Austin Journal of Clinical Immunology

Open Access

Austin Publishing Group

Mini Review

Exploration for Promising Drug Targets Useful for the Development of Novel Antimycobacterial Agents Based on Macrophage Activation and Polarization

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Received: November 15, 2015; **Accepted:** February 26, 2016; **Published:** April 11, 2016

Abstract

The development of new antimycobacterial agents by focusing on unique drug targets related to bacterial virulence factors is urgently desired. For this purpose, mycobacterial proteins involved in interference with the host's intracellular signalling events, which are required for the expression of antimicrobial functions of host macrophages (MΦs), are expected to serve as promising drug targets. From this viewpoint, the present review deals with the possible drug targets, especially those related to the M1- and M2-type polarization of host MΦs.

Keywords: Tuberculosis; Antimycobacterial Agents; Macrophage Polarization; Mycobacteria

Introduction

Tuberculosis (TB), especially Multidrug-Resistant-TB (MDR-TB), is a major global health concern since it is a highly contagious and life-threatening infection [1]. Moreover, intractable *Mycobacterium avium* Complex (MAC) infections, which are frequently encountered in AIDS patients, are currently increasing in the world [2]. Because of these serious situations, it is urgently necessary to develop new drugs exhibiting superior anti-*M. tuberculosis* (MTB) and/or anti-MAC activity by focusing on unique drug targets [3-5]. This can be achieved by logically designing novel antimycobacterial drugs which act on unique drug targets by clarifying the detailed properties of focused drug targets of pathogenic mycobacteria. It may be reasonable to design antimycobacterial compounds that are capable of blocking manifestation of the biological activity of bacterial virulence factors, especially those expressed during intramacrophage infection by pathogens. For this purpose, mycobacterial proteins involved in the bacterial interference of macrophage (MΦ) signaling pathways related to intramacrophage bacterial killing mechanisms may serve as favourable drug targets. Utilizing genomic and proteomic information on such virulence factors, it is possible to identify bacterial genes that encode potential target proteins useful for the development of new chemotherapeutics against mycobacteriosis. After elucidation of the detailed properties of such target proteins encoded by bacterial virulence genes, studies into practical drug design can be initiated by applying three-Dimensional Quantitative Structure Activity Relationship (3D-QSAR) analysis [6]. Notably, it is of marked interest to clarify the biochemical characteristics of bacterial proteins that crosstalk and interfere with the signal transduction cascades of host MΦs particularly those related to MΦ activation and polarization. This review article deals with the profiles of MΦ polarization induced by mycobacterial infection in host MΦs from the viewpoint of searching for unique drug targets for the development of new antimycobacterial therapeutics.

M1 and M2 MΦ polarization

MΦ polarization in bacterial infections, particularly those due to facultative intracellular pathogens including mycobacteria and *Salmonella*, is an important phenomenon for hosts [7,8]. Firstly, various bacteria induce the transcriptional activity of a common host response, which includes the expression of genes belonging to the M1 program, associated with MΦ polarization yielding the M1 MΦ population, which exerts proinflammatory and/or antimicrobial functions. In the activation of MΦs leading to M1 polarization, the NF-κB-mediated cascade plays a central role in intracellular signaling pathways in response to the stimulation of cell surface receptors for proinflammatory cytokines and Pathogen-Associated Molecular Pattern Molecules (PAMPs), such as IL-1β receptor, TNF-α receptor, and Toll-Like Receptors (TLRs) [9]. Secondly, since excessive or prolonged M1 polarization leads to tissue injury and contributes to the pathogenesis [10], the M2 MΦs with immunosuppressive and tissue-repairing functions play critical roles in the resolution of harmful inflammation via the production of anti-inflammatory mediators [7,8,10]. Indeed, in M2 MΦs, arginine metabolism is shifted to the production of ornithine and polyamines via arginase 1 [11-14]. However, some investigators argue against the classification, because these MΦs might be able to change from one phenotype to another, differing from the case of T cell subsets [11]. These investigators prefer to call M1 and M2 MΦs "classically activated MΦs" and "alternatively activated MΦs", respectively. In this context, Murray et al. recently proposed a new nomenclature for these MΦ populations (activation standards), such as M(IL-4), M(Ig), M(IL-10), M(GC), M(IFN-γ), and M(LPS), indicating stimulation scenarios (the specific conditions for MΦ activation) [15].

M1 MΦs are induced to develop by the Th1-derived cytokine IFN-γ alone or in combination with other macrophage-activating cytokines (TNF-α and GM-CSF) and certain microbial stimuli such as LPS. In contrast to this, Th2-derived cytokines, IL-4 and IL-13, have

Citation: Tomioka H. Exploration for Promising Drug Targets Useful for the Development of Novel Antimycobacterial Agents Based on Macrophage Activation and Polarization. Austin J Clin Immunol. 2016; 3(1):1029.

Table 1: Profiles of M1 and M2 macrophage populations[a].

Macrophage populations	Stimulation/activation with	High-level expression of enzymes, receptors, etc.	High-level production of cytokines, chemokines, and other molecules
M1 macrophages	IFN-γ, TNF-α, LPS	iNOS[b], CD80, CD86, IL-1RI, IL2Rα, IL-7R, IL-15Rα, CCR7,TLR2, TLR4, FcR, MHC II, IPD, Batf2, COX-2	TNF-α, Type 1 IFN, IL-1β, IL-6, IL-12, IL-23, CCL2, 3, 4, 5, 8, 9, 10, 11, 15, 19,CXCL9, 10, 11, 16,ROI, RNI
M2a macrophages	IL-4, IL-13,	Arg-1[c], Ym1[c], Fizz1[c], CD163, IL-1R II, CXCR4, TLR5, MHC II, MR, SR,COX-1, galectin-3	TGF-β, IL-10, IL-1ra, CCL13, 17, 18, 22, 23, 24, polyamine
M2b macrophages	ICs, LPS, TLR, IL-1R ligand	iNOS, CD86, MHC II, MR	TNF-α, Type 1 IFN, IL-1β, IL-6, IL-10, CCL1, ROI, RNI
M2c macrophages	GCs, IL-10, TGF-β	Arg-1, CD163, CD14, CCR2, TLR1, TLR8, MR, SR, galectin-3	TGF-β, IL-10, IL-1ra, polyamine
M2d macrophages (TAM)	IL-6, LIF, MCF	CD14, CD163, VEGF, ILT3, VTCN1	TGF-β, IL-10, CCL18, polyamine

[a]Previous findings described in the following papers are summarized: in References [7,11,12,16-23].

[b]**Abbreviations Used:** iNOS: inducible Nitric Oxide Synthase; IL-1R: IL-1 Receptor; TLR: Toll-Like Receptor; FcR: Fc Receptor; IPD: Indoleamine-Pyrrole 2,3 Dioxygenase; Batf2: Basic leucine zipper transcription factor 2; COX: Cyclooxygenase; ROI: Reactive Oxygen Intermediates; RNI: Reactive Nitrogen Intermediates; Arg-1: Arginase-1; Ym1: M2-associated chitinase-like protein; Fizz1: cysteine-rich secreted protein FIZZ1 found in inflammatory zone (resistin-like molecule-α); IL-1ra: IL-1 receptor antagonist; MR: Mannose Receptor; SR: Scavenger Receptor; ICs: Immune Complexes; GCs: Glucocorticoids; LIF: Leukocyte Inhibitory Factor; MCF: Macrophage Chemotactic Factor; VEGF: Vascular Endothelial Growth Factor; ILT3: Ig-Like Transcript 3; VTCN1: V-set domain-containing T-Cell activation inhibitor; TAM: Tumor-Associated Macrophage.

[c]Applicable only in the case of mice.

been demonstrated to generate M2 MΦs [11,14]. M2 MΦs consist of four subpopulations: M2a MΦs (called "alternatively activated MΦs") induced with IL-4 and IL-13; M2b MΦs (called "type II-activated MΦs") induced with an immune complex and TLR/IL-1 receptor ligands via Fc receptors, complement receptors, and TLR; M2c MΦs generated in response to IL-10 and glucocorticoid hormones; and M2d MΦs characterized by an IL-10^{high}, IL-12^{low} M2 profile with some features of tumor-associated MΦs [6,7,12,16-20]. However, Murray's proposal regards the M2a, M2b, M2c, M2d categories as inadequate, because they cause unnecessary complexity in understanding the modes of M2 polarization [15].

In general, M1 and M2 MΦ populations have distinct phenotypes because of differential profiles of gene expression as shown in Table 1 [21]. Firstly, typical M1 MΦs possess a phenotype with high-level production of IL-12 and IL-23 but low-level expression of IL-10. They are efficient producers of cytotoxic effector molecules, such as Reactive Oxygen Intermediates (ROIs) and Reactive Nitrogen Intermediates (RNIs) and inflammatory cytokines, including IL-1β, TNF-α, and IL-6. Thus, M1 MΦs participate as inducer and effector cells in polarized Th1 responses and play roles in resistance against bacterial pathogens and tumors [11-13]. In contrast, the various forms of M2 MΦs share a phenotype with low-level production of IL-12 and IL-23 but high-level expression of IL-10. In general, M2 MΦs, typically M2a MΦs, are characterized by low-level production of proinflammatory cytokines such as IL-1β, TNF-α, and IL-6. However, M2b MΦs, which are characterized by high-level of IL-10 and CD86 expression, but low-level IL-12 and arginase 1 expression, are effective producers of IL-1β, TNF-α, and IL-6, as in the case of M1 MΦs [12,17,20,22]. In addition, M2b MΦs retain high level expression of inducible Nitric Oxide Synthase (iNOS) and RNI production [14,20]. Generally, M2 MΦs have high levels of mannose (typically M2a and M2c MΦs), scavenger (typically M2c MΦs), and galactose-type receptors. In addition, M1 MΦs and the various forms of M2 MΦs have distinct chemokine and chemokine receptor repertoires [23]. Notably, M2 MΦs principally play important roles in polarized Th2 reactions. For instance: (1) they promote the killing and encapsulation of parasites; (2) they promote tumor progression and tissue repair and remodeling; and (3) they have immunoregulatory and anti-inflammatory functions [11,24]. In addition, it has been reported that M2 MΦs inhibited the generation of M1 MΦs [24].

In this context, Tatano et al. recently reported interesting findings as follows [25]: They indicated that mycobacterial infection induces suppressor MΦs, which possess unique phenotypes (IL-12^{+}, IL-1β^{high}, IL-6^{+}, TNF-α^{+}, iNOS^{+}, CCR7^{high}, IL-10^{high}, arginase 1^{-}, mannose receptor^{low}, Ym1^{high}, Fizz^{low}, and CD163^{high}) differing from those of M1 and M2 populations. Interestingly, the MΦs exhibit strong activity to induce Th17 cell expansion in addition to their suppressor activity against T cell mitogenesis in response to TCR stimulation. These findings indicate the existence of MΦ subsets differing from M1 and M2 populations.

Profiles of MΦ polarization induced by mycobacterial infections

The common response of MΦs to bacterial infections induced by intracellular bacteria, such as MTB, *M. bovis* BCG, and *Legionella pneumophila*, involves the up-regulation of gene expression characteristic of M1 polarization [7,13]. These microorganisms induce genes encoding cytokines such as IL-1β, TNF-α, IL-6, and IL-12, cytokine receptors such as IL-7 receptor and IL-15 receptor α, chemokines, such as CCL2, CCL5, and CXCL10, and the chemokine receptor CCR7. On the other hand, IL-1 receptor antagonist (IL-1ra) appears to be the only gene associated with M2 polarization of MΦs that is expressed after bacterial challenge [7,26]. Some bacterial pathogens have evolved sophisticated strategies to prevent M1 polarization but promote M2 polarization [7,13]. With respect to mycobacterial diseases, the following profiles are known. Firstly, during the early phase of MTB infection, M1 polarization of host MΦs is evident and this is in agreement with the clinical profiles of patients with active TB. However, a small population of TB patients exhibits M2 polarization, which can be reversed by effective chemotherapy, suggesting the role of M2 polarization in the chronic evolution of TB [7]. For example, Redente et al. reported the following [27]: Soon after MTB infection of mice, the IFN-γ content in Bronchoalveolar Lavage (BAL) fluid increased, and BAL MΦs became those corresponding

to the M1 subtype, as characterized by the increased expression of iNOS and production of RNIs. As inflammation progressed in the infected mice, the amount of IFN-γ in BAL fluid and iNOS expression by BAL MΦs decreased and, thereafter, the IL-4 content in BAL fluid and arginase 1 expression by BAL MΦs rose, indicating that M2 polarization occurred in the BAL MΦ population. A recent study by Guler et al. provided interesting findings as follows [28]: They indicated that the absence of IL-4 receptor α on MΦs did not play a major role in pathologic profiles of MTB infection in mice in terms of host mortality, bacterial burden, histopathology, or T-cell proliferation. Interestingly, there was no difference in the lung expression of iNOS (M1 marker) and Arginase 1 (Arg1) (M2 marker) during MTB infection between IL-4Rα-depleted and wild-type mice. These findings suggest that IL-4Rα-mediated signalling is not crucial in the generation of the M2 MΦ population, which down-regulate the expression of the host's antimycobacterial resistance. Therefore, the concept may be reasonable that various M2 MΦ subsets, such as M2a, M2b, M2c, and M2d MΦs, are actually generated under specific immunological conditions in hosts.

Development of novel anti-TB drugs based on MΦ polarization-related drug targets

As previously described by the present author [5,6], a number of studies have been and are currently being carried out to develop antituberculous drugs based on novel drug targets related to mycobacterial virulence. To carry out such searches for new drug targets useful for TB drug development, it may also be reasonable to focus on mycobacterial virulence factors, which regulate MΦ polarization toward M1 and M2 MΦ subsets. Recent findings reported by Wang et al. indicate that maltose-binding protein of *Escherichia coli* up-regulates the expression of TLR2 and TLR4 on RAW264.7 MΦs, which is accompanied by the subsequent activation of NF-κB and p38 MAPK, leading to the potentiation of IL-12 and nitric oxide production, characteristic of M1 MΦs [29]. Generally, mycobacterial components containing a lipid moiety are also known as TLR triggers that cause the potentiation of MΦ inflammatory responses and M1 polarization [30-32]. However, some of these components, namely lipoproteins, such as the 19-kDa LpqH protein, are known to inhibit the MΦ response to IFN-γ, causing the down-regulation of M1 polarization [33]. In addition, mycobacterial lipoglycans, such as lipomannan and Mannosylated Lipoarabinomannan (Man-LAM), and Phosphatidylinositol Mannosides (PIMs) are known to act as potent inhibitors of host inflammatory responses because of their ability to down-regulate M1 polarization of MΦs [34-36]. In this context, Court et al. reported that PIMs are also effective in down-regulating the TLR2/TLR4- and TLR2/TLR6-mediated M1 polarization of MΦs, leading to the reduced MΦ production of proinflammatory cytokines, such as TNF-α and IL-12 [37]. Thus, the TLR-mediated induction of MΦ polarization toward M2 type MΦs is suggestive of the active participation of TLRs, especially TLR2, in MΦ polarization. For instance, when two kinds of human MΦ population, which had already been polarized toward the M1 state by IFN-γ treatment or polarized toward the M2c state by IL-10 treatment, were re-stimulated with the TLR2 ligand P3C in combination with soluble immune complexes, both of these M1 and M2c MΦ populations were found to further polarize to the M2 MΦ subset (mainly M2a MΦs) with an increased ability to generate IL-10 [38]. Notably, Richardson et al. recently reported interesting findings whereby, in MTB-infected MΦs, TLR2-MyD88-mediated signaling induced with mycobacterial ligands, subsequently activated multiple signal-transduction pathways and outcomes as follows [39]: (1) the NF-κB pathway, which leads MΦs to M1 polarization characterized by the potentiation of MΦ microbicidal functions, in terms of an increased expression of iNOS, proinflammatory cytokines like IL-12, and MHC II molecules, and (2) the Tpl2-ERK pathway, which leads to M2 polarization of MΦs, thereby causing the elevated expression of anti-inflammatory IL-10 and Arg1 synthesis but lowered expression of IL-12. The authors stated that this finding indicates that the Tpl2-ERK pathway may contribute to immune evasion and the persistence of latent infection by MTB pathogens through some kinds of mechanism, such as an altered cytokine balance (shift from an IL-12-dominant to IL-10-dominant state) and reduction of antigen processing and presentation. In this context, it was also reported by Khan et al. that OmpU (an outer membrane protein of *Vibrio cholera* acting as a pathogen-associated molecular pattern) induces M1 polarization via the activation of TLR1/TLR2 [40]. They found that OmpU induced the formation of the TLR1/TLR2 complex, leading to MyD88 recruitment to the TLR1/TLR2 complex and the subsequent recruitment of IRAK1 followed by the activation of the NF-κB pathway, causing M1 polarization.

The signaling pathways of MΦs at the downstream of TLR2 and IRAKs are important for signal transduction [31]. IRAK-4 plays important roles in TLR2-originated signaling cascades for the up-regulation of MΦ antimicrobial functions characteristic of M1 polarization. Deleterious mutations in the IRAK-4 gene cause an increase in host susceptibility to bacterial infection because of MΦ unresponsiveness to TLR ligands [41]. On the other hand, IRAK-M is known to act as a negative regulator of TLR signaling [36]. Notably, Man-LAM of MTB has been reported to suppress TLR4-mediated M1 polarization of MΦs, based on the induction of IL-12 expression by MΦs, through an IRAK-M-mediated signaling pathway [36]. In this case, Man-LAM inhibits IRAK-TRAF6 interaction, directly attenuating activation of the NF-κB-mediated pathway by inducing the expression of IRAK-M. In this context, Manda-Lala, et al. reported an interesting finding that MTB restricts the M1 polarization of MΦs and reduces proinflammatory responses of MΦs through its cell envelope-associated serine hydrolase, called "Hydrolase important for pathogenesis 1" (Hip1) [42]. According to them, MΦs stimulated with the *hip1*-KO MTB mutant strain generate higher levels of proinflammatory cytokines (TNF-α, IL-1β, IL-6, etc.). In the case of MΦ activation due to infection with the *hip1*-KO MTB mutant, the enhanced activation of the TLR2-MyD88 signaling pathway is responsible for the elevated cytokine production. Notably, Hip1-mediated blocking of TLR2 signaling is dependent on the enzymatic action of Hip1. Therefore, it is thought that Hip1 restricts the onset and magnitude of MΦ proinflammatory cytokine response by limiting TLR2-dependent activation in an enzymatic activity-dependent manner. With special reference to TLR4-mediated MΦ polarization, the following has been reported: Firstly, the heat shock protein DnaK of *Francisella tularensis* has been reported to induce the activation of MAPKs and NF-κB in Dendritic Cells (DCs) and production of the proinflammatory cytokines IL-6, TNF-α, and IL-12, as well as low levels of IL-10, and the up-regulation of CD40, CD80,

and CD86 characteristic of M1 polarization [43]. In contrast, Lopes et al. recently reported the opposite finding whereby mycobacterial DnaK polarizes murine born marrow-derived MΦs and peritoneal MΦs to the M2-type phenotype [44]. They reported that treatment of MΦs with DnaK protein from MTB causes the M2-type polarization of MΦs, based on the increase in Arg1 activity and IL-10 production and the potentiated expression of Fizz1, Ym1, and CD206. Moreover, the DnaK-treated MΦs acquired a tumor growth-promoting ability. The different findings between the above two studies may be due to a difference in the experimental conditions used by these researchers, that is, differences in test phagocytes (MΦs and DCs) and bacteria (*F. tularensis* and MTB). Irrespective of this, these findings indicate that promising drug targets related to mycobacterial virulence factors for the development of novel antituberculous agents may be explored among mycobacterial components, which regulate intracellular signaling pathways linked to TLRs, particularly those located in the downstream pathways of TLRs, thereby determining the courses of MΦ polarization.

The development of new drugs for the treatment of TB has been slow. Indeed, only limited numbers of new drugs, including rifabutin, rifapentine, delamanid, and bedaquiline, have been approved for clinical use [45,46]. Thus, it is also desirable to improve the pharmacokinetics of TB drugs in terms of *in vivo* drug stability and drug delivery. Since MTB can persist in the intramacrophage milieu for a long period of time, ideal therapy for TB requires the effective delivery of anti-TB drugs into MΦs, especially into bacteria-engulfing phagosomes of MΦs. Firstly, liposomes are ideal lipid vesicles for directing TB drugs to infection sites [47,48]. Using liposome-encapsulated drugs, it is possible to deliver the total dose required over a prolonged time period in a single administration, without causing any severe side effects. Moreover, liposome technology enables the highly targeted delivery of the drugs to host MΦs. Although there are few studies on the effects of liposomal vesicles on MΦ polarization, some researchers reported interesting findings, as follows: Cruz-Leal, et al. indicated that mouse peritoneal MΦs were activated to the M2 state by treating them with ovalbumin-encapsulating liposomes comprising phosphatidylcholine and cholesterol, leading to high Arg1 activity [49]. Nevertheless, responding to LPS stimulation, such M2-type MΦs were re-differentiated to the M1 phenotype, characterized by the high-level production of nitric oxide and decreased generation of IL-10 [49]. This indicates that the liposome vesicle itself can induce an M2-like profile in peritoneal MΦs, which is reprogrammable to the M1 phenotype in the presence of M1-polarization signals induced by LPS stimulation. In this context, liposomal vesicles of dipalmitoylphosphotidylcholine have been reported to potentiate the activation of peritoneal MΦs responding to LPS stimulation in terms of the expression of cytotoxic activity against tumor cells [50]. Interestingly, the combined effect of the liposomes and LPS in up-regulating MΦ M1 polarization is correlated with the changes in the properties of the rough endoplasmic reticulum membranes of MΦs [50]. Secondly, some investigators have been assessing the usefulness of microsphere technology [51,52]. This technology facilitates effective chemotherapy against intractable TB. Barrow et al. developed microspheres comprising lactide and glycotide copolymers (poly (lactic-coglycolic acid): PLGA) as biodegradable and biocompatible excipients for antituberculous drugs [53]. Such microsphere preparations enable the controlled release of encapsulated drugs over long periods [51]. Although there have been only very limited numbers of studies with special reference to the effects of microsphere particles on MΦ polarization, Bitencourt et al. reported an interesting finding whereby certain types of PLGA microsphere induced NF-κB activation in J774-1 murine MΦs, leading to the M1 polarization accompanied with up-regulation of the MΦ TNF-α producing ability [54]. Notably, it was reported by Nagao et al. that lipid rafts on the cell membrane of mouse J774 MΦs and rat alveolar MΦs play an important role in the internalization of polystyrene latex microspheres during MΦ phagocytosis [55]. However, they reported the very limited participation of lipid rafts in the signal transduction, which is related to MΦ activation toward M1 polarization in terms of the increased expression of proinflammatory cytokines (TNF-α, IL-1β, and IL-6) l [55]. Taken together, these findings on the effects of liposomal and micrsphere particles upon the direction of MΦ polarization suggest that it is important to consider such situations on the practical use of drug-delivery systems, based on liposome- and microsphere-encapsulated antituberculous drugs, for the clinical treatment of TB patients.

Concluding Remarks

The present global prevalence of TB strongly necessitates the accelerated development of new antituberculous drugs based on unique antimicrobial mechanisms. It is reasonable to design antimycobacterial agents that are capable of blocking expression of the biological activity of virulence factors of MTB organisms, particularly those expressed during intramacrophage infection. Since the whole MTB genome contains as many as 4,000 genes, our studies must be undertaken by selectively focusing on a small number of target proteins. In this context, it is of marked interest to clarify the molecular and biological characteristics of bacterial proteins, which play significant roles as virulence factors by interfering with the signal transduction cascades of host MΦs. A number of researchers are currently engaged in studies to elucidate action profiles of mycobacterial proteins in intramacrophage signalling pathways. As described in the above sections, MTB proteins acting as virulence factors affecting MΦ signalling events, which play important roles in MΦ polarization, may be promising as drug targets for the development of novel anti-TB drugs. The molecular biological information concerning such types of mycobacterial virulence factor will serve as a useful experimental tool for drug design based on 3D-QSAR analysis [6,56].

Conflict of Interest

The people providing the funds for this study had no input in any aspect of this paper. There was no conflict of interest for any of the author.

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Austin J Clin Immunol - Volume 3 Issue 1 - 2016
ISSN : 2381-9138 | www.austinpublishinggroup.com

Citation: Tomioka H. Exploration for Promising Drug Targets Useful for the Development of Novel Antimycobacterial Agents Based on Macrophage Activation and Polarization. Austin J Clin Immunol. 2016; 3(1):1029.