[26,27,40] The most likely explanation for this phenomenon is that M2b inhibits macrophage conversion from quiescent M0 to M1, resulting in a decrease in anti-pathogens (Fig. 2).[26,27,40,135,141]

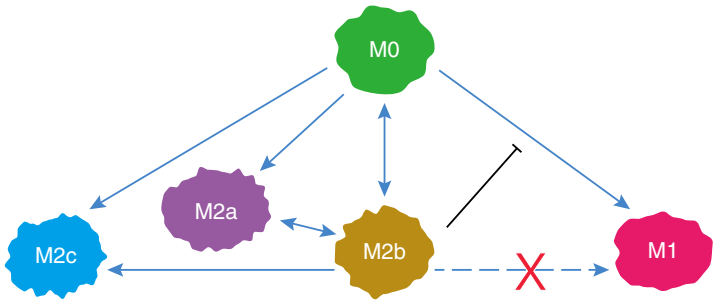


**FIGURE 2 Phenotypic conversion in different types of macrophages.** M0 macrophages can polarize to M1 or M2 (M2a, M2b, M2c) in response to different inducers. M2b macrophages can convert to the other subtypes of M2 macrophages in response to different stimuli. Notably, M2b macrophages inhibit the conversion from M0 to M1. Moreover, M2b cannot repolarize to M1 during exposure to M1 inducer

## 4.2 | M2b macrophages in autoimmune diseases

M2b macrophages play an important role in inflammatory diseases, especially in autoimmune or autoinflammatory diseases. Studies have shown that M1 macrophages play an important inflammatory role in the pathogenesis of systemic lupus erythematosus (SLE), and M2b macrophages actually have a direct role in causing SLE.[41] In ALD-DNA-inducible murine models of LN, infiltrated macrophages in nephritic tissues exhibit M2b functional polarization (IL-10$^+$, TNF-$\alpha^+$, IL-1$\beta^+$, IL-6$^+$, MCP-1$^+$, iNOS$^+$, CD80$^+$, CD86$^+$, MHCII$^+$, CD11b$^+$, PD-L1$^+$).[79,89,93,118] In addition, a recent study has shown that renal M2b macrophages (IL-10$^+$, LIGHT$^+$, CD80$^+$, CD86$^+$) are markers of disease remission in LN.[142] Furthermore, ALD-DNA and IC can induce macrophage polarization to M2b in vitro (IL-10$^+$, TNF-$\alpha^+$, IL-1$\beta^+$, IL-6$^+$, MCP-1$^+$, iNOS$^+$, CD80$^+$, CD86$^+$, MHCII$^+$).[78–80,89] The accepted mechanism of LN is that the deposition of IC causes damage in the renal tissue. M2b macrophages induced by ALD-DNA or/and IC in the renal tissue release many factors that may lead to sustained kidney damage.

In addition, resident macrophages play a crucial role in maintaining intestinal homeostasis and have an important effect on the development of inflammatory bowel disease (IBD).[143] Dextran sodium sulfate (DSS), an inducible chemical compound of IBD, can directly induce M2b macrophage polarization (LIGHT$^+$, SPHK1$^+$).[48] The probable mechanism for this phenomenon is an inhibitory effect of IL-10 secretion by M2b macrophages on pathogen clearance, augmenting inflammation, and causing IBD onset.[48] Moreover, M2b (CCL1$^+$, IL-6$^+$) represent a dominant subpopulation of monocytes in patients with active systemic juvenile idiopathic arthritis, an inflammatory disease of childhood.[90] In these autoimmune diseases, autoantibodies exist and react with the antigens to form IC, resulting in M2b macrophage polarization. These data suggest that M2b macrophage may be a key mediator of the initiation and progression of autoimmune diseases.

## 4.3 | M2b macrophages in diseases of the nerve system

In mammals, macrophages derived from blood monocytes and activated microglia (brain-resident macrophages) indefinitely persist at the site of SCI.[6,144] After SCI, M2b macrophages, the key macrophage subtype regulating the proliferative phase of repair, are improperly activated.[6] In addition, the age-dependent decrease in M2b macrophage (CD86$^+$, IL-10$^+$) is associated with impaired functional recovery and enhanced tissue damage after mild-moderate SCI in aged mice.[32] The probable underlying mechanism is that M2b macrophages release high levels of anti-inflammatory IL-10, facilitating neuroprotection through noninflammatory mechanisms including direct neuronal activation of PI3K/Akt.[32,145,146] These data indicate that M2b macrophages may improve tissue repair after SCI.

Inflammatory responses in the brain, which can be demonstrated by changes in the properties of microglia, are a common feature of human neurodegenerative diseases including Alzheimer's disease (AD).[92] M1, M2a, M2b, and M2c microglia are found in the brain of AD patients.[147] In the early stage of AD, microglia are apparently polarized to either M1 or M2a macrophages, whereas the markers for M1, M2a, and M2c are elevated at a later stage of AD.[147,148] Interestingly, microglia are polarized to M2b macrophages (CD86$^+$, CD64$^+$) in the brain of AD in Down syndrome (DS) patients with the deposition of high levels of amyloid-$\beta$ (A$\beta$).[148] Furthermore, intracranial injection of IVIg, anti-A$\beta$ antibody or IgG into the brain parenchyma of A$\beta$-depositing transgenic mice stimulates M2b polarization (CD86$^+$, CD64$^+$) and promotes the clearance of A$\beta$ deposits.[70] M2b macrophages not only inhibit inflammation but also phagocytize and remove A$\beta$ in the AD murine model.[70] These data indicate that M2b macrophages may play an important role in improving brain diseases and nerve injury.

## 4.4 | M2b macrophages in glycolipid metabolic disorders

Macrophages are the main component of adipose tissue immune cells (40–60% of all immune cells in fatty tissue) and obesity significantly increases the number of adipose tissue macrophages.[149] In the adipose tissue of obese individuals, the percentage of macrophages in the stromal vascular fraction may reach up to 40–50% in the case of the morbidly obese, as compared to approximately 5–10% in lean individuals.[150,151] Under normal physiologic conditions, the resident macrophages of fatty tissue belong to the M2 phenotype, which are important in the homeostasis of adipose tissue.[150,152,153] However, the number of M1 macrophages increases in the adipose tissue of obese individuals, which contributes to the inflammatory processes and insulin resistance.[153] The effects of the glycolipid metabolic disorder on the macrophage phenotypic change may be distinct in different tissues. Macrophages exposed to the diabetic environment are also preferentially polarized toward M1, contributing to multiple pathologies in the target organs.[154] M1 cells are the main macrophages in the adipose tissue of obese people.[153] Additionally, macrophages in the peritoneal cavity and the cecal tissue from high-fat fed mice present M2b polarization (IL-10$^+$, TNF-$\alpha^+$, MR$^+$, Dectin-1$^+$) at the site of

infection that is associated with an increased susceptibility to gastrointestinal candidiasis.[31] Moreover, rosiglitazone (PPAR-$\gamma$ ligand), an anti-diabetic drug, can induce the macrophage phenotypic switch from M2b to M2a in a STAT-6 dependent manner.[31,155,156] Additionally, M2a polarization after treatment with rosiglitazone favors gastrointestinal fungal elimination independently of reduced blood glucose.[31]

### 4.5 | M2b macrophages in cardiovascular diseases

Both pro-atherosclerotic and anti-atherosclerotic functions have been demonstrated for macrophages in atherosclerosis.[150] M1 macrophages display a proinflammatory profile and are found in rupture-prone lesions, which suggests that this subtype of macrophage has pro-atherosclerotic effects and is associated with plaque vulnerability.[11,12] IL-4-dependent M2a macrophages promote oxidized low-density lipoprotein (oxLDL) uptake through CD36 and are abnormally high in patients with symptomatic atherosclerotic carotid plaques.[11] Importantly, heat-killed *S. aureus* (HK-SA) reduce the number of inflammatory Ly-6C$^{hi}$ monocytes in the circulation and attenuate leukocyte recruitment, resulting in significant inhibition of macrophage infiltration in atherosclerotic plaques in vivo.[76] Furthermore, HK-SA induces bone marrow-derived macrophages (BMDMs) to switch to the M2b phenotype (IL-10$^+$, TNF-$\alpha^+$, PD-L1$^+$) in vitro,[76] which suggests that M2b macrophages may have anti-atherosclerotic effects via inhibition leukocyte infiltration.

In myocardial disease, our recent study indicated that M2b macrophages (IL-10$^+$, LIGHT$^+$, F4/80$^+$) have cardioprotective effects.[24] We induced BMDM polarization to M2b macrophages by exposure to LPS and IC. Then, we transplanted M2b macrophages into the myocardial I/R injury zone and found that the serum cardiac troponin I (cTnI) level, infarct area, and apoptosis index were decreased in the group of transplanted M2b macrophages. The cardioprotective effect of the transplanted M2b macrophages occurs via their reduction of NF-$\kappa$B signaling activation and of the up-regulated expression of A20 in heart caused by I/R injury.

These observations suggest that macrophages play crucial roles in cardiovascular diseases, and interventions in macrophage polarization may provide a novel therapeutic opportunity to combat cardiovascular diseases.

### 4.6 | M2b macrophages in tumors

Within the tumor, macrophages are a major stromal component, in which they are commonly termed TAM, which exhibit functions similar to M2 macrophages and can be characterized as the M2d subtype.[20–22,157] Among tumor-infiltrating cells in some cancers, macrophages represent the largest population of cells, contributing to at least one-third of the total tumor mass.[158–160] Mounting evidences have shown that M2d macrophages can release some factors that directly stimulate tumor cell survival, proliferation, motility, and angiogenesis, and affect the tumor microenvironment via paracrine cytokines, leading to tumor metastasis and invasion.[8,11,12,157,161,162]

In addition to M2d, other subtypes of macrophage are present in tumor tissues and play important roles in tumor survival, metastasis, and invasion. M1 macrophages are proinflammatory, promote Th1 responses, and display tumoricidal activity by producing large amounts of toxic intermediates (NO and ROS).[8,11,12] Like M1, M2a and M2c macrophages from monocyte polarization possess anti-tumorigenic effects in hepatocellular carcinoma (HCC), but the underlying mechanisms are unclear.[162] A recent study has shown that CD14$^+$ monocytes isolated from advanced HCC patients show the M2b phenotype (CD68$^+$, CCL1$^+$) and do not possess the properties of M2d (CXCL8$^+$).[25] Additionally, macrophages in tumors of HCC patients are also identified as the M2b phenotype (IL-12$^-$, IL-10$^+$, CCL1$^+$, iNOS$^-$).[25] Accumulating data have shown that M2b monocytes/macrophages can promote the growth, invasion, and recurrence of cancers in vitro and in vivo.[25,28,162,163] These observations indicate that M2b macrophages may be one important component of TAMs, demonstrating different quantities in different cancers. Further studies are needed to investigate the percentage of M2b in TAMs of different tumors and the molecular mechanism by which M2b macrophages promote tumor development.

## 5 | M2B MACROPHAGE POLARIZATION STIMULATION

Polarization is a hallmark of macrophages in response to stimulation with various agents. Different phenotypes of macrophages can switch to other subtypes in response to different stimulants (Fig. 2). Although the internal environment is complex and various, it can be modified by exogenous stimuli, which induce the activation and polarization of macrophages, thereby improving some diseases. In this section, we will focus on stimuli leading to M2b macrophage polarization, including inducers and inhibitors.

### 5.1 | Inducers of M2b macrophages

LPS plus IC is the classical inducer of M2b macrophage polarization.[6–8,11,43,71,75,90] IL-1$\beta$ in combination with IC is also used to induce macrophage polarization to M2b in vitro.[8,11,41,140,164] Additionally, DSS, a polyanionic derivative of dextran, which is usually employed as an inducer in the colitis model, can induce increases in LIGTH and IL-10 (biomarkers of M2b) in mice peritoneal macrophages in vitro.[48] In addition, ALD-DNA, HK-SA, orosomucoid 1 (ORM1), and serum amyloid-A (SAA) can switch mouse and human macrophages from other phenotypes to the M2b subtype in vitro.[76,78,79,89,141,162] There two mechanisms for M2b macrophage polarization induced by ALD-DNA: (a) ALD-DNA can bind to TLR9, activating the TLR pathway[165,166]; (b) ALD-DNA induces the production of anti-DNA antibodies or/ and binds to these antibodies to form ICs that activate the FcR pathway.[167,168] In animal models and in patients, alcohol abuse, acute radiation exposure, and severe burns can stimulate macrophage conversion from a quiescent phenotype to M2b macrophages.[26,49,50,135,136] Some studies have shown that catecholamine levels are increased during the acute phase in the plasma of severely burned patients and can up-regulate the expression of high-mobility group box 1 (HMGB1) in macrophages, triggering

CCL2 production.[136,169,170] Additionally, CCL2 polarizes macrophages toward the M2b phenotype.[137] These data indicate that some of these inducers may have therapeutic effect for diseases with or caused by excessive inflammation.

### 5.2 | Inhibitors of M2b macrophages

Due to its formidable effects in promoting infection and inhibiting the immune response, strategies to inhibit M2b polarization are of interest to reduce the infection and activate immunity. Recent studies have advanced this possibility. CCL1 is a specific marker of M2b macrophages and is essential for the maintenance of M2b properties.[40] In 2012, Kobayashi and his colleagues reported that M2b macrophages disappear after treatment with CCL1-ODN (binds to CCL1 RNA to modulate its function) in the MLNs of irradiated mice.[50] Accumulating evidences have demonstrated that CCL1-ODN treatment can inhibit M2b polarization by reversing M2b to the quiescent state (M0) in monocytes/macrophages of humans and mice (Fig. 2).[25–27,29,40,49,135,141] These data suggest that CCL1-ODN is a useful inhibitor of M2b in vivo and in vitro. Furthermore, Kobayashi et al have reported that recombinant CCL2 treatment can induce M2b polarization from resident monocytes and that M2b monocytes are not generated from quiescent monocytes after cultivation with burn patient sera pretreated with CCL2 antibody.[137] In addition, rosiglitazone, a PPAR-$\gamma$ ligand that is approved for glycemic control in people with type 2 diabetes, can switch the M2b subtype of tissue resident macrophages induced by high fat food toward M2a polarization in the peritoneal cavity and cecal tissue, facilitating intestinal *Candida* elimination (Fig. 2).[31] Propranolol, a noncardioselective sympatholytic $\beta$-blocker that is mainly used to treat various cardiovascular diseases, inhibits the production of IL-10 and CCL1 (markers of M2b) in monocytes caused by severe burn.[136] These data indicate that these approved drugs may have therapeutic effects in immunologic/inflammatory diseases caused by M2b macrophages. The unequivocal mechanisms of PPAR-$\gamma$ ligand and $\beta$-blocker in inhibiting M2b polarization and the role of these drugs in immunologic/inflammatory diseases remain to be demonstrated.

## 6 | CONCLUDING REMARKS

The concept of macrophage polarization has been increasingly appreciated and gradually accepted. Over the past decade, M2b polarization has attracted increasing attention. As illustrated in this review, many molecules have been used as markers of M2b, but some of them are not specific. In addition, a wide variety of stimuli can induce M2b macrophage activation, and multiple factors coordinate a complex network to drive macrophage M2b polarization. Additionally, M2b macrophages possess both protective and pathogenic roles in various diseases. Nevertheless, the accepted characteristic molecules of M2b macrophages and the roles of M2b in pathophysiology are still unclear. Thus, in future work, it will be important to study the distinguishing characteristics of the different subtypes of macrophages, especially the tissue-resident macrophages originating from the yolk sac, because this knowledge will facilitate our ability to compare findings between research groups and different macrophages and expand our understanding of the unique contributions of macrophages, especially M2b macrophages, in multiple physiologic and pathologic processes. Furthermore, a uniform nomenclature for macrophages and their subtypes will also become increasingly important given that the research about the subtypes and functions of macrophages will most rapidly increase in the next few years. Another question that need to be answered concerns the precise mechanisms of M2b polarization and depolarization, so that we can choose some small molecules to induce or inhibit M2b polarization for treating some diseases caused by M2b macrophages in the further.

### AUTHORSHIP

L.-X.W., S.-X.Z., and H.-J.W. wrote the manuscript and designed the figures. X.-L.R. edited the manuscript. J.G. wrote and edited the manuscript.

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### DISCLOSURES

The authors declare no conflicts of interest.

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