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Dual Role of Inflammation in Prognosis and Prevention of Tuberculosis

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Abstract

The high death rate and progressive spread of tuberculosis emphasizes the need to address the complexities associated with the disease and its treatment. Complications associated with the disease are associated with the process of inflammation. Host defense system protects the body against pathogen by various inflammatory responses and the same are utilized by the pathogen as an offensive tool to progress inside the host. The genetic factors which determine the expression of inflammatory markers affect the onset of the disease and its treatment. The susceptibility to infection, progression to active or latent form and dissemination to the other sites are governed by the inflammatory responses generated by the host. The prognosis of tuberculosis is not the pathogenic infection but the outcome of the host- pathogen interactions, most of which are still not understood. In this review we discuss the major host inflammatory responses during *Mycobacterium tuberculosis* infection and their role in progression and/or containment of the infection. In addition the possible role of anti-inflammatory drugs as adjunct to the current anti-tuberculosis treatment will be reviewed.

Keywords: Cytokines; Inflammation; *Mycobacterium tuberculosis*; Tuberculosis

Introduction

Mycobacterium tuberculosis has emerged as the most successful bacterial pathogen infecting 9 million and causing mortality of almost 2 million persons per year, making tuberculosis the highest toll taking bacterial disease [1]. Multiple factors are involved in the success of *Mycobacterium tuberculosis* infection which includes contagious spread of the disease, difficult diagnosis and patient non-compliance. *Mycobacterium tuberculosis* co-infection with HIV and emergence of multi-drug resistant strains of *Mycobacterium tuberculosis* further increase the incidence of tuberculosis cases in the world [2]. One of the most important features which make *Mycobacterium tuberculosis* highly successful bacterial pathogen is its ability to survive inside the host for longer time. It is able to overcome the host defense by various mechanisms. The oldest concept given by D'Arcy Hart for *Mycobacterium tuberculosis* survival in macrophage is the escape of *Mycobacterium tuberculosis* from the lysosome [3], however, the exact mechanism is still unknown. Tuberculosis occurs either in active or latent form, depending upon the immune status of the host. Adequate immune response of host can eliminate infection in the initial stage only whereas inadequate immune responses result in development of active disease *Mycobacterium tuberculosis* can exist in dormant state and develops into active state when immune system gets compromised or reinfection of the pathogen occurs (Figure 1).

Inflammatory response- the defensive strategy of host against *Mycobacterium tuberculosis*

The core of immune response to every infection is inflammation and *Mycobacterium tuberculosis* is no exception to this phenomenon. The host immune response against *Mycobacterium tuberculosis* begins immediately after their phagocytosis by macrophages through interaction with various pathways which include its complex association with Toll-like receptors (TLRs) and mannose receptor [2,5]. TLRs are set of antigen pattern recognizing receptors (PRRs) among which TLR2 has important role in generating tuberculosis immunity [6]. After interacting with components of *Mycobacterium tuberculosis*, these receptors generate innate immune responses which in turn lead to activation of adaptive immune response [7,8]. The interaction with Toll-like receptors enhances the expression of adhesion molecules and secretes pro-inflammatory cytokines, such as TNF-α, interleukin-1b (IL-1b), interleukin-6 (IL-6) and interleukin-12 (IL-12) in host cells. TNF-α can either stimulate apoptosis in macrophages to suppress the intracellular replication of mycobacteria or induce Reactive Oxygen Intermediates/Reactive Nitrogen Intermediates (ROI/RNI) mediated killing of phagocytosed bacilli. IL-6 is involved in macrophage and cytotoxic T cell differentiation. IL-12 induces IFN-γ to differentiate $CD4^+$ T cells in Th1 effectors [9]. Cytokines can also direct neutrophils, monocytes, lymphocytes to the sites of infection which stimulate $CD4^+$ and $CD8^+$ T-cells to amplify the antimicrobial capacity of macrophages. T-cells produce several cytokines such as IFN-γ, TNF-α, IL-2, 6, 8 and 12 which help in further activating anti-bacterial properties of macrophages, granuloma formation and induction of Th1 cells, respectively. $CD8^+$ T cells also display cytotoxic activity to eliminate the pathogen. The activated macrophages also engulf the escaping bacteria and subsequently prevent the spread of infection [10]. Infected dendritic cells reach the lymph nodes where they stimulate generation of Th1cells which are carried to the site of infection where they produce cytokines and generate T cell response to enhance stimulation of macrophages [11]. Cytokines convert the loci of infection into granuloma by attracting immune cells to surround the infectious site and induce Delayed Type Hypersensitivity (DTH) response. Cytokines like IFN-γ and TNF-α augment the bactericidal activity of macrophages by increasing the surface expression of MHC class II molecules for antigen presentation,

enhancing the secretion of inflammatory mediators and promote the granuloma formation [12].

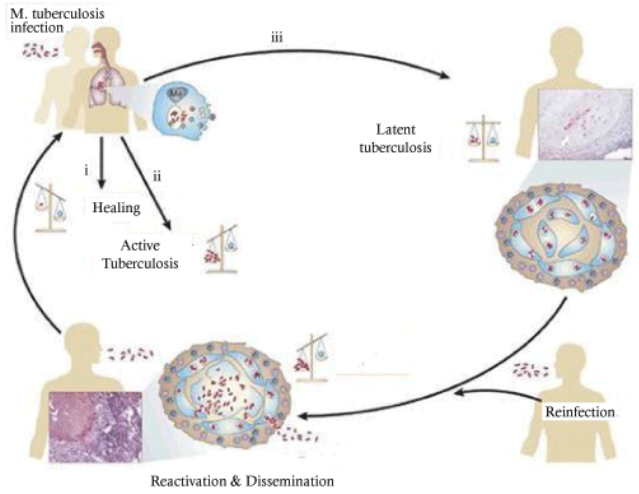

Figure 1: Modes of tuberculosis progression inside the host. i) Individuals with strong immune system are able to eliminate the pathogen. ii)Individuals with weak immune response develop active tuberculosis iii) Immunity and pathogenic activity balance each other and result in latent form of tuberculosis which reactivates on further infection or by weakened immune system [4].

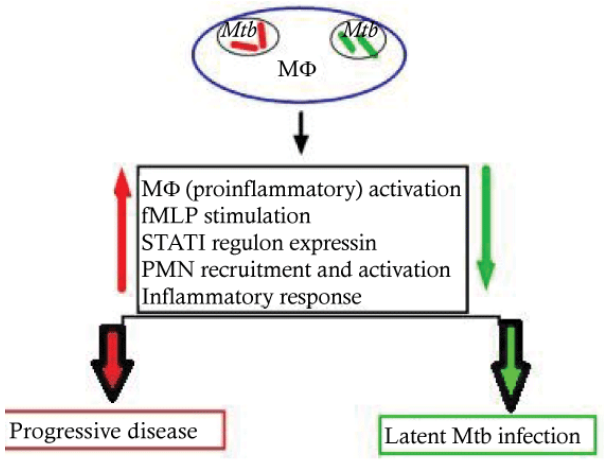

Figure 2: Schematic illustration showing differential expression of host genes after infection with different strains of *Mycobacterium tuberculosis*. Strain stimulating genes of innate immune response upregulate inflammatory genes causes active tuberculosis while *Mycobacterium tuberculosis* strain which down regulates the expression of these genes generates latent tuberculosis [14].

Granuloma consists of infected macrophages surrounded by different types of immune cells viz epithelioid macrophages, foam cells, lymphocytes and a fibrous capsule at the periphery of the granuloma. Granuloma represents delicate state of balance between preventing spread of infection in host and protection of *Mycobacterium tuberculosis* from immune reactions [13]. Whether the infection will stabilize as latent form of tuberculosis or develops into active tuberculosis is not determined at time of infection. Studies on rabbit model of pulmonary tuberculosis have shown that Mycobacterial strains that are able to upregulate expression of inflammatory genes after 6 h of infection result in active disease while strains that downregulate expression of these molecules at this time point cause latent tuberculosis (Figure 2) [14].

Inhibition of inflammation as a survival strategy for *Mycobacterium tuberculosis* in host

Mycobacterium tuberculosis subverts host cell immune response and harnesses cellular machinery to make a niche inside the host cell [15,16]. The bacterial cell wall has a highly complex structure which acts as mechanical barrier of *Mycobacterium tuberculosis* against host has been recently shown to have anti-inflammatory function as well. *Mycobacterium tuberculosis* secretes a complex variety of glycosylated compounds present in the cell wall during infection which acts as immunomodulatory molecules. p-hydroxybenzoic acid derivatives (p-HBADs) are synthesized by *Mycobacterium tuberculosis* to inhibit the production of inflammatory cytokines, particularly interferon-γ (IFN-γ) by T-cells [18]. *Mycobacterium tuberculosis* controls the host cell machinery through its transcription factor sigma-E involved in the modulation of the host inflammatory response against the pathogen. Sigma E belongs to the family of extra cellular factors which get expressed in *Mycobacterium tuberculosis* when it infects the macrophage and resides inside it [19]. Sigma-E downregulates the expression of host transcriptional regulator, T-bet which is associated with generation of long lasting Th1 response by inducing the expression of IFN Y and decreasing expression of IL-10 [20]. Though interaction of *Mycobacterium tuberculosis* with macrophage receptors (TLR-2) leads to immune activation in host but prolonged exposure to *Mycobacterium tuberculosis* ligand (19 kd lipoprotein, LprG) has been found to inhibit MHC-II antigen processing in primary human macrophages and THP-1 cells. LprG component of *Mycobacterium tuberculosis* binds TLR-2 and inhibits expression of MHC II molecules on the surface of antigen presenting macrophages. Lack of MHC-II epitope on the surface of antigen presenting macrophages prevents the activation of MHC-II-restricted $CD4^+$ T cells thus inhibition of MHC-II antigen processing becomes effective immune evasion strategy for pathogen [21,22]. Moreover, *Mycobacterium tuberculosis* and its cell wall component Lipoarabinomannan (LAM) are potent inducers of the anti- inflammatory cytokine TGF-β. LAM mediated induction of TGF-β is dominant over the induction of the pro-inflammatory cytokines TNF-α, IL-1β and IL-6 and anti-inflammatory cytokine IL-10 which counteract macrophage activation and microbicidal activity of inflammatory molecules [23]. *Mycobacterium tuberculosis* modifies its acetylated cell wall peptidoglycan to n-glycosylated form; this confers resistance to lysozyme and β-lactam antibiotics [24]. Glycosylation also enhances nucleotide-binding oligomerization domain containing protein-2 (NOD-2) dependent immune activation [24]. This further increases activation of immune response, generates more immune cells and helps in granuloma formation .

Effect of inflammation on progression of disease inside the host

Host immune system plays a crucial role in eradication of *Mycobacterium tuberculosis* infection or its persistence as a latent tuberculosis infection. When immune response of the host is neutralized by pathogen, the generated inflammatory response leads to

host tissue destruction [25]. Twenty years before Dannenberg described this inflammatory tissue destruction as the fifth stage among the five stages of *Mycobacterium tuberculosis* pathogenesis viz (1) onset; (2)symbiosis between macrophages and bacilli; (3)caseous necrosis formation produced by Tissue Damaging Response (TDR); (4)interplay between Macrophage Activating Response (MAR) and TDR; and (5)liquefaction of caseous tissue. An interplay between MAR and TDR inside alveolar sacs where primary infection foci are located, determine the outcome of the infection [26]. Activation of latent tuberculosis occurs due to caseation of granulomas causing cavitation and tissue destruction. Lung tissue destruction occurs due to degradation of fibrillar collagens which are highly resistant to enzymatic degradation. These are only cleaved by collagenolytic Matrix Metallo Proteinases (MMPs) which are secreted by macrophages in response to *Mycobacterium tuberculosis* infection [27]. MMPs also govern the granuloma formation and tissue destruction during progression of tuberculosis pathology [28]. MMPs are family of zinc dependent proteases that can collectively degrade all components of extracellular matrix. Besides their role in tissue remodeling, these regulate varied aspects of inflammation and immunity via interactions with pro-inflammatory cytokines and chemokines [29]. The rise of MMPs in tuberculosis pathology and their role in tissue destruction occurs via inflammatory processes generated during course of disease [30]. Though immune response during initial stage of infection is beneficial to host but during chronic phase of *Mycobacterium tuberculosis* bacterial growth and limit immunopathology [31]. Marzo and colleagues have described a murine C3HEB/FeJ model for lung histopathology and inflammatory damage during transition of latent tuberculosis infection to active form. The effects of the administration of drugs with anti-inflammatory activity in murine model show lower levels of pro-inflammatory mediators such as TNF-α, IL-17, IL-6 and CXCL5, a lower bacillary load, better histopathology, and increased survival compared with untreated controls which have massive intra-alveolar neutrophilic infiltration, rapid granuloma growth, caseous necrosis and liquefactive necrosis. Increasing levels of pro-inflammatory mediators were detected in lungs [32] This study highlights the destructive effects of high inflammatory response during tuberculosis progression and control of the disease by regulation of inflammation. In tuberculosis patients, severity of *Mycobacterium tuberculosis* infection is associated with excessive inflammatory reactions. Patient studies reveal that significantly higher levels of TNF-α and TGF-β are present in sera of patients with advanced tuberculosis in comparison to patients with mild-moderate tuberculosis. Likewise patients with large tuberculosis cavities have higher concentrations of TNF-α and IL-1β than patients who have small or no cavity [33]. DBA/2 mice which are susceptible to *Mycobacterium tuberculosis* are characterized by excessive lung inflammation, tissue damage, and failure to control bacterial growth, do not show recruitment of T-regulatory cells at the site of inflammation. T-regulatory cells are immune suppressive cells that prevent the generation of aggressive host immune response which in turn prevents tissue damage and spread of bacteria to other host cells hence validates that suppression of immune response leads to better tuberculosis pathology [34]. These human and animal studies show that susceptibility to tuberculosis is an outcome of host's inability to control inflammatory host damage. Hence, progression of tuberculosis pathology is connected to regulation of various types of inflammatory networks [35] as shown in Figure 3.

The earlier studies of Amanda *et al. [36]* have shown the role of inflammation in enhancing the disease pathology. Mice lacking TLR2 (TLR2KO), in comparison with wild type (WT) mice, exhibit excaberated cellular infiltration and inflammation in the lungs and fail to stably control bacterial burden during chronic infection, thus showing inflammations an offensive tool for *Mycobacterium tuberculosis* [36]. Role of 5-lipooxygenase (5-LO) deficiency in survival of *Mycobacterium tuberculosis* infected mice due to its role in decreasing inflammation and reduced tissue necrosis has been reported [37]. T regulatory cells, which prevent the aggressive immune response, stop the transition from latent tuberculosis infection to the active tuberculosis showing the importance of inflammatory response in cavitations and pathogenesis during tuberculosis.

Like most of the pathogenic diseases, tuberculosis was thought to be an outcome of failed immunity but latest advances in tuberculosis research point towards new links between the disease and immunity. Disruption of fine balance between inflammation and host defense is reported to play a role in pathogenesis of tuberculosis [38,39]. Increased as well as decreased inflammatory response can contribute towards high susceptibility of the host to the pathogen [40,41]. In zebra fish model of *Mycobacterium tuberculosis*, either increased or decreased level of TNF-α (due to higher or lower levels of leukotriene A4 hydrolase (LTA4H) respectively) leads to increased susceptibility to *Mycobacterium tuberculosis* infection [42]. Low-LTA4H levels reduce microbicidal activity of macrophages which leads to higher bacterial load resulting in necrosis of the overladen macrophages [43]. The high LTA4/TNF-α level cause necrosis of infected macrophages despite their enhanced anti-bacterial activity [42]. The same phenomenon was observed in tubercle meningitis where a common single nucleotide polymorphism that regulates LTA4H expression was associated with tubercle meningitis severity [42]. This adds to the role of host genetics in coding severity or susceptibility to disease via hyper or hypo inflammation in addition to the role of pathogen virulence. Homozygosity of alleles for both high and low expression of LTA4H leads to similar increase in disease severity [44]. The mechanism behind these findings describe mitochondrial reactive oxygen species (ROS) as critical mediators of both phenotypes. ROS- dependent cell necrosis is mediated by two pathways that participate in cell death [45]. TNF-α dually mediates resistance and susceptibility to *Mycobacterium tuberculosis* through mitochondrial reactive oxygen species has been reviewed and considered for therapeutic applications [46].

Inflammation as interplay between tuberculosis and human immunodeficiency virus (HIV) infection

The dual infection of tuberculosis and HIV has been termed as "accursed duet" [47]. HIV co- infection promotes the rapid progression of Tuberculosis after infection or reinfection and also increases chances of reactivating latent Tuberculosis [48]. That is why co-infection with *Mycobacterium tuberculosis* is responsible for one third of mortality due to Acquired Immune Deficiency Syndrome (AIDS). Globally, around 14.8% of patients with tuberculosis are co-infected with HIV and 50-80% tuberculosis patients in sub-Saharan parts of Africa are HIV-infected. Both HIV and *Mycobacterium tuberculosis* are able to make successful survival in macrophages from where it can spread to other cells [49,50]. HIV-1 co-infection of macrophages with *Mycobacterium tuberculosis* leads to increased pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) and decreased IL-10 [51]. Both HIV and *Mycobacterium tuberculosis* stimulate TNF release from infected cells, and TNF hampers bacterial growth while enhancing HIV replication by activation of NF-$_{\kappa}$B pathway which

increases transcription of HIV-1 long terminal repeats [52-54]. These cytokines also promote viral expansion beyond tissue macrophages by recruiting new host cells around the site of inflammation which act as carriers of the virus and strongly enhance viral expansion to T cells [53] Even the diminished levels of lL-10 in HIV co-infected *Mycobacterium tuberculosis*, which cause decrease in viral replication during early hours of infection lead to significant increase in viral load after 72 h as compared to *Mycobacterium tuberculosis* uninfected macrophages. *Mycobacterium tuberculosis* and HIV also survive in DCs. While *Mycobacterium tuberculosis* down regulates pro-inflammatory activity and antigen-presenting function of DCs [55,56]. HIV can also manipulate DC manipulated T cell functions, DC migration and thus contribute to pathogen dissemination [57,58]. The DC-expressed C-type lectin receptor DC-SIGN (DC- Specific Intercellular-adhesion-molecule-3-Grabbing Non-integrin) facilitates transmission and immune escape of both *Mycobacterium tuberculosis* and HIV [59,60]. Interaction of HIV viral envelope glycoprotein gp120, and DC-SIGN leads to efficient spread and transmission of the virus to $CD4^+$ T cells [61-64] *Mycobacterium tuberculosis* targets DC-SIGN and inhibits pro- inflammatory IL-12 and TNF production and induction of IL-10 by DCs [65,66]. In tuberculosis patients HIV infection is facilitated by various mechanisms based on inflammatory mediators. The increased expression of co-receptors CXCR4 and CCR5, increasing pro-inflammatory cytokines, especially TNF and down-regulation of CCL5 by *Mycobacterium tuberculosis* are involved in HIV progression in *Mycobacterium tuberculosis* infected patients [67,68]. Both HIV and *Mycobacterium tuberculosis* are able to survive successfully in macrophages. "

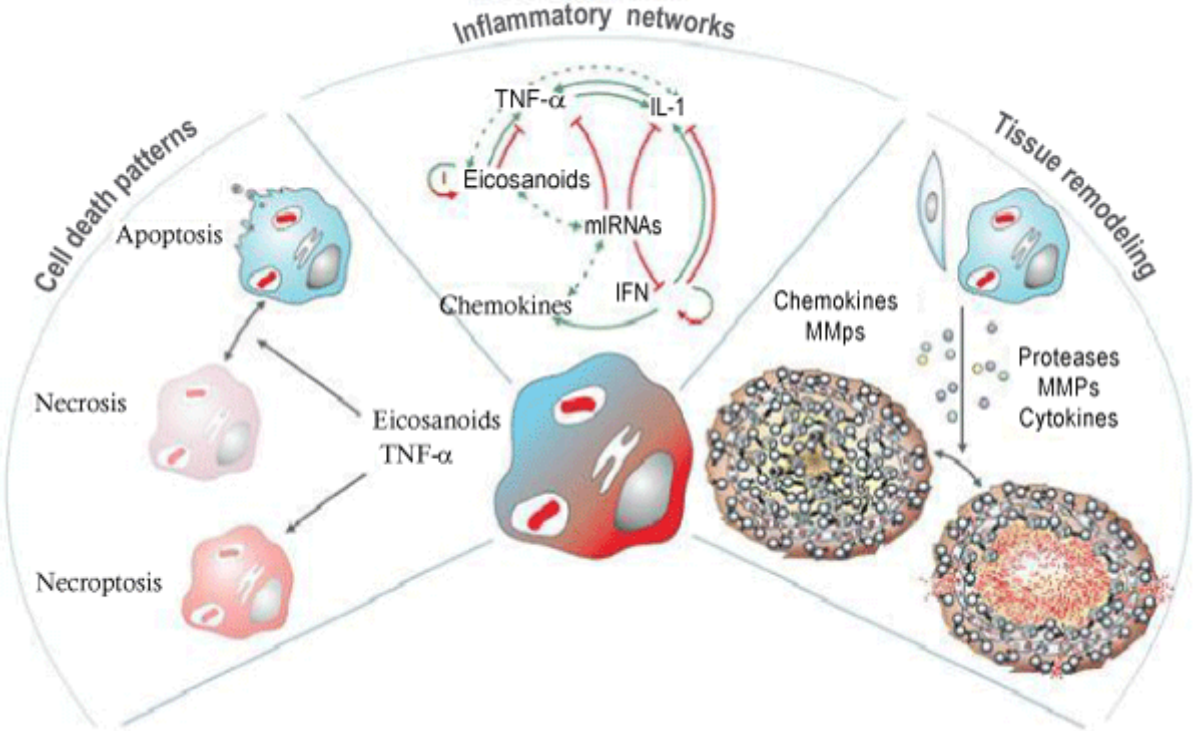

Figure 3: Multiple layers of regulation of inflammation in tuberculosis . Central panel: interactions of *Mycobacterium tuberculosis* with professional phagocytes results in activation of several pathways, which concur to induce inflammation. IL-1 necessitates differential requirement for caspase-1 and subsequently inflammasome activation in infected myeloid cells. Left panel: distinct proteinaceous and lipid mediators impact on the fate of the infected cell. Eicosanoids direct cell death (apoptosis vs. necrosis), while abundant TNF-α favors necroptosis and hyper-inflammation. Right panel: genesis of nascent granulomas is controlled by immune and non-immune cells via chemokines and cytokines. Local abundance of proteases and cytokines regulate transition of solid granulomas to necrotic ones. Matrix-metalloproteinases, modulate the extent of tissue damage [36].

Immune reconstitution diseases associated with mycobacterial infections

Individuals coinfected with HIV and *Mycobacterium tuberculosis* when treated with Highly Active Antiretroviral Therapy (HAART) for treatment of HIV develop Immune Reconstitution Inflammatory Syndrome (IRIS) [69,70] which increases immune response to *Mycobacterium tuberculosis* leading to increased host inflammatory response. The host again generates a type-1 response which restores interferon-γ secretion and cell-mediated immune responses to mycobacteria [71]. This abrupt generation of increased immune response leads to the uncontrolled tissue-damage and is termed as IRD [72]. *Mycobacterium tuberculosis* associated IRD has various life-threatening manifestations like acute respiratory failure, airway obstruction, peritonitis, splenic rupture and expanding intracranial lesions. Possibility of occurrence of IRD varies from person to person due to polymorphism in cytokine genes which influence the rate of clearance of antigenic molecules from the body. HIV infection disrupts immune responses to *Mycobacterium tuberculosis* resulting in diminished tissue damage and increased bacillary loads [55]. HIV positive patients with *Mycobacterium tuberculosis* infection show, few

clinical symptoms of tuberculosis, inspite of active mycobacterial infection and very high bacillary load. Shelburne et al., mention that majority of reported cases of immune restoration disease (IRD) associated with *Mycobacterium tuberculosis* infection arise within the first 3 months of antiretroviral therapy [61,62].

Further 2-23% HIV-seronegative patients receiving anti-tuberculosis therapy show paradoxical reactions [73]. Manifestations associated with paradoxical reactions vary in severity from mild fever and minor lymph node enlargement to severe respiratory failure and neurological deterioration. Paradoxical reactions are outcome of altered balance of pro-inflammatory and immunosuppressive immune mechanisms during initial stages of anti-tuberculosis treatment [74,75]. Amongst South African HIV-seronegative patients suffering from pulmonary tuberculosis additional weight loss and functional deterioration has been reported during the first month of anti-tuberculosis therapy [76]. These changes were temporally associated with a rise in the serum concentration of TNF-α thus indicating higher pro-inflammatory response involved in the worsening of the disease even after the treatment. Higher levels of TNF-α have also been correlated with such observations in other studies related to chronic obstructive pulmonary disease [77,78].

Inflammation in extra-pulmonary forms of tuberculosis

Extra pulmonary tuberculosis consists of about 15-20% of all HIV negative and 50% of HIV- positive cases of tuberculosis [79]. Literature provided us with the contradictory reports of cytokine profiles in extra-pulmonary cases of tuberculosis. Some studies showed similar cytokine levels in sera from persons with various tuberculosis manifestations, while others found that circulating levels of cytokines such as IFN-γ and CXCL-9 differ based on the site of tuberculosis disease [80,81]. Christina et al. , have mentioned that patients with latent tuberculosis had higher level of cytokines than the patients with previous pulmonary tuberculosis which inturn had higher levels of the cytokines than patients with previous extrapulmonary tuberculosis. Uninfected individuals had lowest levels of cytokines [82]. IFN-γ production after stimulation with *Mycobacterium tuberculosis* peptides varied with severity of the diseases in persons with pulmonary tuberculosis [82]. Inadequate production or maintenance of memory T lymphocytes could potentially lead to the development of tuberculosis at sites distant from the site of primary infection after initial control of *Mycobacterium tuberculosis* infection, explaining why persons with previous extra-pulmonary tuberculosis produce low cytokine levels. Recent studies have shown that persons with previous extra-pulmonary tuberculosis had the highest levels of IL-17 that participates in the early defense against *Mycobacterium tuberculosis* infection and increased frequencies of regulatory T cells and intracellular expression of FoxP3 [83].

Pleural tuberculosis is an outcome of late hypersensitive reaction to *Mycobacterium tuberculosis* antigens which are released upon rupture of sub pleural caseous focus [75]. Inflammatory process generated in the pleural cavity causes vascular permeability and influx of leukocytes into pleural space, causing the accumulation of fluid and cells [85]. Inflammatory response triggered by the mycobacteria or its antigens is responsible for limiting or aggravating the disease [86]. Production of TGF-β seems to be related to the physiopathology of pleural thickening [87]. In low concentrations, TGF-β possesses pro-inflammatory activity (pleural tuberculosis and healthy contacts of tuberculosis carriers) and anti-inflammatory activity in high concentrations (pulmonary tuberculosis). Systemic inflammatory markers like IL-8, TNF-α and VEGF, characterize pleural tuberculosis whereas elevated levels of the factors involved in cell-mediated immunity such as IL-12p40 and Soluble CD40 ligand (sCD40L) are associated with pulmonary tuberculosis [88]. $CD4^+$ T-cell depletion in macaques resulted in pulmonary tuberculosis dissemination to extra pulmonary sites at very early stages of infection, though $CD4^+$ T-cell deficiency progressed to pulmonary tuberculosis [89]. Dissemination of tuberculosis infection to CNS causes tuberculous meningitis which is serious form of tuberculosis. It accounts for 9.8% of extrapulmonary tuberculosis but kills one third of the infected individuals and leaves 50% of the survivors with disabilities [90-93]. As a consequence of inflammation, the clinical manifestation of central nervous system tuberculosis like hydrocephalus and vasculitis occur, resulting in infarction and causing potentially irreparable neurological damage [94]. Although the causative agent of the disease is *Mycobacterium tuberculosis*, the inflammatory reaction observed in tuberculosis is a result of hypersensitivity reaction which even after bacterial eradication can lead to brain damage. Matrix Metalloproteinases (MMPs) which have been discussed for their role in tissue destruction in pulmonary tuberculosis earlier in this review have their implications in inflammatory tissue destruction in tubercle meningitis as well. Among various types of MMP-s, MMP-2 and MMP-9 digest type IV collagen and laminin, which are found in the basement membrane and play a major role in the breakdown of the blood brain barrier as well as in tissue damage. In central nervous system-Tuberculosis the increased MMP-9 secretion is relatively unopposed by a corresponding rise in tissue inhibitor of MMP-1 i. e. TIMP-1 concentrations, resulting in a matrix-degrading phenotype [95]. Human studies have shown that MMP-9 is not present in the normal cerebrospinal fluid but has been but increased levels of MMP-9 in CSF of tubercle meningitis patients indicating their definite role in complicating the disease [96]. This study demonstrates that the MMP-9 levels persist during the late course of tubercle meningitis which suggests that the MMPs might be associated with the development of late complications.

Adjuvant therapy of tuberculosis with reference to inflammation

World Health Organization (WHO) report of 2007 emphasizes the potential role of adjunctive immunotherapy in addition to the standard chemotherapy, in shortening the duration of tuberculosis treatment [97]. Thomas et al., [98] present the concept of host directed therapeutics that modify the host immune responses or alter metabolic state of the pathogen to optimize inflammatory responses and improve lung pathology [98]. Numerous targets for the host directed therapies have been documented but here we focus on the targets which are related to the inflammatory responses. Calcitriol, the active metabolite of vitamin D, has been found to have multiple roles in tuberculosis therapy. It induces innate as well as adaptive antimicrobial responses i. e. cytokine responses, induction of reactive nitrogen/oxygen intermediates, antimicrobial peptides and IL-12 secretion by antigen-presenting cells. Clinical trials with vitamin D accelerated sputum smear conversion, Increased lymphocyte count, and enhanced the suppressive effect of treatment on monocyte count. Additional effects include increased levels of inflammatory markers and chemokines. Treatment-induced suppression of antigen-stimulated Th1 cytokine responses was enhanced but treatment-induced suppression of antigen-stimulated IL-4, CCL5 and IFN-α secretion was attenuated with adjuvant usage of vitamin-D [99]. Eicosanoids have role in

controlling the inflammatory reactions involved in macrophage response to tuberculosis [99,100]. Several FDA-approved drugs that inhibit enzymes in the eicosanoid pathway are available. Amongst these, aspirin and other non-steroidal anti-inflammatory drugs are used for the treatment of asthma [101]. Aspirin along with ibuprofen (iso-butyl-propanoic-phenolic acid) has been reported to enhance the mycobactericidal effect of pyrazinamide [102]. The therapeutic effects of non-steroidal anti-inflammatory drugs are being applied for controlling host directed therapeutics against tuberculosis. Recent report on sterilization effect of combination of these non-steroidal anti-inflammatory drugs (Aspirin and Ibuprofen) against tuberculosis has been demonstrated which suggest that non-steroidal anti-inflammatory drugs can be promising adjuvants in tuberculosis treatment [103]. Cytokines can be used as potential adjuvants because they intervene the regulation of immune responses at numerous pathways. Patient clinical trials with IFN-γ have shown improved results in tuberculosis therapy, though some limitations are still there [104,105]. TNF-α is an immunomodulator which maintains dormancy of the bacteria and inhibits the generation of active tuberculosis but this activity of the cytokine occurs with generation of high inflammatory response. The adjuvant therapy against TNF-α is used to hamper the destructive effects of its inflammatory response and to potentiate the effects of drugs which act more efficiently on replicating population of bacteria. Wallis et al examined this concept by treating HIV-1-infected pulmonary tuberculosis patients with TNF inhibitor, etanercept at the initiation of tuberculosis drug treatment. Responses to tuberculosis treatment were improved in subjects treated with Etanercept. Improvement in body mass, performance score and number of involved lung zones, cavitary closure and time to sputum culture conversion was observed due to Etanercept treatment. Beside, Etanercept treatment resulted in a 25% increase in CD4 cells in HIV tuberculosis patients [106,107]. Higher cAMP levels have also been reported to inhibit TNF-α production of macrophages [108]. Phosphodiesterase inhibitors have been tested as adjuvants for tuberculosis treatment. The impact of two FDA approved Phosphodiesterase inhibitors (cilostazol and sildenafil) on bacterial survival and disease pathology is documented in murine tuberculosis models. The administration of Phosphodiesterase inhibitors along with standard tuberculosis therapy resulted in shortening the treatment period in *Mycobacterium tuberculosis* infected mice. Improved health measures on gross level and histopathological disease parameters were improved with the therapy [108]. To address the issue of tissue destruction during tuberculosis infection which is mainly caused by up regulation of MMPs, the use of MMP inhibitors has been evaluated [27,29,109]. Role of MMP-1 during tissue degradation in MMP-1 expressing transgenic mice has been studied [110-112]. The alveolar walls of *Mycobacterium tuberculosis*-infected wild-type mice remained intact in areas of macrophage infiltration in contrast, in mice expressing human MMP-1, the alveolar walls were destroyed in areas of infection. MMP-1 inhibitor, R032-3555 has been decreased *Mycobacterium tuberculosis* induced MMP-1 in primary human monocytes [113]. This inhibitor has been also has been for safe human for treatment of rheumatoid arthritis [114]. MMP inhibitor (BB-94) showed increased mortality of infected animals when administered on the day of infection but no significant mortality was observed when treated after one month infection. The immune response was deviated to type-2 cytokine profile. Another animal study with same inhibitor showed that BB-94 treated mice had significantly decreased numbers of pulmonary and blood-borne *Mycobacterium tuberculosis* early during disease, increased collagen deposition within early granulomas and significantly decreased pulmonary leukocyte recruitment when compared to vehicle-treated, *Mycobacterium tuberculosis* -infected mice [111]. The results of these studies are not consistent and much promising, they clarify the role of MMP modulation on tuberculosis phenotype. Antifibrotic therapies seem to have potential for use in tuberculosis because of their potential to reduce lung damage, improve pharmacokinetics of drugs, and allow better entry of protective immune cells into diseased tissues. Their role has been evaluated in lung inflammatory diseases like asthma, Chronic Obstructive Pulmonary Disease (COPD), Idiopathic Pulmonary Fibrosis (IPF) [77,115]. However, these adjuvants have pleiotropic effects and potential toxicities which limit their benefits for treatment of the disease. Pirfenidone which was recently approved for idiopathic pulmonary fibrosis provides one such example [116].

Conclusion

Tuberculosis is not a disease of inadequate immunity, but the disease of imbalanced immune response. The role of inflammation begins with progression of the infection into latency or active disease and lasts till tissue destruction of the host even after eradication of pathogen. Both host and microbe utilize this phenomenon to struggle for their successful survival. Inflammation determines susceptibility of host to contract the disease and worsens the complications of the tuberculosis and its associated diseases. The problems of treatment related complications may arise due to generation of inappropriate inflammatory responses. Thus, in tuberculosis therapy, killing of only pathogen is not mandatory, but the immunological imbalance created due to infection needs to be addressed.

Future Perspectives

The host pathogen interactions, causing immune imbalance, which can be targeted for therapy need to be unveiled. New adjuvant therapeutics and elimination of limitations associated with present adjuvants need to be developed. The genetic factors behind the immune responses must be therapy targeted for the elimination of the disease. Concept of tailor made therapy needs to be followed during treatment of the patients to make treatment beneficial at individual level.

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