The Dynamics of Macrophage Function in Reparation of Natural Immune System in Tuberculosis Disease

Christina Destri[1], Jusak Nugraha[2], Muhammad Amin[3], Djoko Agus Purwanto[4]

[1] Doctoral Student. Doctoral Program of Medical Science, Faculty of Medicine, Airlangga University, Indonesia, [2]Professsor, Department of Clinical Patology, Faculty of Medicine, Airlangga University, Indonesia, [3]Professsor, Department of Internal Medicine, Faculty of Medicine, Airlangga University, Indonesia, [4]Professsor, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Airlangga University, Indonesia

Abstract

Macrophages related with pathogen was involved the ability of Mycobacterium tuberculosis (Mtb) to developing mechanisms to prevent macrophage attacks and the aim of this study was to find the relationship between specific role of macrophages in natural immune system in tuberculosis (TB) disease. The research design of this study used literature reviews from various journals and it was accessed in Google Scholar and various medical science websites who bublessed less than 10 years. Localization of mycobacteria in granulomas form and activation of macrophages ability to kill and eliminate pathogens also the movement of M1 to M2 polarization as an important part for the host to prevent widespread tissue damage. However, the loss of the immune system suppression by M1 and Th1 molecules will give benefit to fertility development of Mtb in the environment of immunity M2 / Th2. The results of this study showed that the dynamics of macrophages in tuberculosis disease is a balance of Mtb's ability to escape from the immune system. The effectiveness of anti-TB treatment repair the immune system and eliminate Mtb.

Keywords: *Natural immunity; macrophages; tuberculosis*

Introduction

The host's of natural immune system that initiates the TB pathogenesis was occured through receptor interactions on macrophage pattern recognition receptors (PRR) including toll like receptors (TLRs), cytosolic receptors such as RIG-I-like receptors (RLR), NOD-like receptors (NLR) and C-type lectin receptor (CLR). The identification of microbial components such as pathogenic associated molecular patterns (PAMP), so PRR induces intracellular signaling networks to activate transcription factors that regulate the gen involvement in inflammatory responses and antipathogen immunity. IFN type-1 in macrophages was associated with Serine / Threonin kinase, TANK-binding kinase 1 (TBK1) facilitated the phosphorylation of interferon regulatory factor (IRF). The role of TLR2, TLR4 and TLR9 are important as a natural immune response against Mtb, especially TLR4 in macrophages associated with Myeloid differentiation factor 88 (MyD88) adapter. It was associated with IRAK-4 and IRAK-1 by interactions in the death domain. IRAK4 have phosphorylation and immediately activate IRAK1 to collaborate with TRAF6 than lead to oligomerization and activation to be large form complex and lead to the activation of transcription factors NF-kB and AP-1 [(1)].

The success live of Mtb in macrophages is due to the ability Mtb to convert antimicrobial cells into recipient cells. Mtb hacks the host defense mechanism by manipulating the host's cellular pathways, innate immune response, and cell death pathways to take the advantages [(2)]. Inhibition of phagosome fusion in lysosomes is an important mechanism of Mtb, because it is to inhibit macrophage phagosome / lysosome maturation. Transcription of proinflammatory factor NF-κB (nuclear factor kappa B) regulates phagolysosome fusion during infection [(3)]. Phosphatidylinositol 3- phosphate (PI3P) is an important component in macrophage cell membrane which is it on the surface of endosome and phagosomes. After the invasion of Mtb biosynthesis becomes low and by the pathway, lipoarabinomannan toxin (LAM) with

calmodulin-dependent of PI3P suppresses the lysosome phagosome fusion process [4]. Toll-like receptors (TLRs) is not as phagocytic receptors but it as detectors of different particles. However TLR collaborates with other non-opsonic receptors to stimulate the ingestion process [5].

The intervention of an anti-inflammatory suppressive effect by suppressing nuclear factor-kappa B (NF-kB). Pyrazinamide treatment influences the host immune response by decreasing pro-inflammatory cytokine production in Mtb infection. The administration of first-line anti-TB therapy to pleural TB patients will induces polarization of pleural macrophages towards M2, so this study showed that anti-TB treatment was modulated the host immune response [6]. The interaction between host, Mtb and treatment are influence each other and it are able to mediate immunomodulation and bring the successful of treatment, so it will be main discussion in this study review.

Immunology response to tuberculosis

Mtb is an intracellular pathogen that lives and develops in macrophages, where the stages of the immune response to this bacterial infection are complex. The observations among humans and mice showed that the role of interleukin-12 (IL-12) and interferon gamma (IFN-γ) were mediated the T cells function to control the Mtb infection. nflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and IL-1 were played a major role in immune defense toward TB mycobacteria [7]. The interaction of MTB and cells in innate immune systems and adaptive were given the secretion of chemokines and cytokines, namely tumor necrosis factor-α (TNF-α), interleukin-1 family (IL-1β, IL-18), IL-12, and IFNγ. TNF-α plays an important role in granuloma formation, an important mechanism in isolation and in limitation of mycobacterial replication. IL-1β production is important, as a signaling mediator toward essential components of host defense toward mycobacteria, defects in IL-1 receptors caused weak of granuloma formation and low in body defense system. The role of IFNγ is to activate macrophages, as a killers and eliminate mycobacteria, increasing the expression of MHC II molecules, so there is an improvement antigen presentation to T cells. IFN$\gamma\gamma$ produced by natural killer (NK), CD4 +, and CD8 + cells through the delivery of endogenous IL-12 and IL-18 by macrophages and dendrite cells [3].

Mtb infection induces IFN type-1 expression in human and mice macrophages as well as in dendritic myeloid cells. Serine / Threonin kinase, TANK-binding kinase 1 (TBK1) is the central directive for IFN type-1 expression in Mtb that infects host cells. TBK1 facilitates the phosphorylation of interferon regulatory factor (IRF). IRF3 and IRF5 have been known as a facilitator of IFN type-1 in Mtb infecting host cells. Pattern recognition receptor (PRR) was associated with TBK1 phosphorylation and IFN type-1 expression in mycobacterial infections response, including Nod like receptor NOD2. It is an interferon gene stimulator (STING) either directly or through cyclic activation of GMP-AMP synthase (cGAS), such as the toll on receptor-4 (TLR4) [8]. The pattern recognition receptor (PRR) coded by the germline, as an important part in microbial components and initiates the activation of innate immunity and inflammation for pathogen elimination. PRR expressed on innate immunity cells and other cells like epithelial cells, including surface and endosome receptors such as toll like receptors (TLR), cytosolic receptors like RIG-I-like receptors (RLR), NOD-like receptors (NLR) and C -type lectin receptor (CLR). Microbial components such as pathogenic associated molecular patterns (PAMP), PRR induces intracellular signaling networks to activate transcription factors that regulate gene involvement in inflammatory responses and antipathogen immunity. The innate immunity signal also stimulates dynamic changes in micondria, lead to specific gene expression and pathogen elimination so that adaptation can change the environment [9].

As known that TLR2, TLR4 and TLR9 are plays an important role in innate response against TB. TLR2 forms dimers with TLR1 or TLR6, they was known as diacylated or triacylated lipoproteins. Lipoarabinomannan (LAM), lipomannan (LM), and phosphatidylinositol mannoside (PIM) from Mtb are also recognized via TLR2. Although, it has been showed in vitro that TLR2 played an important role in several aspects control of antigen presenting cell effector function, TLR2 deficiency models study was not affected in secondary immune response to Mtb. In other study who used mice as intervention group, it showed that TLR4 played an important role in development of the host's

natural immune system to Mtb responding. Stimulation via TLR9 invitro induces IL-12 production in dendritic cells [1]. Myeloid differentiation factor 88 (MyD88) was gave important role to establishing a protective response against Mtb. This adapter binds with TLR cytoplasm and connects to IRAK-4 and IRAK-1 via death domain interactions. IRAK4 into phosphorylation activating IRAK1 and immediately associated with TRAF6 and leading to oligomerization and activation. The posterior binding of Ubc13 and Uev1A promotes TRAF6, TAB2 recruitment and TAK1 activation to large form complex and leads to the activation of transcription factors NF-kB and AP-1 [1].

The MyD88 adapter is a central component in TLR signaling, specify in downstream signaling cascade that leads to NF-kB activation and transcription of factor AP-1 in inflammatory cytokines production. TRIF Signaling adapter will activate IRF-3 transcription factor to induce IFN-β secretion [1]. The two main signaling pathways of innate immunity as first defense against Mtb pathogens infection, including NF-κB as a pro-inflammatory signal and mitogen activated protein kinase (MAPK) or called extracellular signal regulated (ERK) as an intermediate signal chain protein between surface receptors cells and DNA in cell nucleus [10]. Multiple signaling pathways such as NF-κB pathway, MAPK cascade including ERK signaling, jun N-terminal kinase (JNK), and p38 MAPK were affected essential cellular processes in innate immune system and cell differentiation proliferation [11]. Innate immunity plays an important role as a host defense against Mtb, in the begin recognizing innate immunity cells process toward pathogen associated with molecular pattern (PAMP) by pattern recognition receptor (PRR) [3].

The macrophages role in Mycobacterium tuberculosis infection

Macrophages as phagocytic components in immune system, it are fundamental cell to understanding the basic principles of natural immune response and host defense functions such as microorganisms phagocytosis, engulfing dead cells, and inflammatory cytokines production [12]. An estimated that humans have approximately 0.2 trillion macrophage cells in their body and it can identify in almost all parts of the body. The development of concept was gived the understanding to macrophage cells that they are capable to renewing cells independently in tissue, but if the macrophage cells in suppress condition, then monocyte will recruit monocyte in the blood circulation so it moves into tissue macrophages by adopting the local tissue macrophage phenotype [13].

The tissue macrophages develops continuously throughout the life and every time the macrophages pressured the environmental, so the population quickly filled with monocytes from blood circulation [14]. This monocyte was the first to be strongly involved in pro-inflammatory response against microorganisms and increasing the ability of macrophages to carry out scavenging [15]. Monocytes are components of immunity cells that play an important role, especially in natural immune responses, it are naturally heterogeneous and have the ability to differentiate into monocyte-derived macrophages or monocyte dendrite-derivate cells and act as an intermediary bridge for natural and acquired immunity responses [16].

The successful of Mtb to live in macrophages is due to the ability to convert antimicrobial cells into recipient cells. Mtb hacks the host defense mechanism by manipulating the host's cellular pathways, innate immune response, and cell death pathways to take the advantage [17]. Macrophages play an important role in tuberculosis, being a center of infection, macrophages are able to induce and respond to inflammation and as part of the natural and acquired immune system, and macrophages are an intermediary for tissue damage and repairing system [18]. Macrophages are not only professional phagocytic cells but also very active secretory cells. Macrophages produce various types of proteins in relatively small amounts such as components in complement cascade [19]. Active macrophages produces neutral proteinases such as urokinase, elastase, collagenase, various metalloproteinases and all are involve in fibrinolysis, tissue degradation and remodeling [20].

Phagocytosis in macrophages is a complex process in digesting and elimination pathogens process, removing cells undergoing apoptosis, and the basic process of tissue homeostasis. Phagocytosis is divided into four stages, namely the introduction of target particles, activating the signal for internalization process, phagosome formation

and phagosome maturation [21]. The receptors located on plasma membrane of phagocytic cells and it can be divided into non-opsonic and opsonic receptors. Non-opsonic receptors are able to recognize the present of molecular groups on target cell surface in phagocytes, where the opsonin receptors recognize host opsonins that bind and take outside particles to swallowed and digested. Opsonins can be in antibodies form, complement, fibronectin, mannose binding lectin, and milk fat globulin (lacthaderin) [22][23].

Phagocytosis and autophagy process occurs in lysosome degradation. Phagocytosed bacteria will face reactive oxygen species and nitrogen species so the production of proinflammatory cytokines will increases the strength of the host response. In tuberculosis, Mtb takes thr advantages by using host defense mechanisms, manipulating host cellular, natural immune responses and cell death pathways [17]. The ingestion process of bacteria by phagocytosis mechanism causes the rapid maturation of phagosomes in antimicrobial phagolysosomes [24]. Phagosome acidification requires lysosomal hydrolase and antimicrobial peptides and essential nutrients such as iron when a toxic burst of zinc (Zn) is formed [25]. PRR activation by microorganisms increases the antimicrobial ability of phagosomes by promoting the recruitment of NADPH oxidase [26]. NADPH oxidase produces reactive oxygen species (ROS) to kill microorganisms and promotes the phagosome maturation pathway, namely LC3 phagocytosis [27].

Inhibition of phagosome fusion in lysosomes is an important mechanism to inhibit macrophage phagosome / lysosome maturation. The transcription of pro-inflammatory factor NF-κB (nuclear factor kappa B) regulates phagolysosome fusion during infection [3]. Phosphatidylinositol 3- phosphate (PI3P) is an important component of macrophage cell membranes in endosome and phagosome surface. After the invasion of Mtb biosynthesis becomes low and through the pathway, so lipoarabinomannan toxin (LAM) with calmodulin-dependent of PI3P are suppresses the lysosome phagosome fusion process[4]. Toll-like receptors (TLRs) didn't give function as phagocytic receptors but as detectors toward outside particles. However, TLR collaborates with other non-opsonic receptors to stimulate ingestion process [5].

The first stage of phagocytosis is the detection of particles by phagocytic cells which are support with special receptors in cell membrane. Outside particles such as pathogenic microbials can directly recognized molecular-binding receptors and indirectly through opsonins. Some receptors binds PAMP but not directly initiate phagocytosis. TLR and several G-protein couple receptors prepared cells to phagocytosis process by inducing phagocytosis integrin activation [28]. The outside particles are recognize phagocytic cells by using disolving bind molecules, then they are ingested and digested. This molecule called an opsonin which use as a bridge between phagocytic cells and the particles to digest process. Antibody molecules (IgG) and complement components are important opsonins that can effectively induce phagocytosis [29]. The Fcg (FcgR) receptor is a family of glycoproteins which expressed in cell membrane of leukocytes and it capable to bind Fc area from IgG molecule [28]. Complement receptors1 (CR1), CR2, CR3, CR4 and CRIg are complement receptors that recognize components of the complement cascade and deposit on phagocytes surface target [30]. The interaction of particles and phagocytic cell receptors are series signals that trigger phagocytosis activation. he changes of membrane shape and the role of actin cytoskeleton are to forming pseudopods that will cover all particles being a "phagocytic cup" at contact area center between particles and phagocytic cell receptors [28]. Macrophages has differentces in phenotype, where alveolar macrophages are the first macrophages to encounter Mtb tobe an adaptation form and minimizes tissue damage. This causes alveolar macrophages have weak control Mtb [31].

Mycobacterium tuberculosis and oxidation stress

The elimination of mycobacteria by macrophages can be done by the oxygen reactive form and nitrogen species, phagosome acidification, and lysosome phagosome fusion. This activity leads to being phagosome maturation, increases phagosome acidification and mycobacterial killing in macrophages [3].

The formation of ROS takes place through catalyzed reactions by oxidase enzyme or the cytochrome p 450 enzyme, but the cells balanced the antioxidants production such as SOD, CAT and GPx [32]. The binding of Mtb component and Toll-like receptor

(TLR) are an important pathway in host immune response. The initial interaction of Mtb with monocytes / macrophages induces mitogen-activated protein kinase (MAPK) which plays an important role in promoting antimicrobial activity and the production of immune effector molecules such as tumor necrosis factor-*a* (TNF-*a)*) [33]. MAPK is one of the key transducers and it also the results of Mtb stimulation which can affect the signaling pathway to proinflammatory immune response [34]. The differences of proinflammatory response in Mtb infection depends on the MAPK signaling setting so the determination of Mtb pathogen state and outcome of infection comes from MAPK activation and modulation [35]. ROS produced cells can act as signaling molecules so they can respond to various cell surface receptors, for example ROS involved intracellular signaling pathways like MAPK and nuclear factor -kB pathway [36].

Polarization of macrophages

The simple goal of immune system is to prevent or treat the disease based on the immune system operates. The immune system, especially in the involvement of macrophages (M), includes a fairly complex process. Type 1 (M1) and type (M2) macrophages are represent the main opposite activities of macrophages. M1 activity is to inhibit cell proliferation and cause tissue damage, while M2 promotes cell activity and repairing tissue. This activity illustrates that innate immunity controls adaptive immunity and not vice versa [37]. Macrophages are heterogeneous and the function is depend on the exposure of cytokines environmental and inflammatory molecules. The balance of factors in environment can influence the different polarizations of macrophages. Macrophage polarization is an important determinant in natural immune response to intracellular bacterial infection.

M1 macrophages promotes powerful proinflammatory and antimicrobial activity by producing the efficiency of ROS and NO more efficient against intracellular pathogens, matrix degradation and tissue damage. The M2 phenotype has an immunity regulatory role that functions to limit tissue damage. The production of anti-inflammatory cytokines such as IL-10 and TGF-b promotes fibrosis and wound healing [38]. M1 or known as classic macrophages showed an inflammatory phenotype activity where M2 or alternative macrophages showed an anti-inflammatory phenotype activity. The interaction between macrophages and active T cells triggers are lead adaptive immunity system to release of cytokines and then they are modulates back to each other [39].

M1 stimulation is classify based on the ability prototypes response and inflammatory markers, roles, receptors, and signaling pathways in differ substantially. The stimulation of IFNγ is the main cytokine and associated with M1 activation also the main product of Th1 cells, NK cells and macrophage cells and their produce of cytokine. The IFNGR-1 and IFNGR-2 form IFNγ receptor. These receptors recruit janus kinase (Jak) 1 and Jak2 adapters to activate signal transducer, activator of transcription 1 (STAT1) and interferon regulatory factors (IRF) such as IRF-1 and IRF-8. In humans, gene mutations can caused by low expression of these receptors and worsening immunodeficiency [40].

M1-M2 polarization is strictly controlled by signaling paths set and transcription and post-transcription network settings. The M1 phenotype stimulated microbial products or pro-inflammatory cytokines (IFNγ, TNF-α or TLR ligand), and characteristics of M1 macrophages include high levels of antigen, abundant production of IL-12, IL-23, nitric oxide (NO) and reactive oxygen intermediate (ROI). Conversely, an M2 was observed in a non-infectious environment and leaded to an improvement of conditions. Furthermore the M2 responses amplification of IL-4, IL-10 or IL-13. Characteristics of M2 are upregulation of Dectin-1, DC-SIGN, manose receptors, scavenger a receptors, scavenger receptors B-1, CD163, CCR2, CXCR1 and CXCR2. M2 not produce NO or ROI but produces ornithine and polyamine in arginase pathway [41].

M1 and M2 macrophage communication pathways lead tobe polarization, mainly based on the balance of STAT1 and STAT3 / STAT6 activities, strictly regulate the polarization and activity of macrophages. The main activities of NF-κB and STAT1 are promotes polarization of M1 and resulting in cytotoxic and pro-inflammatory functions in tissue destruction form. In contrast, the main activity of STAT3 / STAT6 is dominate IL-4, IL-13 induction and IL-10 increases the polarization of M2 macrophages. This situation is related with immune tolerance and tissue repair. Peroxisome proliferator activated receptor (PPAR δ and PPARγ) are

controls certain aspects of M2 macrophage activation and oxidative metabolism. Kruppel like factor 4 (KLF-4) is a downstream STAT6 participates in promotion of M2 function by suppressing NF-κB / HIF-1α dependent transcription [41].

Macrophages are immune effector cells and antigen in cells, it plays an important role in the development of tuberculous granulomas, and also an histological features with complex structures found in tuberculosis. Mtb infection can affect the polarization of monocyte derivate macrophages by transforming macrophages from M1 to M2 in Mtb infection [42]. Granuloma TB is an organized structure with the main components of macrophages, epitheloid cells, multinucleated giant cells and lymphocyte cells [43]. The function of granulomas is to localize mycobacteria and prevent infection spread so the development of granulomas can determine in depth of infection by Mtb [44].

The terms of M1 and M2 are follows Th1 / Th2 classification system. It can determine the main state of macrophage polarization activation, which is M1 polarization induced by lipopolysaccharide (LPS) or interferon gamma (IFN-g), it called classical activation and lead to proinflammatory response, increasing microbicidal function and anti-tumor capacity. However, M2 polarization occured in predominance of interleukin-4 (IL-4) or IL-13, it called alternative activation which acts as an intermediary for the development of tissue repair and tumor growth 9-12 [45].

M1 macrophages induced by IFN-g and LPS produce inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS) and cytokines IFN-g, IL-1b, and tumor necrosis factor *a* (TNF-*a*) give suppressive effect on pro-inflammatory and cytotoxic, where M2 macrophages are stimulated by IL-4, IL-10, IL-13 and secrete IL-10, transforming growth factor-*b* (TGF-b), involved as an immune-regulator and tissue remodeling process damaged [46]. Recent studies said that mycobacterium tuberculosis has modulator potential in macrophage polarization [47]. In Mtb infection, M1 phenotype increased the regulation of early phase of the disease, but in further direction M2 occurs in intermediate and late stages of the disease [44].

Multidrug resistant TB (MDR-TB) is TB with resistance to isoniazid and rifampicin while extensively drug resistant TB (XDR-TB) is MDR-TB that resistance to fluoroquinolone treatment and second-line injection drugs [48]. The ability of pathogens to get out from the host immune system is an important factor in treatment failure or MDR-TB / XDR-TB incidence. The consumtion of anti-TB drugs in long term is a concern, and it able to eradicate Mtb. In this situation can affect the immune defense system in host and the effects of drugs has direct complications [49]. The effects of anti-TB drugs such as Rifampicin exerts in suppressive anti-inflammatory effect by suppressing nuclear factor-kappa B (NF-kB) in neurodegenerative diseases. Pyrazinamide treatment influences the host immune response by decreasing pro-inflammatory cytokine production in Mtb infection. First-line intervention of anti-TB therapy to pleural TB patients is induces polarization of pleural macrophages to M2, so from this study showed that anti-TB treatment was able modulated the host immune response [6].

The movement of M1 to M2 polarization is an important mechanism for host to prevent the spread of tissue damage, but the loss of suppression in immune system by M1 and Th1 will activate molecules and develop Mtb fertility in M2 / Th2 immunity environment [50]. The role of IRAK-M is as an intermediary for monocytes polarization, macrophages and pulmonary epithelial cells in host signaling pathway and it modulates macrophage polarization to Mtb. IRAK-M has positive correlation with Mtb number in macrophages infection process. The lung tissue showed direct polarization towards M2 during TB infection so there is little tissue damage, but provide good development facilities for Mtb. In other condition is IRAK-M knockdown inducing polarization towards M1 [51].

The successful of TB treatment depends on the interactions between the host, Mtb and treatments that influence each other. Mtb's defense against macrophage attack is a key factor in tuberculosis development. An important defense mechanism for Mtb is the ability to act as an immunomodulator from M1 polarization towards suppressing M2 polarization. However, the existence of anti-TB treatment with long time is expect to be able to mediate immunomodulation and it quite extensive, lead tobe treatment success [52].

Conclusion

The pathogen mechanism of TB is able to influence

the polarization of macrophages derivete monocytes via the transformation of M1 tobe M2. The movement of polarization of M1 tobe M2 is an important mechanism for host, because it will prevent widespread tissue damage. However, the loss of suppression immune system by M1 and Th1 will activate molecules and it also will give benefit to development of Mtb fertility in M2 / Th2 immunity. Long-term use of anti-tuberculosis drugs is essential to eliminate Mtb host's immune defense system and drug effects have direct complications.

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References

1. Zuniga J, Diana TG, Teresa SM, Tatiana S, Julio G, Edmond JY. Cellular and Humoral Mechanism Involved in the Control of Tuberculosis. Clinical and Developmental Immunology 2012 March 17;2012(5)1-18.
2. Upadhyay S, Mittal E, Phillips JA. Tuberculosis and The Art of Macrophage Manipulation. Pathogen and Disease 2018 Jun; 76(4): fty037
3. Gutierrez M, Bibhuti B, Luisa J, Edith E, Elsa A, Gareth G. NF-Kappa B Activation Controls Phagolysosome Fusion-Mediated Killing Of Mycobacteria By Macrophages. J. Immunol 2008 Aug 15;181(4):2651-63.
4. Vergne, I., Chua, J, Deretic, V. Tuberculosis Toxin Blocking Phagosome Maturation Inhibits A Novel Ca2+/Calmodulin-PI3K Hvps34 Cascade. J. Exp. Med 2003 Aug 1; 198(4):653-659.
5. Iwasaki A, Medzhitov R. Control of Adaptive Immunity by The Innate Immune System. Nat Immunol 2015 Apr;16(4):343-53.
6. Cho, H, Yun-Ji L, Jhingook K, Won-Jung K, Chang-Hwa S, Min-Woong K. Different Macrophage Polarization Between Drug-Susceptible And Multidrug-Resistant Pulmonary Tuberculosis. BMC Infectious Diseases 2020 Jan 29;20(1):81.
7. Donovan M, Schultz L, Duke, T, Blumenthal A. Type I Interferons In The Pathogenesis of Tuberculosis: Molecular Drivers And Imunological Consequences. Frontiers Immunology 2017 Nov;1-20.
8. Kleinnijenhuis J, Marije O, Leo, A, Joosten, Mihai G, Reinout VC. Innate Immune Recognition Of Mycobacterium Tuberculosis. Clinical and Developmental Immunology 2011 Apr 7; 2011: 405310.
9. Mukhopadhyay S, Nair S, Ghosh S. Pathogenesis In Tuberculosis; Trancriptomic Approaches To Unraveling Virulence Mechanism And Finding New Dug Targets. FEMS Microbiology Review 2012 March;36(2):463-85.
10. Zhang, Q, Cao X. Epigenetic Regulation Of The Innate Immune Response To Infection. nature review immunology 2019 Jul;19(7):417-432.
11. Li J, Qi-Yao C, Yong, Z, Bing L, Jing W, Xiao-Bo Q, Cui HL. Mycobacterium Tuberculosis Mce3E Suppress Host Innate Immune Responses By Targeting ERKI/2 Signaling. The Journal of Immunology 2015 Apr 15; 194(8):3756-67.
12. Qiang L, Jing W, Yong Z, Pupu G, Qiyao C, Bingxi L, Yi S, Lingqiang Z, George FG, Cui H. Mycobacterium Tuberculosis Mce2E Suppresses The Macrophage Innate Immunre Response And Promotes Epithelial Cell Proliferation. Cellular and Molecular Immunology 2019 Apr;16(4):380-391.
13. Byrne AJ, Mathie S, Gregory L, Llyod C. Pulmonary macrophages: key players in the innate defence of the airways. Thorax 2015 Dec;70(12):1189-96.
14. Laar LV, Wouter S, Prijk S D, Liesbet M, Charlotte L, Gert V I, Eik H, Rudi B, Yvan S, Bart N L, Martin G. Yolk sac macrophages, fetal liver, and adult monocytes can colonize an empty niche and develop into functional tissue-resident macrophages. Immunity 2016 Apr 19;44(4):755-68.
15. Auffray C, Darin K, Emilie N, Brigitte S, Celine L, Noah A, Julia L, Karine B, Laura C, Marc A, Thierry M, Israel C, David A, Ana C, Gregoire L, Frederic G. CX3CR1+CD115+CD135+common macrophage/DC precursor and the role of CX3CR1 in their response to inflammation. J Exp Med 2009

Mar 16;206(3):595-606.

16. Wang J, Kubes P. A Reservoir Of Mature Capacity Macrophages That Can Rapidly Invade Visceral Organs To Affect Tissue Repair. Cell 2016 Apr 21;165(3):668-78.
17. Sampath P, Moideen K, Ranganathan, U, Bethunaickan R. Monocyte Subsets: Phenotypes and Function in Tuberculosis Infection. Frontiers in Immunology 2018 Jul 30;9:1726
18. Marakalala M, Martinez F, Pluddemann A, Gordon S. Macrophage Heterogeneity in the Immunopathogenesis of Tuberculosis. Frontiers in Microbiology 2018 May 23;9:1028.
19. Chung L, Keshav S, Gordon S. Cloning The Human Lysozyme Cdna: Inverted Alu Repeat In The Mrna And In Situ Hybridization For Macrophages And Paneth Cells. Proc. Natl. Acad 1988 Sep;85(17):6227-31.
20. Shrestha A, Megeney L. The Non-Death Role Of Metacaspase Proteases. Front. Oncol 2012; 2: 78.
21. Rosales C, Eileen Q. Phagocytosis: A Fundamental Process in Immunity. BioMed Research International 2017;2017:9042851.
22. Canton J, Neculai D, Grinstein, S. Scavenger Receptors In Homeostasis And Immunity. Nature Reviews Immunology 2013 Sep;13(9):621-34.
23. Flanagan R, Jaumouille, Grinstein S. The Cell Biology Of Phagocytosis. Annual Review of Pathology: Mechanism of Disease 2012 September 9 Vol. 7:61-98.
24. Flanagan R, Cosio G, Grinstein S. Antimicrobial Mechanisms Of Phagocytes And Bacterial Evasion Strategies. Nat Rev Microbiol 2009 May;7(5):355-66.
25. Botella H, Levillain F, Peyron P. Mycobacterial P1-Type Atpases Mediate Resistance To Zink Poisoning In Human Macrophages. Cell Host Microbe 2011 Sep 15;10(3):248-59.
26. Nunes P, Demaurex N, Dinauer M. Regulation Of The NADPH Oxidase And Associated Ion Fluxes During Phagocytosis. Traffic 2013 Nov;14(11):1118-31.
27. Martines J, Malireddi R, Rosebrock T. Efferocytosis Is An Innate Antibacterial Mechanism. Cell Host Microbe 2012 Sep 13;12(3):289-300.
28. Rosales C, Querol E U. Fc Receptor: Cell Activators And Antibody Function. Advances in Bioscience and Biotechnology 2013 Volume 4, pp. 21-33.
29. Rosales, C. Fc Receptor And Integrin Signaling In Phagocytes. Signal Transduction 2008 January 11;7(5)386-401.
30. Campagne M, Brown E. Macrophage Complement Receptor And Pathogen Clearance. Cellular Microbiolog 2007 Sep1;7(7)2095-2102.
31. Rajaram M, Ni B, Dodd C, Schlesinger L. Macrophage Immunoregulatory Pathways In Tuberculosis. Seminar in Immunology 2014 Dec;26(6):471-85.
32. Botham K, Mayes P. The Respiratory Chain & Oxidative Phosphorilation. In: Illustrated Biochemistry Ed 28th McGraw Hill Lange, 2009..
33. Blumenthal A, Stefan E, Martin E, Hans F, Norbert R. Control Of Mycobacterial Replication In Human Macrophages: Roles Of Extracellular Signal-Regulated Kinase 1and 2 And P38 Mitogen-Activated Protein Kinase Pathways. Infect Immun 2002 Sep; 70(9): 4961–4967.
34. Yang C, Chang S, Ji-Sook L, Saet J, Jae-Hee O, Jongsun P, Hwa-Jung K, Jeong-Kyu P, Tae-Hyun P, Eun-Kyeong J. Intracellular Network Of Phosphatidylinositol 3-Kinase, Mammlian Target Of The Rapamycin/70 Kda Ribosomal S6 Kinase1, And Mitogen-Activated Protein Kinases Pathways For Regulating Mycobacteria-Induced IL-23 Expression In Human Macrophages. Cell Microbiol 2006 Jul;8(7): 1158-1171.
35. Schorey J, Cooper A. Macrophage Signalling Upon Mycobacterial Infection : The MAP Kinases Lead The Way. Cell Microbiolo 2003 March 3;5(3) 133-142.
36. Asehnou K, Derek S, Sanchayita M, Jae Y, Edward A. Involvement Of Reactive Oxygen Species In Toll-Like Reseptor 4 - Dependent Activation Of NF-Kb. J. Immunol 2004 Feb 15;172(4):2522-9.
37. Mills C. M1 and M2 Macrophages: Oracle of Health and Diasease. Critical Review in Immunology 2012;32(6):463-88.
38. Thiriot J, Martinez Y, Torres A. Hacking The Host: Exploitation of Macrophage Polarization By Intracellular Bacterial Pathogens. Patogen and Disease 2020 Feb;78(1)10-21.
39. Das, P. et al. Selective M1 Macrophage Polarization In Granuloma -Positive And Granuloma-Negative Crohn's Disease, In Comparison To Intestinal Tuberculosis. Intestinal Research 2018; 16(3).

40. Martinez F, Gordon S. The M1 And M2 Paradigm Of Macrophage Activation: Time For Reassesment. F1000Prime Reports 2014 Mar 3;6:13.
41. Wang N, Liang H. Zen K. Molecular Mechanism That Influence the Macrophage M1-M2 Polarizaton Balance. Frontiers in Immunology 2014 Nov 28;5:614.
42. Huang Z, Qing L, Yang G. Mycobacterium tuberculosis-Induced Polarization of Human Macrophage Orchestrates the Formation and Development of Tuberculous Granulomas In Vitro. Plos One 2015 June;10(6):e0129744.
43. Egen J, Antonio G, Carl G, Nathalie W, Alan S, Ronald S. Macrophage And T Cell Dynamics During The Development And Disintegration of Mycobacterial Granulomas. Immunity 2008 Fe;28(2) 271-284.
44. Villarino L, Verollet C, Maridonneau-Parini I, Neyrolles. Macrophage polarization: convergence point targeted by Mycobactrium tuberculosis and HIV. Front Immunol 2011 Sep; 2: 43.
45. Li W, Katz B, Spinola M. Haemophilus ducreyi-induced interleukin-10 promotes a mixed M1 and M2 activation program in human macrophages. Infection and Immunity 2012 Dec; 80(12): 4426–4434.
46. Arora S, Kapil D, Beamon A, Pragnya D, Mansoor A. Macrophages: Their Role, Activation And Polarization In Pulmonary Diseases. Immunobiology 2018 Apr;223(4)383-396.
47. Mattila J, Olabisi O, Diane K, Simeone M, Jin H, Seok Y, Laura E, Clifton E, Edwin K, Denise E, Sidney M, Philana L, Joanne L . Microenvironments In Tuberculous Granulomas Are Delineated By Distinct Populations Of Macrophage Subsets And Expressions Of Nitric Oxide Synthase And Arginase Isoforms. J Immunol 2013 Jul 15;191(2):773-84.
48. WHO. Global tuberculosis report. Geneva: World Health Organization 2017.
49. Tauber S, Nau R. Immunomodulatory Properties Of Antibiotics. Curr Mol 2008 Jan;1(1):68-79.
50. Kahnert A, Seiler P, Stein M. Alternative Activation Deprives Macrophages Of A Coordinated Defense Program To Mycobacterium Tuberculosis. Eur J Immunol 2006 Mar;36(3):631-47.
51. Shen P, Li Q, Ma J. IRAK-M Alters The Polarity Of Macrophages To Facilitate The Survival Of Mycobacterium Tuberculosis. BMC Microbiol 2017 Aug 23;17(1):185.
52. Mendez S, Ryan T, Meleana H, Lu H, Patricia G, Michael H, John T. The Antituberculosis Drug Pyrazinamide Affects The Course Of Cutaneous Leismaniasis In Vivo And Increases Activation Of Macrophages And Dendritic Cells. Antimicrob Agents Chemother 2009 Dec; 53(12): 5114–5121.