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Highlighting the Importance of Matrix Metalloproteinase 1, 8, and 9 Expression during the Progression of *Mycobacterium tuberculosis* Infection

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ABSTRACT

Tuberculosis (TB) is one of the major threats to public health; annually it kills more than 1.5 million people around the globe. Tuberculosis is caused by an intracellular pathogen named *Mycobacterium tuberculosis* (*Mtb*). This *Mtb* enters the lung through the respiratory passage by inhalation in healthy individuals. Infection of this disease starts from the settlement of *Mtb* to the lung alveoli of the host from the external bacilli air droplets. After settlement, the multiplication of *Mtb* results in the induction of innate immunity through the alveolar macrophages. Compared to other infectious diseases, tuberculosis infection was transmitted rapidly by the infected aerosols released from infected persons to healthy persons through the air. After infection, disease development results in the formation of drug-resistance TB (DR-TB) with four subcategories, i.e. Single-drug resistant TB (SDR-TB), multi-drug resistant TB (MDR-TB), extensive drug-resistant TB (XDR-TB), and total-drug resistant TB (TDR-TB). As a result, this DR-TB may act as a major source of TB death due to spontaneous antimicrobial resistance (AMR). This AMR makes the anti-TB drugs ineffective. In the current scenario, researchers are trying to find the drug target to decrease tuberculosis progression instead of drug resistance. The present review reports that the outcome of research studies showed that matrix metalloproteinase (MMP) may act as a suitable target for treating *Mtb* infection with the help of specific proteinase inhibitors. Recent reports have shown the specific role of matrix metalloproteinases 1, 8, and 9 in the disease progression and its role in normal homeostasis mechanism with the help of specific animal models/*In vitro* models.

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1 Introduction

Infectious diseases like tuberculosis (TB), smallpox (SP), and polio (P) have been present since the evolution of humans, and these infectious diseases are primarily caused by *Mycobacterium tuberculosis* (*Mtb*), variola virus, and poliovirus, which will affect the lungs, skin, and brain stem respectively. Recent developments in vaccination technologies resulted in the maximal eradication of smallpox and polio disease development in the human population (Chai et al. 2018; Pollard and Bijker 2020; Kayser and Ramzan 2021; Sakai and Morimoto 2022). As a result, nowadays more attention is given to identifying effective drug targets for treating TB. At present, TB is ranked among the top 10 leading causes of death on a global scale and stands as the primary cause of death resulting from an infectious disease (Tiberi et al. 2018; Dartois and Rubin 2022; Singh 2023). During diseased conditions, the causative pathogen (CP) of *Mtb* spreads through the air when it is released by coughing or sneezing by the infected person. After release into the air, CP travels as an aerosol through the natural ventilation pattern (NVP). As a result of NVP, it reaches the lungs of an uninfected person through inhalation of aerosols. Once *Mtb* reaches the lung alveoli, it will try for multiplication with the help of the host system and colonize the lungs. Majorly the progression of TB occurs in the host system due to the weakening of the host immune response (Jones-López et al. 2016; Patterson and Wood 2019; Dartois and Rubin 2022; Singh 2023). In normal conditions, the progression of initial TB infection cannot be controlled easily, and it may advance to active primary disease (APD), particularly in children. Treatment of APD may result in partial control of *Mtb* progression, and further, it enters a latent state which further weakens the immune system. This progression was typically triggered by the breakdown of granulomas and uncontrolled replication of *Mycobacteria*, leading to disease in the host system's primary and secondary organs (Figure 1). This *Mtb* infection and its progression may also depend on contact with the infected person, social, behavioural, and environmental factors like poor hygiene, alcohol consumption, pollution, and smoking (Lönnroth et al. 2009; Narasimhan et al. 2013; Bhargava et al. 2013; Chandrasekaran et al. 2017; Stewart et al. 2020; Dartois and Rubin 2022; Singh 2023). In the present review, we have shown the unexplored role of matrix metalloproteinases (MMPs) and their sub-classes in the progression of TB.

2 Role of *M. tuberculosis* pathogenesis in the development of tuberculosis

Tuberculosis (TB) is one of the leading causes of mortality spread by the transmission of *M. tuberculosis* (Adami and Cervantes 2015; Bloom et al. 2017; Bussi and Gutierrez 2019; Furin et al. 2019; Sia and Rengarajan 2019; Chai et al. 2020; Boom et al. 2021; Zhou et al. 2021). According to the reports of the Centers for Disease Control and Prevention (CDC), nearly 1.6 million people die due to this infectious disease which affects the lungs. Infection of the disease caused by the settlement of *Mtb* to the lung alveoli of the host from the external bacilli air droplets (Smith 2003; Adami and Cervantes 2015; Cohen et al. 2018; Chai et al. 2020; Boom et al. 2021). After settlement, the multiplication of *Mtb* results in the activation of the innate immune response through the alveolar macrophages through sequential steps involved in disease development (Figure 2) (Smith 2003; Adami and Cervantes 2015; Cohen et al. 2018; Chai et al. 2020; Boom et al. 2021; Lovey et al. 2022; de Waal et al. 2022).

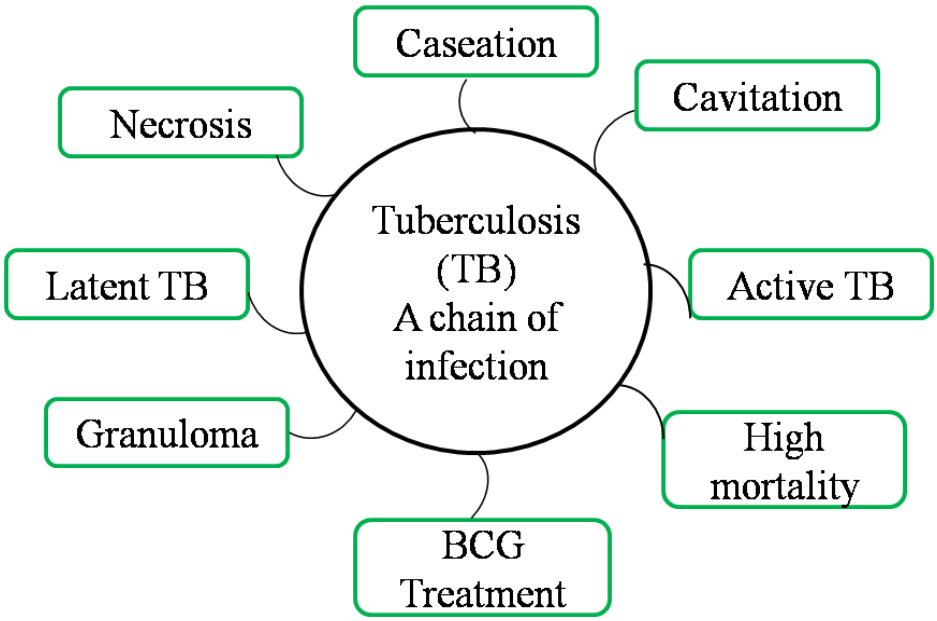

Figure 1 Cyclic diagram showing the chain of infection caused by *Mycobacterium tuberculosis*

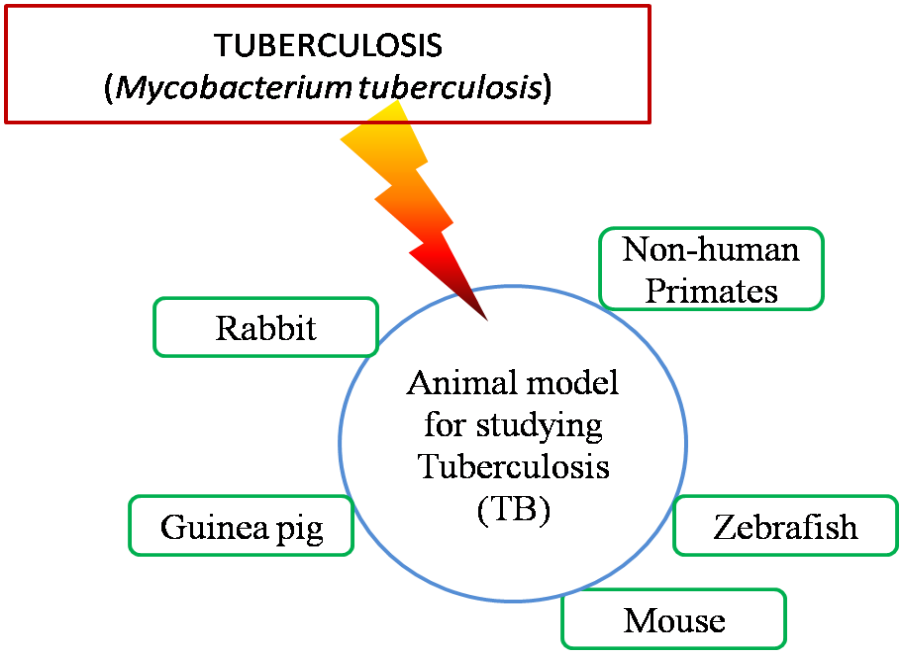

Figure 2 Animal model for studying *Mycobacterium tuberculosis* infection

In disease development, different *Mtb* strains are involved with genotypic resistance. The development of genotypic resistance results in the formation of drug-resistant TB (DR-TB). Later on, DR-TB is further classified into four subcategories i.e. single-drug resistant TB (SDR-TB), multi-drug resistant TB (MDR-TB), extensive-drug resistant TB (XDR-TB), and totally-drug resistant TB (TDR-TB) (Furin et al. 2019; Pontali et al. 2019; Singh et al. 2020; Khawbung et al. 2021; Singh and Chibale 2021).

Recent reports have shown that DR-TB acts as a major source of TB death due to spontaneous antimicrobial resistance (AMR) (Palomino and Martin 2014; Kurz et al. 2016; Murray et al. 2022). This AMR may also reduce the activity of certain drugs used in the treatment of TB including rifampicin, isoniazid, ethambutol, pyrazinamide, ethionamide, moxifloxacin, streptomycin, kanamycin, amikacin, capreomycin, cycloserine, Linezolid, Bedaquiline, Delamanid and Pretomanid (Kurz et al. 2016; Angula et al. 2021; dos Anjos et al. 2022; Ushtanit et al. 2022). Other than reducing the effect of the drug, TDR-TB will make the available first and second lines of anti-TB drugs made it to ineffective (Gothi and Joshi 2011; Vasava et al. 2017; Adeniji et al. 2020; Singh and Chibale 2021; Yusoof et al. 2022). Limitations in drug susceptibility testing lead to develop biomarkers to identify TDR-TB (Singh and Chibale 2021; Yusoof et al. 2022).

3 Impact of Matrix Metalloproteinase in the normal homeostasis mechanism

Matrix metalloproteinase (MMPs) belongs to a superfamily (metzincin) of enzymatic proteins, which depends on zinc and calcium. This MMPs family is highly conserved across different species, and till today, 25 MMPs have been identified in vertebrates, and 24 of them are present in humans (LaFever et al. 2017; Sabir et al. 2019; Laronha and Caldeira 2020). Identified MMPs are responsible for functions that vary from the release of growth factors, acting as membrane-bound enzymes, growth & death receptors, and regulating extracellular matrix in different species. These identified MMPs are further differentiated into five different sub-families: collagenases, gelatinases, stromelysins, elastases, and membrane-type MMPs (Rosenberg 2002; Visse and Nagase 2003; Laronha and Caldeira 2020; Cabral-Pacheco et al. 2020; Zipfel et al. 2020). Representative MMPs of five different sub-families are tabulated in Table 1.

Among the representative MMPs, MMP-1, 3, 7, and 8 are located together in a single gene cluster, which will emphasize their critical role in initial physiological processes. These MMPs are responsible for the tissue remodelling of connective tissues including angiogenesis, morphogenesis, etc. MMP – 1, 8 plays a major role and includes the degradation of triple-helical fibrillar collagen in bone and ligaments. MMP-3 and MMP-7 are responsible for the degradation of extracellular matrix. Thus, the above-listed MMP plays a fundamental digestive process in the maintenance of physiological hemostasis mechanism (Loffek et al. 2011; Cui et al. 2017; Gonzalez-Avila et al. 2019; Cabral-Pacheco et al. 2020; Zipfel et al. 2020). The general functions of different MMPs are indicated in Table 2.

These MMPs are initially synthesized as inactive proenzymes (also known as zymogens), which consist of an N-terminal signal peptide,

Table 1 MMP subfamily and its examples

S. No	Matrix metalloproteinase (MMP) Subfamily	Examples	References
1	Collagenases	MMP-1,8 and 13	Gho et al. 2018; Falconer et al. 2019; Bocaneti et al. 2023
2	Gelatinases	MMP-2, and 9	Hannocks et al. 2019; Ligi et al. 2020; Nikolov and Popovski 2021
3	Stromelysins	MMP-3, and 10	Piskór et al. 2020; Raeeszadeh-Sarmazdeh et al. 2022
4	Elastases	MMP-7, and 12	Hao et al. 2019; Heinz 2020
5	Membrane-type MMPs	MMP-1 to 5	Kumar et al. 2018; Rohlwink et al. 2019; Cabral-Pacheco et al. 2020

Table 2 General functions of MMPs

S.No	Process	Functional activity	References
1.	Development	1. Embryonic development 2. Blastocyst implantation 3. Nerve growth	Loffek et al. 2011; Rohlwink et al. 2019
2.	Homoeostasis	1. Nerve regeneration 2. Bone remodelling 3. Angiogenesis 4. Wound-healing	Loffek et al. 2011; Rohlwink et al. 2019
3.	Reproduction	1. Cervical dilatation 2. Ovulation 3. Endometrial cycling	Loffek et al. 2011; Rohlwink et al. 2019

prodomain, and catalytic domain. Activation of inactive proenzymes results in the cleavage of N-terminal signal peptide by the secretary pathway followed by the prodomain and catalytic domain (Yong et al. 2001; Cerdá-Costa and Gomis-Rüth 2014; Rohlwink et al. 2019; Gomis-Ruth and Stöcker 2023). As a result of cleavage, minimal pro-MMPs are formed in the intermittent stage of MMP activation. Further, activation of pro-MMPs can occur in *in vitro* and *in vivo* conditions. During *in vitro* conditions, the pro-MMPs can be activated using chemical agents like sodium dodecyl sulphate (SDS), thiol-modifying agents and oxidized glutathione. However, *in-vivo* conditions use more complex processes in the activation of pro-MMPs, like recruitments of other MMPs or different classes of proteinases such as neutrophil elastases and plasmin (English et al. 2001; Rosenblum et al. 2007; Vandenbroucke and Libert 2014; Sabir et al. 2019; Zipfel et al. 2020; Almutairi et al. 2023).

To prevent excessive and destructive activity during normal haemostasis mechanism, MMPs activity is subjected to control at multiple levels, including gene expression regulation (both transcriptional and post-transcriptional), proenzyme activation, and the action of natural inhibitors (Wang and Khalil 2018; Gonzalez-Avila et al. 2019; Madzharova et al. 2019; Laronha and Caldeira 2020; He et al. 2023). These inhibitors include α2-macroglobulin found in the bloodstream and tissue inhibitors of metalloproteinase (TIMPs) in the tissues. TIMPs are endogenous proteins that serve as regulators and exhibit tissue-specific, constitutive, or inducible expression. Four members in the TIMP family, known as TIMPs 1-4, inhibit MMP activity through non-covalent binding. TIMP-3 is noteworthy for its ability to act on both MMPs and tumor necrosis factor (TNF)-α converting enzyme (TACE) (Murphy 2011; Gonzalez-Avila et al. 2019; Madzharova et al. 2019; Rohlwink et al. 2019; Laronha and Caldeira 2020; Zapata-Acevedo et al. 2022; He et al. 2023).

4 Role of matrix metalloproteinase (MMP) expression in disease management

The significance of MMPs and TIMPs in maintaining health and their involvement in disease processes has attracted increasing attention. Exploring how the control of these substances influences pathological conditions and their impact on the release of cytokines, reactive oxygen species (ROS), and growth factors could provide valuable insights for improving disease management. Dysregulated MMPs and their TIMPs are notably associated with various pathological conditions, such as matrix weakening, microglial activation, autoimmune diseases, inflammation, tissue damage, cancer development, fibrosis and improper blood vessel formation. However, these substances are involved in additional activity, including cell proliferation, apoptosis, and adhesion, by cleaving bioactive molecules that regulate these activities (Quintero-Fabián et al. 2019; Cabral-Pacheco et al. 2020; Ma et al. 2021; He et al. 2023).

4.1 Role of metalloproteinase 1 (MMP1) as a therapeutic target for the treatment of *M. tuberculosis* infection

Recent reports showed that whenever *Mtb* infected with human primary monocytes results in the regulated MMP1 more effectively

than other MMPs like MMP3, MMP7, MMP8, MMP10, MMP12, and MMP14 (Kumar et al. 2018; Rohlwink et al. 2019; Sabir et al. 2019). Initially, Elkington et al. (2011) reported that an increase in MMP-1 secretion/upregulation might link to TLR-2 signaling instead of live mycobacterial induction in its upregulation. Furthermore, *Mtb* infection enhanced monocyte migration through an extracellular matrix-coated transwell system. Consequently, the upregulation of MMPs led to a functional increase in matrix degradation by the infected cells (Elkington et al. 2011; Randall et al. 2015; Peddireddy et al. 2017; Rohlwink et al. 2019; Sabir et al. 2019; Tiwari and Martineau 2023).

Targeting MMP-1 activity makes it possible to reduce the pathological processes contributing to the morbidity and mortality associated with tuberculosis infection. P-amino-salicylic acid, which has been employed in TB treatment for six decades but with an unclear mechanism of action, inhibits MMP-1 secretion by *Mtb*-infected macrophages (Rand et al. 2009; Elkington et al. 2011; Stek et al. 2018; Sabir et al. 2019; Kirwan et al. 2021). This suggests that an established TB treatment might work by limiting tissue damage. Furthermore, they demonstrated that Ro32-3555, a compound that has been evaluated in phase III clinical trials for arthritis, can effectively suppress MMP-1 activity driven by *Mtb* (Rohlwink et al. 2019; Sabir et al. 2019; Tiwari and Martineau 2023). Since MMP-1 may be responsible for causing matrix destruction in TB, hence it is a promising therapeutic target for mitigating immunopathology in the disease (Elkington et al. 2011; Rohlwink et al. 2019; Sabir et al. 2019; Guler et al. 2021; Tiwari and Martineau 2023).

4.2 Impact of matrix metalloproteinase 9 (MMP 9) in the regulation of immune response

A robust link between the activity and immune response of matrix metalloproteinase 9 (MMP 9) has become increasingly evident. MMPs have been demonstrated to play a role in regulating the immune response to infectious pathogens and the broader inflammatory processes (Lee et al. 2005; Cabral-Pacheco et al. 2020; Quintero-Fabián et al. 2019; Sabir et al. 2019; de Almeida et al. 2022). Multiple investigations have revealed that MMPs, with a particular focus on MMP-9, are expressed during different stages of tuberculosis, such as active cavitary tuberculosis, pleuritis and cases of meningitis. Infection of THP-1 cells with *Mtb* results in an increased expression of MMP-9. Signaling pathways mediated by specific receptors control this upregulation of MMP-9. In tuberculosis (TB) patients, the levels of various MMPs in the blood may vary between genders, but this variation doesn't appear to be associated with the severity of the disease (Hoheisel et al. 2001; Ravimohan et al. 2018; Rohlwink et al. 2019; Sabir et al. 2019).

Azikin et al. (2017) evaluated MMP-9 levels in children who lived in the same household as those with active TB. Their study found no significant differences in the expression levels of MMP-9 between the group of children exposed to TB and those infected with *Mtb*. Furthermore, the levels of MMP-9 were not affected by factors such as sex, age, nutritional status, or the status of BCG immunization (Rohlwink et al. 2019; Sabir et al. 2019). The reported study shows that the extracellular matrix (ECM) plays a vital role in shaping the structure and composition of the granuloma. It influences how different types of white blood cells move in and out of this dynamic environment and may also affect the positioning of various subpopulations of white blood cells within the granuloma (Gonzalez-Juarrero et al. 2001; Taylor et al. 2006; Diller and Tabor 2022). Mice exposed to *Mtb* through inhalation have been categorized into two groups: susceptible and resistant, determined by their survival rates. This division aligns with variations in aspects such as the recruitment of white blood cells, the structure of granulomas, the production of cytokines, and the expression of adhesion molecules. A recent discovery has indicated that when subjected to *Mtb* infection in a laboratory setting, macrophages from a mouse strain known for its resistance to the disease (C57BL/6) produced notably higher levels of MMP-9 mRNA compared to macrophages from a mouse strain known for susceptibility (CBA/J) (Taylor et al. 2006; Carow et al. 2019).

In one study, Taylor et al. (2006) investigated the activity of MMPs in promoting the initial spread of *Mtb* bacilli outside the lungs of the resistant strain. C57BL/6 mice were exposed to about 500 colony-forming units (CFUs) of *Mtb* H37Rv through inhalation. Following infection, they were promptly administered an MMP activity inhibitor called batimastat (BB-94). These findings indicated that the dissemination of viable bacilli into the bloodstream was more pronounced in mice receiving the control vehicle than in those receiving the MMP inhibitor. This suggests that MMPs may play a role in the hematogenous spread of *Mtb* (Taylor et al. 2006; Polena et al. 2016; Rohlwink et al. 2019). While there were statistically significant differences between the groups in terms of CFU counts in the spleen and blood during the early phase of infection at day 14, there was no observable impact on the growth of *Mtb* in the lungs of mice treated with BB-94 compared to those treated with the carrier later in the infection process (Taylor et al. 2006; Ammerman et al. 2018; Zhu et al. 2021).

4.3 Role of matrix metalloproteinase 8 (MMP 8) in the regulation of NF-kB pathway

In tuberculosis (TB), neutrophils were found to produce matrix metalloproteinase-8 (MMP-8) through a process regulated by the NF-kB pathway. This upregulation of MMP-8 secretion by neutrophils led to the degradation of the extracellular matrix, both in laboratory settings and in samples from respiratory specimens of TB patients. The destruction of collagen caused by TB infection was effectively prevented by doxycycline, an approved inhibitor of

MMPs. Neutrophils release MMP-8, a highly effective enzyme capable of breaking down collagen. Elevated levels of MMPs produced by neutrophils are linked to the progression of disease in Central Nervous System Tuberculosis (CNS-TB), suggesting that neutrophils play a role in the immune response and disease progression in human tuberculosis (Price et al. 2001; Green et al. 2009; Ong et al. 2015; Ravimohan et al. 2018; Rohlwink et al. 2019; Sabir et al. 2019; Poh et al. 2021; Lee and Kim 2022; Tiwari and Martineau 2023).

Furthermore, it was also observed that neutrophil extracellular traps (NETs) contained MMP-8 and were elevated in samples obtained from TB patients. Neutrophils were observed surrounding the edges of cavities in the lungs of individuals with pulmonary TB, and the concentration of MMP-8 in sputum samples correlated with the radiological and clinical severity of TB disease. The protein AMP-activated protein kinase (AMPK), a central regulator of catabolic processes, was identified as a driver of MMP-8 secretion by neutrophils. Neutrophils from individuals lacking AMPK secreted lower concentrations of MMP-8. Furthermore, AMPK-expressing neutrophils were detected in lung biopsies from individuals with TB, with evidence of AMPK activation observed in cell nuclei. These findings highlight the significant role of neutrophil-derived MMP-8 in the immunopathology of TB and suggest that it could serve as a potential target for host-directed therapy in the context of this infectious disease (Ong et al. 2015; Ravimohan et al. 2018; Rohlwink et al. 2019; Sabir et al. 2019; Poh et al. 2021; Lee and Kim 2022; Tiwari and Martineau 2023). Besides TB, these MMPs are also involved in developing normal brain and synaptic plasticity. However, aberrant expression of MMPs may lead to neuronal cell death, inflammation, and demyelination in the brain. Further, it develops cognitive impairment due to oral/gut dysbiosis within a host system (Beuron et al. 2019; Behl et al. 2021; Mukilan 2023).

Conclusion

Matrix metalloproteinases (MMPs) belong to a proteolytic family of enzymes and have numerous functions in regulating physiological functions. Some of their important functions include extracellular matrix remodelling, cell migration facilitating, cytokine cleaving, and activation of defensins. These MMPs can result in extracellular matrix breakdown during tuberculosis in the lungs, especially under neutral pH conditions. In normal conditions, MMPs are typically controlled in the body to maintain normal homeostasis mechanisms in the host. During tuberculosis, their uncontrolled activity results in the development of immunopathological processes like tuberculosis, chronic obstructive pulmonary disease, sarcoidosis, and acute respiratory distress syndrome. Dysregulation of MMPs is a significant characteristic of the immunopathology associated with tuberculosis. By downregulating the expression of MMP with the help of some specific protease inhibitors, we can regulate the progress of tuberculosis. The present review laid a path to identify drug targets for tuberculosis as matrix metalloproteinases (MMP) in the near future. Thereby present review focused on the role of MMPs in the maintanence of homeostasis mechanisms and disease progression in a host system. Other than tuberculosis, these MMPs are also involved in brain inflammation and other systematic disorders in a host system. It also opens up the use of MMPs as a potential target for treating neurodegenerative disorders like Alzheimer's disease.

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Author Contributions

SP, and MM performed the conceptualization, study design, original draft preparation, review and editing of the manuscript. PG, GK did the data collection and its organization. HS approved the final manuscript.

Conflicts of Interest

The author declares no conflict of interest to express

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