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Macrophage polarization or repolarization in tuberculosis

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ABSTRACT

Tuberculosis caused by *Mycobacterium (M.) tuberculosis* remains a global public health threat. Over the last few decades, anti-tubercular research mainly focused on mechanisms of identifying by which activated macrophages can slaughter or the proliferation of *M. tuberculosi*s bacilli prevented in a cell-dependent manner. In this regard, for disease resolution, inflammatory cytokines are very crucial. Here, we demonstrate how macrophages act as the first line of defense against the *M. tuberculosis*. Studies have revealed a dual role in *M. tuberculosis* infection played by macrophages. It is worth mentioning that the macrophages are the crucial immune effector and antigen-presenting cells that play the anti-tubercular response, which is the habitat of *M. tuberculosis*, hence, followed by progressing the disease protecting *M. tuberculosis*. This dual role can be correlated with the different macrophage polarization statuses, namely, M1 and M2. Herein, we have stated how the several polarization conditions of macrophages are directly linked to the immune responses during host and *M. tuberculosis* pathogen interactions. We have proposed that macrophage polarization and repolarization are of paramount significance for the anti-tubercular immune response that may involve a sterile cure of the disease. This article summarizes the immune response to *M. tuberculosis*, the polarization states of macrophages during *M. tuberculosis* and the repolarization of macrophages by some agents during some diseases including *M. tuberculosis*, which may be an important factor in the World Health Organization's target to cure tuberculosis by 2035.

KEYWORDS: Tuberculosis; Macrophage polarization; Effector responses; Antitubercular immune response

1. Introduction

Tuberculosis (TB) caused by *Mycobacterium (M.) tuberculosis* poses a serious public health threat in many countries[1–3]. The effects of tuberculosis continue to be a major source of illness and mortality on a global scale. The World Health Organization (WHO) estimates that in 2024, TB will be responsible for nearly 1.5 million annual deaths. Once alveolar macrophages phagocytose *M. tuberculosis* enters the body through inhalation into the lungs, they then travel to the pulmonary interstitial space, where they draw in immune cells such as mononuclear derived macrophages and create tuberculous granuloma by surrounding themselves with germs[4]. Based on the mode of infection, *M. tuberculosis* infection is of two types-latent TB and active TB[5]. In latent TB, the tuberculous granuloma's crucial function is to restrict the infecting bacteria and prevent the infection's spreading (active TB)[6].

Macrophages are the initial line of defense against specific bacteria through phagocytosis, cytokine secretion, and antigen presentation which differentiate from monocytes and bone marrow hematopoietic stem cells[7,8]. Macrophages showed enormous functional plasticity and in response to the microenvironment, they polarize into a definite phenotype. As per their useful features and morphology, macrophages are basically two types: M1 and M2 stand for classically and alternatively activated macrophages, respectively.

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IFN-gamma (IFN-γ) and lipopolysaccharide (LPS) cause macrophages to polarize into M1 cells. M1 macrophages boost the expression of inflammatory cytokines as IL-12, TNF-α, IL-6, iNOS, and CD86. These have the ability to eradicate intracellular infections and tumour cells, hence enhancing the Th-1 immune response[9,10].

In contrast, anti-inflammatory activity is associated with M2 macrophages[4]. As per different stimuli, M2a, M2b, and M2c are the designations for the three subpopulations of M2 phenotypic macrophages, which differ according to various stimuli. Scavenger receptor, mannose receptor, and arginase-1 (Arg-1) expression are induced in M2a macrophages by IL-4 and IL-13, whereas IL-1R ligands and immune complexes activate M2b macrophages, raising IL-10 production and promoting the response of Th2. Following the released pentraxin 3 and chitinase 3 which play a role in wound healing, IL-10 predominantly activates M2c macrophages[11].

Progressive research claimed that macrophages are the primary host cells against *M. tuberculosis* infection, which are crucial immune effector cells capable of tubercular antigen-presentation followed by inducing an anti-TB immune response. On the contrary, *M. tuberculosis*' residence is macrophages, and it defends *M. tuberculosis*[12]. Hence, these host cell macrophages play a significant dual role during the infection of *M. tuberculosis*[4]. It implies that *M. tuberculosis* has progressed some approaches to survive, although it is capable to replicate within the macrophages. *M. tuberculosis* within the macrophages also acts to prevent the fusion of phagosome-lysosome, inhibits the maturation of phagolysosome, and induces M2 macrophage polarization[6]. M2 phenotype macrophages create an oppressive microenvironment. This can promote latent infection and intracellular growth of *M. tuberculosis*. In order to effectively treat tuberculosis, a greater understanding of macrophage polarization during *M. tuberculosis* infection may be helpful[4].

This mini-review summarizes the concept of macrophage polarization, polarization states of macrophages during *M. tuberculosis*, the concept of immune response during *M. tuberculosis*, and macrophage polarization and repolarization by some agents during some diseases including *M. tuberculosis*, which may be directly associated with the disease progression to anti-tubercular immune response and these could be an important factor in the WHO's goal of curing TB by 2035.

2. Subtypes and activation of macrophage polarization and its function

The human system is highly intricate in its functioning due to the association of many different systems. The immune system is complex, with a network of various fighter immune cells in action. An encounter or challenge with any non-native substance triggers a shot of host immune response, provoking innate and adaptive responses against it. Dendritic cells, macrophages, and natural killer cells are the immune cells connected to innate immune response. Among the other immune cells, monocyte-derived macrophages are recognized as very versatile. Earlier considered only to be associated with the host defense and apoptotic cells clearance, but now the plethora of literature indicates that macrophages are more than just phagocytic cells and play a pivotal role in many facets due to their dynamicity and their property to orient to the environment they are defied with[13].

Polarization is often defined as "the activation of the macrophages at a given point in time"[14]. Macrophages can be polarized into two different states of activity, known as M1 (classically activated) and M2 (alternatively activated). These two macrophage subsets have been identified to evoke a wide range of functionalities[15-18]. Secreted cytokines, cell surface indicators, and biological roles of these macrophages vary depending upon the polarization state[19]. The final result of arginine metabolism is M1/M2 polarity that occurs through two opposite pathways. One of them is the iNOS pathway, which generates nitric oxide and citrulline from arginine, resulting in macrophages that resemble M1 cells. The other is the arginase route, which converts the M2-like macrophage-producing enzyme arginase into urea and arnithine[20].

Lipopolysaccharide (LPS) and Th1 cytokines including IFN-γ and TNF-α activate macrophages, which then polarize into M1 macrophages. Nonetheless, the transcription factor, T-bet, plays the crucial role in the Th1 cytokines release[11]. TLR-2, TLR-4, CD80, CD86, and MHC-Ⅱ are several surface characteristics that are present on M1 macrophages. These cells secrete cytokines and chemokines including TNF-α, IL-1, IL-6, IL-12, CXCL 9, and CXCL 10, which have a beneficial effect on normal macrophages, M0 or unpolarized macrophages, and cause them to change into the M1 state. Transcription factors such as NF-κB, STAT1, STAT5, IRF3 and IRF5 are essential for regulating *M1* genes. Additionally, in the case of M1 macrophages, two transcription factors named NF-κB and STAT1 play a vital role in the M1 macrophages' microbicidal and tumoricidal activities[14,21-23]. Pro-inflammatory cytokines produce against bacterial or viral encounters by macrophages leading to M1 polarization. Neutrophils, natural killer cells (NK cells) and T helper cell type 1 or Th1 are engaged by the cytokines, and these compounds increase pro-inflammatory cytokines and kill external pathogens[24]. Moreover, the activity of killing the M1 phenotype is increased by nitrite production. M1 macrophages possess antitumoral (inhibiting the development of tumours) activities and anti-angiogenic (reducing the new blood vessel's growth that supports tumour growth rather than blocking the growth of tumour cells themselves) activities[24]. Unpolarized macrophages enter either M1 (classical activation) or M2 (alternative activation) when the microenvironment changes. Macrophage reprogramming is the term for this trend[24].

On the other hand, parasite infection and anti-inflammatory cytokines (IL-4, IL-10, IL-13, and TGF-β) drive M2 macrophages to become polarized as opposed to unpolarized macrophages[21,22]. The M2 macrophages are only directly activated by IL-4 and IL-

13. Other cytokines like IL-33, IL-25 help to produce T-helper type 2 (Th2) cytokines due to activation of GATA-3 in helper T-cells, which increases the activation of M2 macrophages[25]. In addition, M2 is classified into 3 subgroups, *i.e.*, M2a, M2b and M2c. M2 macrophages are known to be "biomedically important" because of their tissue remodelling properties, explained in many inflammatory disease studies and as inflammation pro-resolvers. M2 macrophages are an integral part of tumour microenvironmental as tumour associated macrophages (TAM) that promote blood vessel formation (angiogenesis), thereby ensuring tumour survival[13,26]. M2 macrophages are identified by the expression of some surface markers such as CD 206, CD 163, CD 209, mannitol receptor, FIZZ 1, YM 1/2. Chemokines and cytokines *i.e.*, TGF-β, IL-10, CCL1, CCL17, CCL18, CCL22 and CCL24[22,27] alter unpolarized macrophage or M0 to M2 polarization state[28]. Transcription factors *i.e.*, STAT6, JMJD3, IRF4, and PPAR control the expression of the M2 genes. Till now, the STAT pathway is the one which activates the M2 macrophages[14]. The M1/M2 polarization signals and their effector functions are summarized in Figure 1.

3. M1 and M2 markers in polarized macrophages

By providing the first line of defense, the phagocytic macrophages are dynamic in nature and play a vital role in innate immunity or natural immunity[29]. Depending upon the microenvironment, macrophages orchestrate between two states, "M1/classical activation" or "M2/alternative activation"[30]. In the 1960s, Mackaness introduced macrophage polarization or macrophage activation[30]. Macrophage polarization has been studied in immunology for several years. M1 phenotype has pro-inflammatory properties and enhances pathogen-killing activity. On the other hand, the M2 phenotype has anti-inflammatory properties, contains tissue remodeling capacity, and they are tumorigenic and designated as an inflammation pro-resolvers[30]. Th1-released IFN-γ or bacterial LPS contribute to M1 polarization, whereas parasite or helminth infection or Th2-released anti-inflammatory cytokines like IL-4 and IL-10 contribute to M2 polarization[24]. Numerous studies disclosed that M1 and M2 phenotypes express unique proteins or specific markers on their surface[31]. CD80, CD68, CD32, CD64, CD86, CCL19 markers are expressed on M1 macrophages, and they can identify these M1 macrophages by those surface markers and M2 macrophages are identified by MRC1, MGL (lectin type receptor), FIZZ1, CD163, CD206, YM-1[13]. M1 effector functions increased in NO generation and pro-inflammatory cytokines IL-12, IL1β, IL-6, and TNF-α generation (Figure 2). M2 macrophages increased arginase 1 and TGF-β[31]. Also, transcriptomic analysis has delineated unique M1 and M2 markers like CD38 and Fpr2 as M1 markers and c-Myc and Erg as M2 markers[31]. In human beings, metabolism is an essential process. Various essential enzymes regulate this metabolism process and are interconnected by many pathways. When one pathway becomes defective and leads to disease, this interconnectivity becomes obscure[32]. Several signaling pathways such as-JAK-STAT, JNK-P13/AKT, NOTCH and TGF-β-SMAD recruit in macrophage reprogramming. The status of polarization is indicated by the regulation of these pathways[24].

4. Macrophage polarization in *M. tuberculosis* infection

After the infection with *M. tuberculosis* or with the revival of latent infection in granulomas, the progress of active tuberculosis may occur[33–35]. Within granuloma, macrophage polarization is decided by type 1 and type 2 inflammatory signals. During M1 polarization, the product of type 1 inflammatory cytokines gives rise to anti-*M. tuberculosis* immune responses, so these cytokines played a major

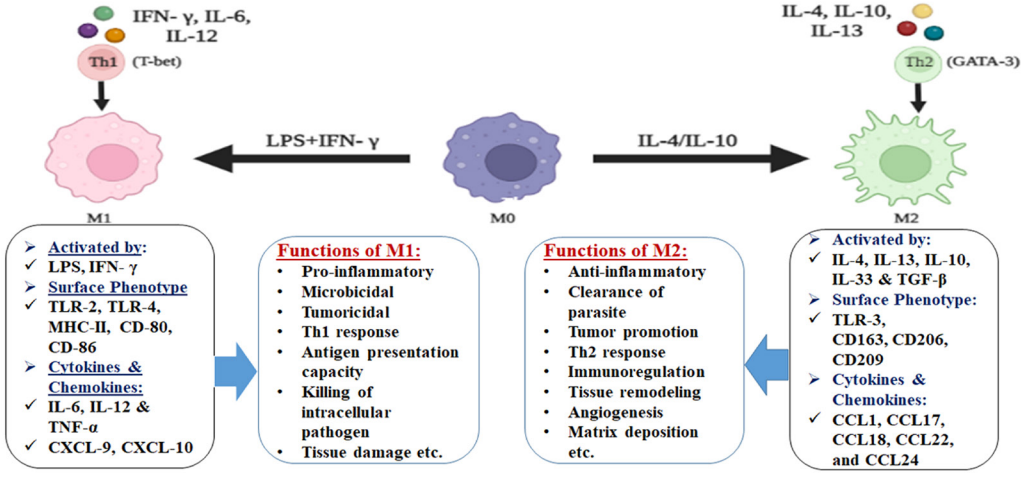

Figure 1. Macrophage polarization and specific function of M1 and M2. In presence of LPS and IFN-γ, M0 macrophage converted to M1 macrophage state. In presence of T-bet transcription factor, Th1 cell recruited M1 macrophage and produced IFN-γ, IL-6, IL-12 cytokines. It produced many surface phenotypes, such as TLR-2, TLR-4, MHC-II, CD-80 and CD-86. It also produced many cytokines and chemokines, IL-6, IL-12, TNF-α, CXCL-9 and CXCL-10. On the other hand, in presence of IL-4/IL-10, M0 macrophage cell was converted to M2 macrophage state. In presence of GATA-3 transcription factor, Th2 cell recruited M2 macrophage cell and produced IL-4, IL-10, IL-13, IL-33 and TGF-β. It produce many surface phenotypes (TLR-3, CD163, CD206, CD209). It also produced many specific cytokines and chemokines.

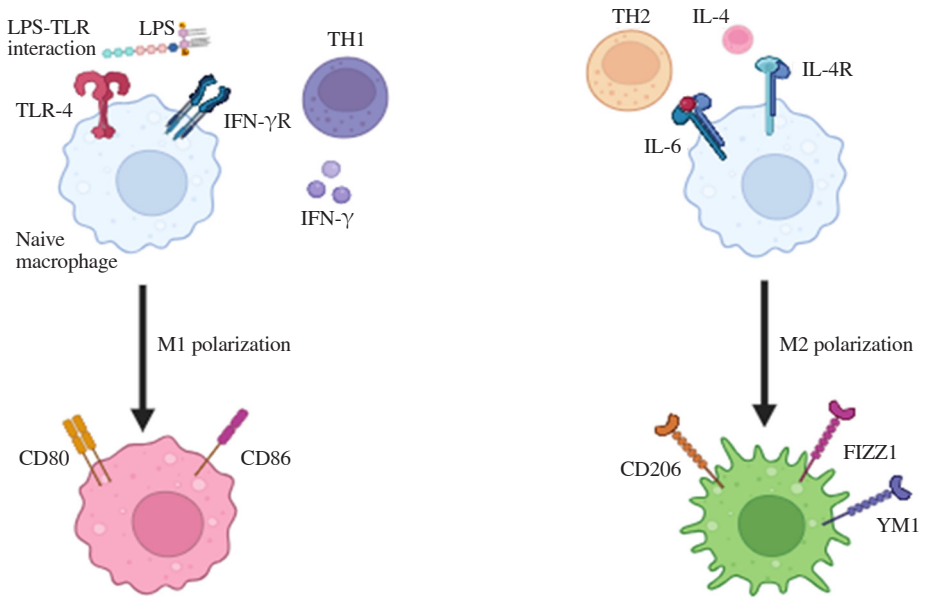

Figure 2. Diagram represents the markers of macrophage polarization.

role in resisting *M. tuberculosis*[36,37] (Figure 3). IFN-γ is described as the driving force behind the M1 program. It has potentiated to destroy *M. tuberculosis*, and it controlled the replication of remainder[38,39]. Other studies strongly support that M1 polarization is also an indicator of the initial phase of the anti-*M. tuberculosis* immune response in several animal models, and it is pretty similar to clinical evidence with active TB[40,41]. In an experiment in a mice model, within the alveolar granuloma compartment, significant amounts of IFN-γ and iNOS signify the M1 polarization during 7 to 30 days post *M. tuberculosis* infection[42,43]. Altogether, the M1 polarization is an integral part of the host immune responses against intracellular pathogenic bacteria and is characterized by the release of proteolytic enzymes, antimicrobial peptides, and pro-inflammatory cytokines and chemokines. It improves phagocytosis and the generation of toxic intracellular granules[38,44].

In addition, the type-2 inflammatory milieu is shifted back to type-1 after effective treatment of TB in infected individuals[45,46]. An earlier report also indicates that M2 signatory IL-4 and IL-13 suppress the autophagy in M1 macrophages and increase *M. tuberculosis* survival[47,48]. Ly *et al*. claimed that higher level type-2 inflammatory signature is skewing the M1 to M2 having ARG1hi iNOSneg in the alveolar granuloma compartment after day 35 up to day 60 during *M. tuberculosis* infection[42,49]. In the later stage, fibrosis in terms of caseous granulomas causes *M. tuberculosis* dissemination, while M2 macrophages obstruct the fibrosis development. It is assumed that the skewing of M2 from M1 shields the immune attack and standstill the pathophysiology caused by *M. tuberculosis*[50].

5. Immune response during *M. tuberculosis*

5.1. Innate immune response during M. tuberculosis

In early and chronic infection, macrophages are the main cellular niche for infection of *M. tuberculosis*, so they play a crucial role in Mycobacterial pathogenesis[51]. Macrophages are the chief cells that encounter the pathogen of *M. tuberculosis*, and phagocytosis of *M. tuberculosis* occurs by the alveolar macrophages as well as during the early stage of *M. tuberculosis* infection. It interacts with a variety of different innate immune cells, including neutrophils, natural killer cells, and dendritic cells[52]. By numerous pattern recognition receptors (PRRs), TLR1, TLR2, TLR4, TLR7, TLR8, and TLR9 are Toll-like receptors. NOD1, NOD2, NLRP3, and NLRC4 are Nod-like receptors. MR, Dectin-1, Dectin-2, Dectin-3 and DC-SIGN, CL-LK, DCIR, Mincle are C-type receptors. *M. tuberculosis* is recognized by those innate immune cells *(e.g.*, dendritic cells, NK cells, *etc.*). To eliminate *M. tuberculosis* pathogen from the host body, the host receives signaling from pattern recognition receptors or PRR and starts to create various cellular functions *i.e.*, apoptosis, autophagy, phagocytosis, and inflammasome activation.

Pathogen-associated molecular patterns, or PAMPs, in *M. tuberculosis* like carbohydrates, glycolipids, and lipoproteins are recognized by PRRs like Nod-like receptors, Toll-like receptors, and C-type receptors at different stages of infection (early and chronic stages), and they form a vast network of interconnected coordinated signalling pathways that speed up gene expression profiles in host cells[53]. In order to demonstrate the significance of inflammatory cytokines, such as IL-1, IFN-γ, IL-12, and

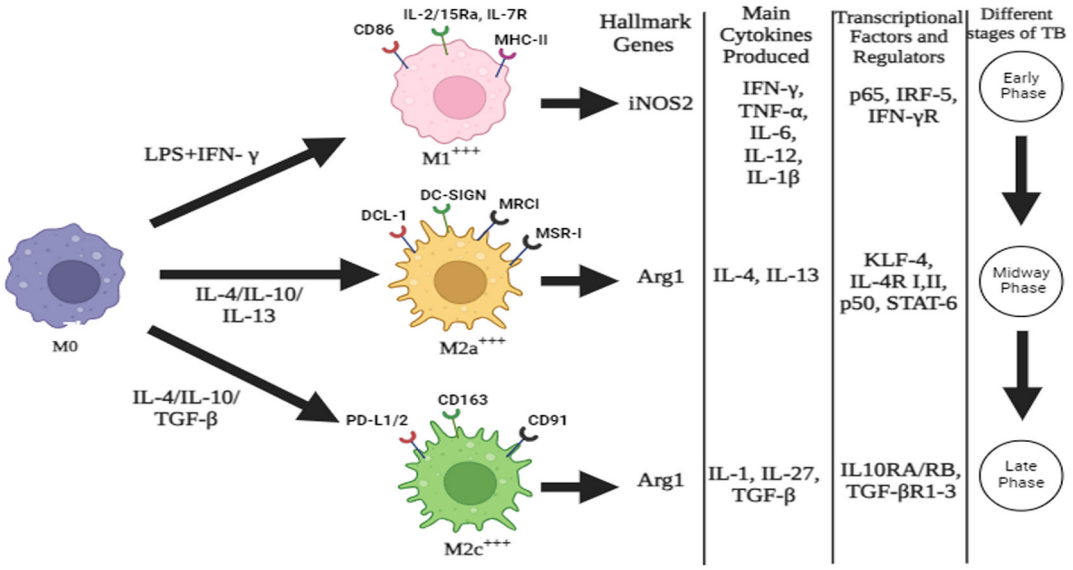

Figure 3. Involvement of surface markers, hallmark genes, cytokines, and transcription factors and the state of macrophage polarization during tuberculosis infection. In presence of LPS and IFN-γ, M0 macrophage was converted to M1 macrophage where many surface markers (CD86, MHC-II, *etc*.) involved and iNOS2 hallmark genes present. In this state, some cytokines were produced, *i.e*., IFN-γ, TNF-α, IL-6, IL-12, IL-1β. Many transcriptions factor, *i.e.*, p65, IRF-5, IFN-γR recruited. In presence of IL-4/IL-10/IL-13, M0 macrophage is converted to M2a macrophage state where many surface markers (DC-SIGN, MRC-I, MSR-I, *etc*) involved and Arg1 hallmark gene present. In this state, IL-4, IL-13 cytokines produced. Here, KLF-4, IL-4R I,II, p50, STAT-6 transcription factors and regulators recruited. On the other hand, in presence of IL-4/IL-10/TGF-β, M0 macrophage is converted to M2c macrophage state, where some surface markers (CD163, CD91, *etc*.) involved. In this state, IL-1, IL-27 cytokines produced. Based on the disease progression stage of tuberculosis, in early phase M1 state, middle phase M2a, and late phase M2c state was observed.

macrophage inflammatory protein-1 (MIP1α/CCL3), gene profiling studies have been conducted proof in the protection against infection of *M. tuberculosis*[54].

The macrophage polarization spectrum is divided into the M1 and M2 phenotypes based on how macrophages develop and operate[14]. Human monocytes develop into M2 macrophages during active tuberculosis, which increases pathogen permissiveness, protease-dependent mortality, and immunomodulation[55]. This process is characterized by the phenotype CD16+CD163+MerTK+pSTAT3+. Mycobacterial DnaK (HSP 70, heat shock protein 70) indexes the M2 macrophages in an IL-10-dependent way[56]. Macrophages are also known as myeloid suppressor cells (MSCs), and these macrophages suppress the T-cell response *via* the secretion and release of TGF-β and IL-10. So, in tuberculosis, these macrophages exhibit both suppressive functions as well as help in the regulation of inflammation and infection[57]. In a histopathology study, granulomas are the characteristics of tuberculosis that contain various transformed macrophages, *i.e.*, epithelial cells, foam cells, and multinucleated giant cells[58]. More recently, it was stated that TLR2 signaling promotes polyploidy of the macrophage, and TLR2 inhibits genomic instability by regulating Myc and ATR expression. It indicates that in presence of persistent inflammatory stimuli, pathways involved in developing cancer cells surprisingly instruct a polyploid macrophage fate and regulate granulomatous tissue remodeling[59].

5.1.1. Pattern recognition receptors for identifying M. tuberculosis in innate immune response

Identification of *M. tuberculosis* by pattern recognition receptors such as C-type lectin receptors (CLRs), nucleotide-binding domain and leucine-rich repeat-containing receptors (NLRs), Toll-like receptors (TLRs), and Cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) is the first step in initiating an innate immune response[60]. In mice models, the most necessary TLRs for controlling *M. tuberculosis* are TLR2 and TLR9, in which *M. tuberculosis* lipoproteins and lipoglycans are recognized by TLR2 and unmethylated CpG DNA are identified by TLR9[61–64].

Mice missing both TLR2 and TLR9 are more unprotected or unsafe than TLR2 or TLR9 single knockout mutants. It indicates that each TLR contributes to the immune response in a nonredundant way[61]. Numerous CLRs have been assertioned to have a functional role in the immunological recognition of *M. tuberculosis* in addition to TLRs. Besides TLRs, CLRs also have a significant role in recognizing *M. tuberculosis*. Moreover, scientists investigated and found that in mutant mice, each individual CLRs have a restricted participation[65,66], which might be partially clarified by redundancy in function. Eventually, in *in vitro* culture of myeloid cells, the NLR NOD2 can detect muramyl peptides generated from peptidoglycan of a bacterial cell wall, giving cytokine responses to the *M. tuberculosis*[67–69]. At some time, when mice are missing NOD2, they become infection resistant and show little vulnerability six months after infection[70].

Three distinct studies claimed that for type Ⅰ interferon production, cGAS is very important, and it indicates that DNA is the pathogen-associated molecular pattern (PAMP) that activates STING[71-73]. On the other hand, *M. tuberculosis* has been established to activate type Ⅰ interferons by direct STING identification of cyclic-di-AMP generated by the bacterium. CLRs, TLRs, and TLRs aid in the immunological response to *M. tuberculosis* by increasing the synthesis of chemokines and pro-inflammatory cytokines. However, bacterial pathogens exploit an antiviral pathway, which is an example of the cGAS-STING pathway, to promote pathogenesis[74].

5.2. Adaptive immunity against M. tuberculosis

The adaptive immune response defends the host from *M. tuberculosis* and regulates bacterial reproduction. Extreme sensitivity to mycobacterial infections is best seen in lymphopenic HIV patients and gene-deficient animals missing MHC class Ⅱ or T-cells in general. Direct antimicrobial activities of antigen-specific T cells and cytokine production are the primary characteristics of the adaptive immune response to *M. tuberculosis* infection[75]. Additionally, the longevity of antigen-specific memory T cells provides the foundation for the creation of vaccines that promote protection against mycobacterial infections[75]. B-cells, γδ T-cells, and CD1-restricted T-cells all have growing roles as well. These offer targeted responses to a wide range of *M. tuberculosis* antigens, which are presented by MHC class Ⅰ and Ⅱ in the traditional manner[76]. The malignancy of adaptive immune responses is caused by severe inflammation or by being rendered inefficient by repeated antigen exposure. CD4 T-cell responses during *M. tuberculosis* infection. CD8 T-cells protect the host from *M. tuberculosis* infection, and inhibitory receptors play a key role in *M. tuberculosis* infection. In addition, certain cells, such as B-cells, T-cells, and γδ T-cells, CD1-restricted lymphocytes, and mucosal-associated invariant T (MAIT), also protect the host from *M. tuberculosis* infection[60].

6. An agent can cause polarization or repolarization of the macrophage's phenotypes

Refai *et al.* claimed that ESAT-6, a plentifully secreted protein of *M. tuberculosis*[77], can switch from M1 polarized macrophages to the M2 phenotype. Interestingly, they also claimed that ESAT-6 moderated the manifestation of pro-inflammatory markers (CD80, CD86, IL-12, IL-23, IL-6, CXCL-10) of fully activated M1 macrophages[78]. Wang *et al.* claimed that pleural macrophages polarize from M1-like to M2-like phenotype after 3.5 days post-treatment of antibiotics (*e.g.* rifampicin, isoniazid, ethambutol, pyrazinamide). They also showed that mediators of the pro-inflammatory markers IFN-γ, TNF-α and IL-6 in tuberculous pleural effusion (TPE), remained decreased significantly after 2-3 days post antibiotics treatment[79]. Pinosylvin, a naturally occurring stilbenoid mostly found in Scots pine trees, alters macrophage polarisation from the pro-inflammatory M1 phenotype to the M2 phenotype, according to Kivimäki *et al*[80]. They asserted that pinosylvin has an effect on M2-type activation and inhibits the expression of M1-type markers. They demonstrated that pinosylvin boosted the expression of mannose receptor C type 1 (MRC1) and arginase-1 (Arg-1) in murine macrophage[80]. According to Chatterjee *et al*. rocaglates, a natural product derivative from *Aglaia* genus plants[81], can direct polarization of macrophage toward the M1-like phenotype and prepare macrophages at little concentrations of the M1 to induce cytokine IFN-γ and to inhibit their sensibility to IL-4, an ideal activator of the M2-like phenotype[82]. By promoting the development of the M1 markers in the cytokine pre-stimulation model, Jayaraman *et al.* claimed that *Oceanimonas* sp. BPMS22-derived PPI (Protein Protease Inhibitor) transformed into an M1-like phenotype from the resting macrophages (M0) and repolarized to M1 from the M2 phenotype. Additionally, they said that the PPI-incited macrophage M1 repolarization from the M2 macrophage phenotype in the *Leishmania donovani* infection paradigm[83]. Tian *et al.* claimed that the CU-CPT22, a TLR2/TLR1 inhibitor[84], transformed the M1 macrophages, induced by LPS, to the phenotype of M2 *in vitro*. The M1 marker CD86's expression is significantly repressed by CU-CPT22 and it also promotes to the M2 marker CD206's expression, and the inflammatory cytokine production in macrophages is inhibited by CU-CPT22. Their results verified that the M1 phenotype is suppressed by CU-CPT22 and it also promotes the M2 macrophage phenotype[85].

According to Chen *et al*, Oligo-Fucoidan extraction from brown seaweed, which is a sulfated polysaccharide[86], induces to M1-like macrophages from polarization of monocyte and repolarized into M1 phenotypes from M2 macrophages. They also claimed that intracellular ROS slaked by Oligo-Fucoidan and M1 macrophage polarization is benefited by mitochondrial superoxide, directly or indirectly. In addition, in *in vitro* process, on M2 macrophage polarization, the chemotherapy drawback is suppressed by Oligo-Fucoidan and in *in vivo* process, infiltration of M2 macrophage is prevented[87]. According to Kou *et al.* IgG/Bb@BRPL, an opsonized nanoparticle, repolarizes to anti-inflammatory M2-phenotype from M1 macrophages *via* ROS rummaging and deactivation of NF-κB pathway, and for local chondrocytes remodeling an additional promising microenvironment. They also claimed that with the help of *in vivo* studies, opsonized IgG/Bb@BRPL remarkably indorsed Osteoarthritis (OA) cartilage regeneration and repair. Their study suggests an opsonization-based drug delivery plan for OA treatment[88]. The combination therapy of ibrutinib and

Table 1. Immunomodulators and macrophage polarization.

Immunomodulators	Source/Identity	Polarization or repolarization	References
ESAT-6	Protein of *M. tuberculosis*	M1 to M2 phenotype	[77,78]
Antibiotics	Rifampicin, isoniazid, ethambutol, pyrazinamide	M1 to M2 phenotype	[79]
Pinosylvin	A natural stilbenoid mainly found in Scots pine plant trees	M1 to M2 phenotype	[80]
Rocaglates	Natural product derivative from *Aglaia genus* plants	Toward M1 phenotype	[81,82]
BPMS22	*Oceanimonas* sp.	M2 to M1 phenotype	[83]
CU-CPT22	A TLR2/TLR1 inhibitor	M1 to M2 phenotype	[84,85]
Oligo-Fucoidan	A sulfated polysaccharide isolated from the brown seaweed	M2 to M1 phenotype	[86,87]
IgG/Bb@BRPL	An opsonized nanoparticle	M1 to M2 phenotype	[88]
Ibrutinib and selinexor	Ibrutinib is a BTK inhibitor, Selinexor, a blood–brain barrier (BBB) permeable small molecule	M2 to M1 phenotype	[89]

selinexor, according to Jiménez *et al*, is capable of increasing mouse survival as well as changing the innate immune response to an additional inflammatory phenotype, which is precisely defined by downregulation of signal regulatory protein α (SIRPα) and PD-1 in M2 macrophages[89]. Additionally, the proportion of M1 macrophages is increased by this combination therapy, and additional M1 and M2-like properties are modulated with the loss of pro-tumoral M2 characteristics. They also claimed that in malignant cells, this combination treatment had a cytotoxic effect and also preferred an anti-tumoral innate immune response through tumor-infiltrating macrophage polarization shifted to M1 inflammatory and decreased SIRP and PD-1 expression in the residual tumor-promoting macrophages of M2[89]. These immunomodulator based macrophage polarization is summarized in Table 1.

7. Challenges in the characterization of M1–M2 polarization

The lethal intracellular pathogen *M. tuberculosis* is able to establish a permanent residence inside the host macrophages. *M. tuberculosis* bacilli uses a number of immune-evasion techniques, such as the suppression of pro-inflammatory markers and the host macrophages' release of the immunosuppressive cytokine IL-10 to delay the resolution of its infection and cause severe immune suppression. A few reports indicated that M1 macrophage polarization resulted in granuloma formation, which has an innumerable role in resolving *M. tuberculosis* infection. However, M1-M2 polarization status in macrophages during tuberculosis is still not well characterized during latent, active, and disease-resolute states that may provide countless efforts to set up the future strategic plan for the sterile cure of tuberculosis, particularly in drug-resistant cases.

8. Conclusions and perspectives

Tissue resident macrophage is the most significant immune effector and antigen-presenting cell. It is in charge of the anti-tubercular immune responses after activation of it. Unfortunately, the host macrophage is also the habitat of *M. tuberculosis* disease and protects *M. tuberculosis*. However, this dual role is not well characterized even through studying different innate and adaptive immune responses against TB. Several reports indicated that macrophage polarization/repolarization status is directly correlated with disease progression and resolved state, which is not yet thoroughly studied during TB. Very few reports indicated that M1 type macrophage polarization can be modulated into the M2 type macrophage polarization and vice-versa by natural, semi-synthetic, and chemical agents as host-directed therapies, antitubercular peptide, first-line drugs, and so many. Hence, the future study on macrophage polarization and repolarization is emerging during *M. tuberculosis* infection mediated tuberculosis. This may contribute to the WHO's mission to eradicate tuberculosis by 2035.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

Both AS and AJ wrote the original draft. AS, SM, RH reviewed, edited and revised the manuscript. SKM conceptualized, supervised, visualized and performed as project administration

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