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Host–Pathogen Interactions in Tuberculosis

Clara Espitia, Eden Rodríguez, Lucero Ramón-Luing, Gabriela Echeverría-Valencia and Antonio J. Vallecillo
Departamento de Inmunología,
Instituto de Investigaciones Biomédicas
Universidad Nacional Autónoma de México
México

1. Introduction

The development of massively parallel DNA sequencing is revealing the scale of mammalian bacterial colonization and suggests that *Homo sapiens* is colonized by between 10^3 and 10^4 bacterial phylotypes. The understanding of the complexity of host-bacterial interactions could explain why only a relatively tiny number of bacteria causing human diseases (Keijser et al., 2008; McKenna et al., 2008; Henderson et al., 2011). Over thousands of years microbes and mammals have co-evolve resulting in extraordinarily sophisticated molecular mechanism permitting the organism to survive together. *Mycobacterium tuberculosis* is one of the best examples of successful coevolution, since the bacilli have infected one third of the human population, but in 90% of the cases without causing overt disease (Bhowruth et al., 2008). The factors that regulate the course and outcome of infection by *M. tuberculosis* are multifaceted and involve a complex interplay between the immune system of the host and survival strategies employed by the bacilli (Mischenko et al., 2004). During the infection process and pathological development of human tuberculosis, *M. tuberculosis* expresses many molecules and recruits others from the host that allow the microorganism to recognize and be recognized by different host receptors. In this way, the knowledge of these interactions at the molecular level is of fundamental importance to understand all the events involved in entry, dissemination and persistence of the pathogenic mycobacteria and in the design of new highly specific therapeutic agents.

In this chapter, we are describing the host and the human pathogen *M. tuberculosis* molecules that are involved in the interactions with innate immune system, Extracellular Matrix Protein (ECM) and fibrinolytic system, the proposal mechanisms of interactions and the biological/pathological consequences are discussed. Also, examples are shown of how genetic variations in host and bacteria regulatory and encoded sequences can affect conditions that influence the relationship between bacteria and their host. Finally considerations are done about how the knowledge of host-pathogen interactions, can be useful in the search of new tools to fight against the disease.

2. Interaction of *M. tuberculosis* with the innate immune system

Tuberculosis is primarily acquired through inhalation of airborne droplets containing the viable bacilli which travel to distal regions of the lung where they are recognized by the pulmonary innate immune system that plays a key role in the recognition of microbes entering via the respiratory route. These early interactions constitute an important link between innate immune response and the subsequent activation of adaptive immune response that although sufficient to contain the microorganisms is enabling to eliminate them. The molecules of bacteria and host involve in these interactions are known as pathogen-associated molecular patterns (PAMPs) and pattern recognition receptors (PRR) respectively (Salgame, 2005).

The PRRs include the Toll-like receptors (TLRs) which are type I transmembrane proteins characterized by an extracellular domain containing leucine-rich repeats and a cytoplasmic tail that contains a conserved region called the Toll/IL-1 receptor (TIR) domain (Medzhitov et al., 1997). Ten human and twelve murine TLRs have been characterized, TLR1 to TLR10 in humans and TLR1 to TLR9, TLR11, TLR12 and TLR13 in mice, the orthologous of TLR10 being a pseudogene. Specific interaction of TLRs with microbial ligands triggering proinflamatory citokines such as TNF-α, IL-1 and IL-12 generated through the adaptor molecule myeloid differentiation primary response protein 88 (MyD88) (Giacomini et al., 2001; Underhill et al., 1999; Kiemer et al., 2008). Moreover, the *in vivo* importance of the TLR-mediated signal in host defense to *M. tuberculosis* was highlighted in studies using mice lacking MyD88, these animals are highly susceptible to airborne infection with *M. tuberculosis*. In contrast, mice lacking individual TLRs are not dramatically susceptible to *M. tuberculosis* infection, suggesting these observations that multiple rather than single TLRs are required for the innate defense against mycobacteria. Remarkably, adaptive immunity is not impaired in MyD88-deficient mice during the course of *M. tuberculosis* infection (Fremond et al., 2004; Scanga et al., 2004; Hölscher et al., 2008).

2.1 Interaction of *M. tuberculosis* with Toll-like receptors

Studies using gene knockout mice have shown a role for TLR2, TLR4, TLR6, and TLR9 (Reiling et al., 2002; Sugawara et al., 2003; Bafica et al., 2005) in protective immunity to mycobacterial infection.

At date, the ligands for TLR2 have been identified and it is now known that TLR2 recognizes *M. tuberculosis* lipoglycans and lipoproteins, as well as and a member of the PE_PGRS family.

2.1.1 Lipoarabinomanan (LAM) and Lipomannan (LM)

LAM and LM are integral parts of the mycobacterial cell wall. They are composed of a carbohydrate backbone made of a *D*-mannan core and a *D*-arabinan domain. Several reports have described a TLR2-dependent cell activation by mycobacterial cell wall lipoglycans (mannose-capped lipoarabinomannan (ManLAM), phosphatidyl *myo*-inositol mannosides (PIM2 and PIM6)). Typically, Man-LAM from pathogenic mycobacteria have been reported to be anti-inflammatory molecules, inhibiting the production of IL-12 and TNF-α and increasing IL-10 production by dendritic cells or monocytic cell lines, whereas

phosphoinositol-substituted LAM from nonpathogenic species are proinflammatory molecules stimulating the production of TNF-α and IL-12 (Means et al., 1999; Jones et al., 2001; Gilleron et al., 2003).

LM, but none of the corresponding LAM, induce macrophage activation dependent on the presence of TLR2 and exerted also a potent inhibitory effect on TNF-α, IL-12p40, and Nitric Oxide (NO) production by Lipopolysaccharide (LPS)-activated macrophages. These results provide evidence that mycobacterial LM bear structural motifs susceptible to interact with different pattern recognition receptors with pro or anti-inflammatory effects (Quesniaux et al., 2004).

2.1.2 LpqH (*Rv3763*) or 19 kDa protein

The 19 kDa cell wall-associated and secreted glycolipoprotein (Garbe et al., 1993), induce apoptosis in differentiated THP-1 cells and monocyte-derived macrophages being this effect TLR2-mediated. This protein also inhibits IFN-γ-regulated MHC-II expression on alveolar macrophages, dependent on TLR2. Although native LpqH is a mycobacterial glycolipoprotein, based upon the use of recombinant where the acylation signal had been removed, it was concluded that it is the polypeptide component of 19 kDa is responsible for signaling through TLR2 and that the lipid moiety is not required (López et al., 2006; Fulton et al., 2004).

2.1.3 LprG (*Rv1441c*) or P27 protein

The LprG is a 27 kDa secreted glycolipoprotein (Gonzalez-Zamorano et al., 2009). It had been shown that after prolonged exposure (>16 h) of human macrophages to this protein, a marked inhibition of MHC-II antigen processing dependent on TLR2 occur. Short-term exposure (<6 h) to LprG stimulated TLR2 dependent TNF-α production. Inhibition of MHC-II antigen processing by mycobacterial lipoproteins may allow *M. tuberculosis*, within infected macrophages, to avoid recognition by CD4 T cells that represent a negative feedback mechanism for control of inflammation that may be subverted by *M. tuberculosis* for immune evasion. As observed with LpqH nonacylated LprG retains TLR2 activity (Drage et al., 2010; Gehring et al., 2004).

2.1.4 LprA (*Rv1270c*)

The LprA a 24 kDa cell wall-associated lipoprotein with no homologs outside the slow-growing mycobacteria induced expression of TNF-α, IL-10 and IL-12. The protein had agonist activity for both human and murine TLR2. LprA also induced dendritic cell maturation as shown by increased expression of CD40, CD80, and MHC-II. In macrophages, prolonged (24 h) incubation with LprA decreased IFN-γ induced MHC-II antigen processing and presentation, consistent with an observed decrease in MHC-II expression. In contrast with LpqH and LprG, only acylated LprA showed the agonist activity (Pecora et al., 2006).

2.1.5 PstS1 (*Rv0934*) or 38 kDa antigen

The 38 kDa a phosphate binding glycoprotein has been considered as an immunodominant antigen for its capacity to evoke a prominent cellular and humoral immune responses in tuberculosis (Espitia et al., 1989a; Zhu et al., 1997). The protein acting through both TLR2

and TLR4, induces the activation of the Extracellular Signal Regulated Kinase (ERK1)/2 and p38 Mitogen-activated protein kinase 1(MAPK1) pathways, which in turn play an essential role in TNF-α and IL-6 expression (Jung et al., 2006).

2.1.6 PE_PGRS33 (*Rv1818c*)

The 45 kDa protein is a member of PE_PGRS family. These sequences were initially described by Poulet and Cole in 1995 as GC rich sequences (PGRS, polymorphic GC repetitive sequence) in the genome of *M. tuberculosis* (Poulet & Cole, 1995). They have a conserved Pro–Glu motif (PE domain) in their N-terminal, and in C-terminal an alanine and glycine rich domain (PGRS domain). Nearly 100 genes belonging to the PE family scattered throughout the *M. tuberculosis* genome (Cole et al., 1998). The PE_PGRS33 is surface exposed protein (Brennan et al., 2001), that elicits TNF-α release from macrophages in a TLR2 -dependent manner. ASK1 (apoptosis signal-regulating kinase 1) is activated downstream of TLR2. ASK1 activates the MAPKs p38 and c-Jun N-terminal kinases (JNK). PE_PGRS33-induced signaling leads to enhanced expression of TNF-α and TNF-α receptor (TNFR1) genes. Release of TNF-α plays the determining role in triggering apoptosis in macrophages challenged with PE_PGRS33 (Basu et al., 2007).

2.2 Interaction of *M. tuberculosis* with non-Toll-like receptors

Several recent findings have indicated that PRRs other than TLRs (non-TLRs) evoke innate immune responses. Among non-TLRs that interact with *M. tuberculosis* are the complement receptors 3 (CR3). The nucleotide-binding oligomerization domain (NOD)-like receptor 2 (NOD2) and members of C-type lectins receptors.

2.2.1 Complement receptor 3 (CR3)

M. tuberculosis can bind to several types of receptors on the surface of mononuclear phagocytes including complement receptors 3 (CD11b/CD18) which is a heterodimer belonging to the leukocyte 2-integrin family. This receptor binds complement fragment C3bi and also contains a carbohydrate binding site. *M. tuberculosis* can bind to the complement receptors via both complement-dependent and independent pathways (Cywes et al., 1997). The presence of human serum containing active complement components was found to enhance the binding of *M. tuberculosis* on the surface of human monocytes and monocyte-derived macrophages. CR3 was identified as the major component in human serum involved in enhancing the adherence and uptake of *M. tuberculosis* by mononuclear phagocytes (Schlesinger et al., 1990). By using affinity blot with C3 complement protein it was found that C-terminal region of *M. tuberculosis* heparin-binding hemagglutinin (HBHA (*Rv0475*) bound human C3. The presence of complement-sufficient serum increased the adherence of the HBHA-coated beads to the J774 cells, suggesting these results that the protein may enhance the adherence and phagocytosis of *M. tuberculosis* to mononuclear phagocytes through the binding of C3 and interaction with C3 receptors on mononuclear phagocytes (Mueller-Ortiz et al., 2001, 2002).

2.2.2 Nucleotide-binding oligomerization domain (NOD)-like receptor 2 (NOD2)

NOD2 also known as CARD15, this protein activates innate immunity in response to peptidoglycan-derived muramyl dipeptide (MDP). Indeed, defects in NOD2 signaling lead

to impaired *in vitro* mycobacteria recognition by human or murine-derived macrophages (Saiga et al., 2011). Studies in macrophages from NOD2-deficient mice indicate that NOD2 mediates resistance to mycobacterial infection via both innate and adaptive immunity (Divangahi et al., 2008).

2.3 C-type lectin receptors involved in the recognition of mycobacteria

C-type lectin receptors are a family of proteins of innate immune system that bind surfactants and mannose-binding lectin protein (MBL). In addition, there are cell-associated C-type lectins, including the mannose receptor (MR), dendritic cell-specific ICAM-3-grabbing nonintegrin (DC-SIGN), DC-associated C-type lectin-1 (Dectin-1) and macrophage inducible C-type lectin (Mincle) (Torreles et al., 2008). Some C-type lectin receptors are expressed on the plasma membrane or on the endosomal/phagosomal membrane, whereas NOD-like receptors are expressed within the cytoplasm. Indeed, distinct patterns of TLR and NOD like receptor-mediated gene expression profiles have been demonstrated in infection with intracellular bacteria (Saiga et al., 2011).

2.3.1 Macrophage Mannose Receptor (MR)

Macrophages primarily use the MR as well as CR3 for the phagocytosis of *M. tuberculosis*. Interaction of pathogenic *M. tuberculosis* with the human MR was first demonstrated by Schlesinger., 1973, and ManLAM was proposed as the molecule responsible for the specific MR-mediated phagocytosis of pathogenic (Schlesinger et al., 1994). It was also demonstrated that engagement of the MR by ManLAM during the phagocytic process directs *M. tuberculosis* to its initial phagosomal niche, thereby enhancing survival in human macrophages in part by limiting phagosome lysosome fusion, being ManLAM responsible for blocks phagosome maturation (Kang et al., 2005). It was also shown that the macrophage MR, may interact with mannose residues of mycobacterial lipoglycoprotein LpqH promoving phagocytosis of mycobacteria (Diaz-Silvestre et al., 2005).

2.3.2 Dendritic-cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN)

This Calcium-dependent carbohydrate-binding protein has specificity for mannose-containing glycoconjugates and fucose-containing Lewis antigens. In recent years, DC-SIGN has gained an exponential increase in attention because of its involvement in multiple aspects of immune function. Besides being an adhesion molecule, particularly in binding intercellular adhesion molecule 2 (ICAM-2) and intercellular adhesion molecule 3 (ICAM-3), it is also crucial in recognizing several endogenous and exogenous antigens. Additionally, the intracellular domain of DC-SIGN includes molecular motifs, which enable the activation of signal transduction pathways (Švajger et al., 2010). Mannosylated moieties of the *M. tuberculosis* cell wall, such as ManLAM or PIMs were previously shown to bind to DC-SIGN on immature dendritic cells and macrophage subpopulations. This interaction reportedly impaired dendritic cell maturation, modulated cytokine secretion by phagocytes and dendritic cells and was postulated to cause suppression of protective immunity to tuberculosis (Geijtenbeek et al., 2003). However, experimental *M. tuberculosis* infections in mice transgenic for human DC-SIGN revealed that, instead of favoring immune evasion of

mycobacteria, DC-SIGN may promote host protection by limiting tissue pathology. Furthermore, infection studies with mycobacterial strains genetically engineered to lack ManLAM or PIMs demonstrated that the ManLAM/PIM–DC-SIGN interaction was not critical for cytokine secretion *in vitro* and protective immunity *in vivo*. The dominant *M. tuberculosis*-derived ligands for DC-SIGN are presently unknown, and a major role of DC-SIGN in the immune response to *M. tuberculosis* infection may lie in its capacity to maintain a balanced inflammatory state during chronic tuberculosis (Ehlers, 2010). Recent studies suggest more varied modes of binding to multiple mycobacterial ligands. Four novel ligands of *M. bovis* BCG that bind to DC-SIGN were identified; chaperone protein DnaK, 60 kDa chaperonin-1 (Cpn60.1), glyceraldehyde-3 phosphate dehydrogenase (GAPDH) and lipoprotein LprG. Of these, only LprG appears to bind DC-SIGN via typical proteinglycan interactions (Carroll et al., 2010). Additional ligands, possibly including the mannosylated 19 kDa (LpqH) and 45 kDa (Apa) glycoproteins had been also proposed as a potential targets of DC-SIGN (Pitarque et al., 2005).

2.3.3 Dendritic cell-associated C-type lectin-1 (Dectin-1)

This is a fungal pattern recognition receptor that binds to β-glucans and triggers cytokine production by facilitating interaction with TLR2 or by directly activating spleen tyrosine kinase (Syk). Recognition of mycobacteria by Dectin-1 has been shown to induce expression of TNF-α, IL-6, and IL-12. The significance of these findings is unclear at present because mycobacteria are not known to contain β-glucans (Yadav & Schorey, 2006; Rothfuchs et al., 2007).

2.3.4 Macrophage inducible C-type lectin (Mincle)

This molecule is expressed in macrophages subjected to several types of stress. Mincle possesses carbohydrate-recognition domain (CRD) within the extracellular region. It has recently been shown that Mincle recognize the trehalose-6,6-dimycolate (TDM, also called cord factor), a mycobacterial cell wall glycolipid that is the most studied immunostimulatory component of *M. tuberculosis*, thereafter modulating macrophage activation. TDM activated macrophages to produce inflammatory cytokines and NO, which are completely suppressed in Mincle-deficient macrophages (Ishikawa et al., 2009).

2.3.5 Pulmonary surfactant protein A and D (Sp-A and Sp-D)

C-type Ca^{2+}-dependent lectins are pulmonary collagenous soluble proteins that are secreted into the alveoli by resident type II alveolar epithelial cells and distal bronchiolar Clara cells. They form a complex structure with lipids and proteins that reduces surface tension of alveoli and promotes lung expansion. These proteins bind to pathogens, mediate uptake into phagocytes, and modulate effector mechanisms such as oxidant production, lung inflammation, and bacterial killing (LeVine et al., 2000). Ferguson and Schlesinger identified ManLAM as a potential ligand of human Sp-D (Ferguson & Schlesinger, 2000). It was also found that purified human Sp-A exclusively binds to alanine and proline-rich antigenic (APA or 45/57 kDa antigen (*Rv1860*) glycoprotein. This result was supported by direct binding of Sp-A to purified APA. Moreover, EDTA addition or deglycosylation of purified

Apa samples completely abolished the interaction, demonstrating that the interaction is Calcium and Mannose-dependent, as expected (Ragas et al., 2007).

2.3.6 Mannose Binding Lectin (MBL)

This 32 kDa protein provides first-line defense against several microbes, the protein possess a collagen-like domain as well as a CRD that binds to high mannose and *N*-acetylglucosamine oligosaccharides present on a range of pathogens, including *M. tuberculosis* (Garred et al., 1997). MBL activates the complement pathway in an antibody-independent manner in conjunction with the MBL-associated serine protease and leads to phagocytosis through the complement or collectin receptors (Berrington & Hawn, 2007).

3. Interaction of *M. tuberculosis* with extracellular matrix proteins

Bacterial species gain access to the human body through different tissues and invasion is generally mediated by bacterial surface and secreted molecules (Sun, 2006). Bacterial colonization, whether benign or pathological, requires the colonizing organism to bind with some avidity to the host. Bacteria have evolved a wide range of molecules, known as adhesins to enable them to bind to selected host molecules. Most high-affinity bacterial adhesins are proteins, and the major targets for them are the host extracellular matrix proteins **(**ECM) which are also present in the cell surface of animal cells (Henderson et al., 2011). Pathogenic bacteria have evolved mechanisms to exploit molecules present in membranes for their own purposes including mediating attachment to target cells through the interaction with ECM proteins such as proteoglycans, fibronectin (Fn) and laminin among others.

Tuberculosis commonly affects the lung but, from the initial focus of infection the bacilli can spread mainly through the blood, but also via lymphatic to other areas of the lung and other organs (Leung, 1999). The dissemination process may allow the bacilli reach regions such as central nervous system, genital tract, intestine, skin, bones, digestive system tissue associated and integumentary system. The ability to spread seems to be determined more by mycobacterial factors since it has been observed that extrapulmonary strains showed a greater ability to spread and were more efficient for the invasion (Mischenko et al., 2004; Garcia de Viedma et al., 2003, 2005).

For many years, it was thought that macrophages were the cells primarily involved in the interaction of tubercles bacilli with the host. However, it is now known that *M. tuberculosis* is also able to invade non-phagocytic cells such as the respiratory epithelial cells and epithelial cells M. Direct adherence and penetration may be important to gain access to the hematogenous and lymphatic systems and therefore dissemination (Menozzi et al., 2002; Teitelbaum et al., 1999). Bacilli also may interact with pneumocytes causing necrosis and destruction of cellular barriers, which could facilitate its passage into the bloodstream and allow the invasion. Binding to ECM may be of relevance to the entry of pathogenic mycobacteria into nonprofessional phagocytic cells (Bermudez et al., 2002).

3.1 Mycobacterial fibronectin binding proteins

Fn is a large and essential multidomain glycoprotein with multiple adhesive properties, functioning as a key link between cells and their ECM. Fn is recognized to be the target

for a large number of bacterial proteins, which are generally considered to function as bacterial adhesins. The ability to bind to Fn has been reported for bacterial pathogens like *Staphylococcus aureus*, *Streptococcus pyogenes* and *Borrelia burgdorferi*, and protozoa like *Trypanosoma cruzi*. Fn plays a vital role in a variety of normal physiological processes, its targeting appears to be another example of the exploitation of a host cell process in the dissemination, establishment and maintenance of infection (Pasula et al., 2002; Henderson et al., 2011). The interaction of Fn with mycobacteria seems to be conserved within the genus. Fn is required for the anti-tumoral effect of *M. bovis* BCG on superficial bladder tumors. Fn is not exposed on normal bladder epithelia, and adhere of BCG cells only occur when uroepithelia is damaged. Blocking of BCG attachment to Fn consequently prevents immune responses and inhibits the expression of anti-tumor (Hudson et al., 1990; Sinn et al, 2008).

3.1.1 Proteins of antigen 85 complex

One of the first proteins described as a Fn binding proteins (FnBPs) were the members of the antigen 85 complex (Abou-Zeid et al., 1988) which consists of three proteins termed antigen 85A, 85B and 85C, encoded by three different genes (*Rv3804c*, *Rv1886c* and *Rv0129c* respectively). They are mycolic acid transferases present in many mycobacteria species. The complex a potent immunogen, is clearly one of the major antigen in the immune response to *M. tuberculosis* infection. For this reason is one of the stronger vaccine candidates (Giri et al., 2006; Romano et al., 2006).

The interaction of antigen 85B with Fn involves the binding of multiple regions of this protein to the collagen-binding domain of Fn (Peake et al., 1993). Peptide mapping of the 84-110 sequence defined residues 98-108 as the minimum inhibitory motif with six residues (FEWYYQ) to be the most important for Fn interaction. This motif forms a helix at the surface of the protein and has no homology to other known prokaryotic and eukaryotic FnBP features and appears to be unique to the mycobacteria (Naito et al., 1998).

3.1.2 Malate synthase G (*Rv1837c*)

This cytoplasmic protein is involved in the glyoxylate pathway. The binding site in malate synthase G (MS) for Fn, lies in a C-terminal region of the protein that is unique to *M. tuberculosis.* The protein is secreted and is anchored on the cell wall by an undefined mechanism. MS expressed in *M. smegmatis* localizes to the cell wall and enhances the adherence of bacteria to lung epithelial A549 cells. Present in the bacterial surface this protein is also able to bind to laminin. These studies show that a housekeeping enzyme of *M. tuberculosis* contributes to its armamentarium of virulence promoting factors (Kinhikar et al., 2006).

3.1.3 Alanine and proline-rich antigenic (APA) (*Rv1860*) or 45/47 kDa antigen

These 40/45 kDa glycoproteins (Espitia et al., 1989b; Dobos et al., 1996) have a very highly conserved alanine and proline-rich 300–350-residue sequence and is apparently unique to mycobacteria. Using synthetic peptides the minimal binding sequence to Fn was determined to be 12 amino acids, 269–280 and sequence necessary for Fn binding is a motif RWFV (273–276). Furthermore, the data suggest that mycobacterial Fn-attachment protein (FAP)

proteins, all of which share the RWFV binding motif, constitute a family of highly homologous proteins that bind Fn in a unique manner (Zhao et al., 1999; Schorey et al., 1996).

3.1.4 PE_PGRS proteins

Although, PE_PGRs are a large family of proteins, the capacity to bind to Fn had been only determine in a few members of the family like Wag22 (*Rv1759c*) antigen (Espitia et al., 1999). More recently, we also found that PE_PGRS33 (*Rv1818c*) and PE_PGRS1 (*Rv0109*) are also bind Fn, being the Fn binding site localized in the PGRS domain, however the motifs involved are unknown (unpublished observations).

3.1.5 Glutamina syntethase A1 (GlnA1) (*Rv2220*)

An essential protein of *M. tuberculosis* that plays a role in nitrogen metabolism. Its enzymatic activity detected in culture filtrates of pathogenic but not of nonpathogenic mycobacteria, has been associated with virulence. Interestingly, we found that GlnA1 was also able to bind to Fn, a feature so far not described in spite of evidence indicating the presence of Fn-binding molecules in the range of 57–60 kDa the GlnA1 molecular mass (Xolalpa et al., 2007).

3.2 Mycobacterial heparin binding protein

Heparin, a sulfated polysaccharide belonging to the family of glycosaminoglycans, has numerous important biological activities, associated with its interaction with diverse proteins. Heparin and the structurally related heparan sulfate are complex linear polymers comprised of a mixture of chains of different length, having variable sequences. Heparan sulfate is ubiquitously distributed on the surfaces of animal cells and in the ECM. It also mediates various physiologic and pathophysiologic processes. In *M. tuberculosis* an heparin-binding protein has been identified.

3.2.1 Heparin-binding hemagglutinin (HBHA) (*Rv0475*)

In 1996, Menozzi *et al*. identified a mycobacterial protein of 199 amino acids with a molecular weight of 28 kDa that binds heparin (Menozzi et al., 1996). This protein promotes the binding of rabbit erythrocytes and mycobacterial aggregation. Antibodies against HBHA inhibit haemaglutination, bacterial aggregation and binding the bacteria to epithelial cells. HBHA binds to sulfated carbohydrates from a region rich in lysine and proline, thus promoting its binding to host tissues (Menozzi et al., 1998). Later, it was demonstrated that this protein is involved in extrapulmonary dissemination in a mouse model of tuberculosis, bacteria mutated in HBHA decreased spread to the lung, liver and spleen and this ability was restored by complementing the mutants with wild-type gene. These results suggest that HBHA is essential for the escape of mycobacteria in the lung and the establishment of extrapulmonary (Pethe et al., 2001).

Menozzi *et al*. showed in 2006 that this protein induces a reorganization of the actin filaments in a barrier of endothelial cells, but does not affect the tight junctions. This protein mediates the binding and internalization of mycobacteria in human laryngeal epithelial cell line (HEp-2) and type II pneumocytes cell line (A549). Apparently lysine rich C-terminal

region is mediating these biological effects (Menozzi et al., 2006). In addition to be an important adhesin in tuberculosis HBHA is also an important antigen.

3.3 Mycobacterial laminin binding proteins

Laminin is a large (900 kDa), highly glycosylated multidomain protein found in all human tissues. The laminins are an important and biologically active part of the basal lamina, influencing cell differentiation, migration, adhesion as well as phenotype and survival. Laminins are trimeric proteins that contain an α-chain, a β-chain, and a γ-chain. The trimeric proteins intersect to form a cross-like structure that can bind to other cell membrane and ECM (Timpl et al., 1979; Aumailley et al., 2005). Adhesion to laminin it is a starting point of tissue invasion for many pathogenic bacteria. Mycobacterial protein capable of binds laminin had been also identified.

3.3.1 Histone-Like Protein (HLP) (*Rv2986c*) or HupB protein

A cationic surface protein of twenty amino acids was identified as laminin binding protein in *Mycobacterium lepra*e (ML-LBP21). This cell wall protein increased the binding of mycobacteria to the surface of Schwann cells through its binding to laminin-2 α chains. ML-LBP21 showed 78% of identity with the HupB/HLP protein of *M. tuberculosis* which is also able to bind to laminin of cell surface of murine sarcoma, epithelial cells and human pneumocytes (Prabhakar et al., 1998; Shimoji et al., 1999; De Melo et al., 2000). In addition, two heparan sulphate binding sites were found in Hlp (Portugal et al., 2008).

3.3.2 Early Secretory Antigenic Target (ESAT-6) (*Rv3875*) or EsxA protein

Comparative studies have identified 16 regions of difference (RD1-16) between the genomes of *M. tuberculosi* and *M. bovis* BCG, of which one deletion, termed RD1, is absent from all *M. bovis* BCG substrains currently used as vaccines. RD1 includes 15-gene locus (ESX-1), which encodes a secretion system type VII that enables the secretion of several proteins including ESAT-6 and CFP-10. Both proteins have been considering relevant for cell immune response against tuberculosis bacilli. ESAT-6 has recently been demonstrated to cause haemolysis and macrophage lysis and also causes cytolysis of type 1 and type 2 pneumocytes. Since both types of pneumocytes express membrane laminin, and ESAT-6 exhibits dose-dependent binding to purified human laminin, these observations suggest that the specific association of ESAT-6 with the bacterial surface is mediated thought laminin (Kinhikar et al., 2010).

3.3.3 Mammalian Cell Entry operon (MCE) proteins

Although, the host receptor for MCE proteins is unknown, it is important to mention that *mce* genes encode adhesins and invasins proteins located on the surface of mycobacteria. The first adhesion of this operon was by Arruda *et al*. in 1993; by using a gene library of *M. tuberculosis* they were able to confer to non-pathogenic *Escherichia coli* the ability to invade epithelial HeLa cells (Arruda et al., 1993). Subsequently, it was demonstrated the existence of other genes arranged in an additional *mce* operons (Parker et al., 1995).

The role of membrane protein MCE-1A in invasion of mycobacteria was demonstrated *in vitro*, this protein induces membrane invagination and entry into HeLa cells. The processes

were inhibited with cytochalasin D and nocodazole indicating that rearrangements in microtubules and filaments are necessary to membrane invagination MCE-1A-mediate. The activity of this protein is given by a domain located in the central region of the protein called INV-3 (Lu et al., 2006). By comparing the predicted secondary structure for MCE-1A, MCE-2A, MCE-3A and MCE-4A proteins was found that there is 70% similarity and contain domains alpha/beta. On analysis by predicting the structure of proteins is found that the beta domain is probably involved in cell binding (Mitra et al., 2005).

4. Pathogen interaction with the fibrinolityc system

The fibrinolytic system is composed by the zymogen plasminogen (Plg), that is activated to serine protease plasmin (Plm) by tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). The activity of tPA and uPA is regulated by plasminogen activation inhibibors 1 and 2 (PAI-1 and PAI-2), whereas Plm activity is regulated by α-2 antiplasmin and α-2 macroglobulin. Plm degrades fibrin deposition in blood cloths and also can activate latent matrix metalloproteinases (MMPs) and other protein molecules. During infectious diseases, the Plg-Plm system also called fibrinolytic system; suffer alteration in their balanced expression, caused mainly by inflammation, besides the binding and interaction of some pathogen molecules with components of this system.

In recent years, several studies have suggested important roles for fibrinolityc system in bacterial infections. The microorganims interact with the Plg-Plm system in different ways; by immobilizing Plg on their surfaces through Plg receptors (PlgR) an event that conducts to activation of Plg by host plasminogen activators (PAS) to generate enzymatically active Plm, or by expressing molecules that can activate Plg by themselves. PlgR have been detected in virus (Chaipan et al., 2009), fungus (Crowe et al., 2003), parasites (Avilán et al., 2011) and bacteria. Among bacteria are *Borrelia burgdorferi* (Fuchs et al., 1994), *Escherichia coli* (Kukkonen et al., 1998; Lähteenmäki et al., 1993; Parkkinen et al., 1991), *Salmonella typhimurium* (Korhonen et al., 1997; Kukkonen et al, 1998; Lähteenmäki et al., 1995), *Neisseria meningitidis* (Ullberg et al., 1992) and *Haemophilus influenzae* (Sjostrom et al., 1997) and group A, B and C of streptococci (Lähteenmäki et al., 2001b; Coleman & Benach, 1999). In contrast to the high number of PlgR described in bacteria, only a few PAs has been identified, the plasminogen activator in *Yersinia pestis* (Pla) (Perry & Fetherston, 1997; Sodeinde et al., 1992), the staphylokinase (SK) of *Staphylococcus aureus* (Esmon & Mather, 1998; Lijnen et al., 1994) and the streptokinase (SAK) of *Streptococcus pyogenes* (Li et al., 1999; Sun et al., 2004).

Pla is an aspartic protease that cleaves Plg at the same peptide bond as tPA and uPA. It is also an adhesin with affinity for ECM and laminin (Kukkonen et al., 2001; Lähteenmäki et al., 2001a, 2001b). SAK and SK are not enzymes themselves, but they form 1:1 complexes with Plg, inducing conformational changes in Plg that allows its activation to Plm. SK in bacterial virulence has been studied most thoroughly in group A streptococci (GAS), which is an invasive pathogen that causes diseases ranging from mild pharyngeal and skin infections to potentially fatal disorders, such as toxic shock syndrome. GAS infects only humans and is specific for human Plg and the role of SK and Plg in GAS infection was confirmed in transgenic mice expressing human Plg (Sun et al, 2004).

Adherence to ECM and Plg activation on bacteria surface either by host or bacteria owns PAs seems to be the mechanisms used for bacteria to colonize and invade the host tissues.

Since similar mechanisms are typical for tumor cell migration and invasion (Mignatti & Rifkin, 1993) where Plm directly degrades laminin, a major glycoprotein of basement and indirectly damages tissue barriers by activating MMPs, the term "bacterial metastasis" is now used in analogy to tumor cells metastasis (Plow et al., 1999; Läteenmäki et al., 2000, 2005).

It is worth of note that although the list of microorganism that possess PlgR is large, many of the identified receptors belong to a group of surface-localized housekeeping enzymes that enhance virulence of several, mainly Gram-positive bacterial species; even though the mechanism of their secretion into the cell surface is not known (Pancholi & Chhatwal, 2003). It is also remarkable that some of PlgR also bound to ECM proteins. Together these observations suggest that Plm-mediated fibrin degradation could be a mechanism that advances the spread of invasive bacteria within the mammalian host (Sun et al., 2004).

4.1 Mycobacteria interactions with human fibrinolytic system

In the course of mycobacterial infections the fibrinolytic activity demonstrated a remarkable increased, the first publication in this field was issued by Smokovitis and colleagues in 1976, showed that intradermicaly inoculation of *M. bovis* BCG in rabbits triggered lesions in the dermis, with increment of focal fibrinolytic activity caused by a PA detected in lesions fluids and by histology and fibrin slide technique; 2 weeks later, when hypersensitivity to the *M. bovis* BCG vaccine became pronounced and caseous centers developed, fibrinolytic activity was particularly high (Smokovitis et al., 1976). An intact coagulation mechanism, including tissue factor generation, appears to be important for the development of skin test induration in humans skin since anticoagulation with warfarin decreased skin test induration and tissue factor generation, but lymphocyte transformation remained unchanged (Edwards & Rickles, 1978).

Macrophages obtained from infected mouse with *M. bovis* BCG and challenged in culture with protein-purified derivative (PPD), had increased plasminogen activator activity that was dependent of presence of T cells, macrophages obtained from infected animals without boosting showed less fibrinolytic activity that those stimulated with PPD and the stimulation was abolished by depletion of T cells (Gordon & Cohn, 1978).

Together these observations indicate that the fibrinolytic system could play an integral role in the tuberculosis inflammatory response. The participation of Plg-Plm system in inflamation has been documented during the last decade. It has been demonstrated that, TNF-α induced the expression of PAI-1 and uPA in adipocytes and in human pulmonary artery cells respectively (Pandey et al., 2005; Wu & Aird, 2005). PAI-2 transcription is also upregulated under the influence of TNF-α in fribrosarcoma cells (Medcalf et al., 1988). Transcription of urokinase receptor (uPAR), protein located in the membrane of numerous cell types, is influenced by TGF-β (Lund et al., 1991). tPA transcription is downregulated by TNF-α in human umbilical vein endothelial cells (Schleef et al., 1988), whereas in fibroblasts from human pulp and gingival fibrolasts TNF-α and IL-1 induce a significant increase of tPA (Chang et al., 2003).

In pleural effusions of tuberculosis patients levels of TNF-α were higher than in complicated parapneumonic and cancer patients, whereas tPA concentration was lower Plg and PAI-1

levels were higher in tuberculosis patients than the other groups. (Aleman et al., 2003). Lu and collaborators, compared the concentration of components of fibrinolytic system in pleural and ascytic fluid from tuberculosis, cancer and liver cirrhosis patients, the results showed higher levels of uPA and uPAR from tuberculosis and cancer patients with respect to cirrhosis patients, whereas tPA level was higher in cancer and cirrhosis patients than tuberculosis patients. PAI-1, Plg and Plm levels in tuberculosis patients where statistically higher than those levels in cirrhosis and cancer patients (Lu et al., 2007).

Serum level of soluble uPAR (suPAR) in tuberculosis patients was analyzed in a community from Guinea Bissau, the results showed an elevated level of suPAR in active tuberculosis; decreasing levels of suPAR where associated with treatment, whereas lower levels of suPAR where related with survival (Eugen-Olsen et al., 2002).

The protease activity of Plm plays an important role in the turnover of ECM in a mice model of *Mycobacterium avium* infection, whereas early dissemination to organs was observed in Plm and tPA deficient mice. The authors also demonstrated that fibrin deposition and Fn increased in Plg deficient mice during the infection in comparison with wild type mice (Sato et al., 2003).

The first evidence of the presence of PlgR and PAs in *M. tuberculosis* was reported by Monroy and collaborators; the lysine-dependent binding of Plg to mycobacteria was demonstrated by FACScan analysis and affinity blotting assays. The specificity of binding and the participation of lysine residues in mycobacterial protein-Plg interaction were tested in the presence of 0.1, 1, and 2 M ε-aminocaproic acid (EACA), a lysine analog. Plg binding proteins of 30, 60, and 66 kDa detected in bacteria protein extracts was abolished by this lysine analog. Furthermore, both soluble protein and total protein extracts could activate Plg only in presence of fibrin matrices, suggesting these results, that Plg activation by *M. tuberculosis* requires attachment of Plg to a target molecule. Moreover, addition of α-2 antiplasmin did not significantly decrease activation of Plg by mycobacterial extracts, showing that pathogen-associated Plm activity is not blocked efficiently by host serpins (Monroy et al., 2000).

Besides, a recently study revealed the identity of several Plg-binding proteins present in *M. tuberculosis* and that Plg bound to mycobacterial receptors is converted into Plm by tPA, the mammalian Plg activator. By proteomic analysis together with ligand blotting assays the identity of several Plg-binding spots in the mycobacteria soluble extracts and culture filtrate proteins was determined. In ligand blotting assay in polyvinylidene difluouride (PVDF) membrane with mycobacterial proteins 2D-SDS-PAGE-resolved reactive spots bound to Plg were detected using an anti-Plg antibody, then by N-terminal sequencing and/or mass spectrometry (MS) fifteen different proteins were identified from reactive spots, identified proteins correspond to DnaK (*Rv0350*), GroES (*Rv3418c*), GlnA1 (*Rv2220*), antigen 85 complex (*Rv3804c*, *Rv1886c* and *Rv0129c*), Mpt51 (*Rv3803c*), Mpt64 (*Rv1980c*), PrcB (*Rv2110c*), MetK (*Rv1392*), SahH (*Rv3248c*), Lpd (*Rv0462*), Icl (*Rv0467*), Fba (*Rv0363c*), and EF-Tu (*Rv0685*). Interaction of Plg with these proteins was inhibited by the lysine analogue EACA, indicating that the binding was mediated by lysine residues. Among of identified *M. tuberculosis* PlgRs; only DnaK, PrcB, GroES, and EF-Tu have the C-terminal lysine.

In same work, binding of Plg to DnaK, GlnA1, and antigen 85B was confirmed with recombinant proteins by ELISA and ligand blotting assays. These results confirmed findings

Mycobacterial protein targets	Host receptors	Binding sites	References
LpqH	TLR2	Unknown	López et al., 2006
	MR	Ch	Diaz-Silvestre et al., 2006
	DC-SIGN?	Ch?	Pitarque et al., 2006
LprG	TLR2	Ch	Drage et al., 2010
	DC-SIGN	Ch	Carroll et al., 2010
LprA	TLR2	Unknown	Pecora et al., 2004
APA	Sp-A	Ch	Ragas et al, 2007
	Fn	^{273}RWFV^{276}	Schorey et al.,1996
	DC-SING?	Ch?	Pitarque et al., 2006
Hlp	Hs	Gly^{46} to Ala^{60}, Thr^{31} to Phe^{50}, C-terminus, Lys rich residues	Portugal et al., 2008 Shimoji et al., 1999
	Lm	C-terminus, Lys rich residues	Soares de Lima et al., 2005
HBHA	Hs	C-terminus, Lys rich domine	Menozzi et al., 1996 Pethe et al., 2000
MS	Fn	40 aa C-terminal region	Kinhikar et al., 2006
	Lm	Unknown	Kinhikar et al., 2006
ESAT-6	Lm	Unknown	Kinhikar et al., 2010
PE_PGRS33	TLR2	Unknown	Basu et al., 2007
	Fn	PGRS domain	Unpublished work
Wag22	Fn	PGRS domain	Espitia et al., 1999
PE_PGRS1	Fn	PGRS domain	Unpublished work
DnaK	DC-SING	Unknown	Carroll et al., 2010
	Plg	Unknown Lys residue	Xolalpa et al.,2007
GlnA1	Fn	Unknown	Xolalpa et al., 2007
	Plg	Unknown Lys residue	Xolalpa et al., 2007
SahH	Plg	Unknown Lys residue	Xolalpa et al., 2007
Lpd	Plg	Unknown Lys residue	Xolalpa et al., 2007
Icl	Plg	Unknown Lys residue	Xolalpa et al., 2007
EF-Tu	Plg	Unknown Lys residue	Xolalpa et al., 2007
MetK	Plg	Unknown Lys residue	Xolalpa et al., 2007
Fba	Plg	Unknown Lys residue	Xolalpa et al., 2007
Antigen 85 complex	Fn	^{98}FEWYYQ^{103}	Naito et al., 1998
	Plg	Unknown Lys residue	Xolalpa et al., 2007
Mpt51	Fn	Unknown	Naito et al., 1998;
	Plg	Unknown Lys residue	Xolalpa et al., 2007
PrcB	Plg	Unknown Lys residue	Xolalpa et al., 2007
Mpt64	Plg	Unknown Lys residue	Xolalpa et al., 2007

Mycobacterial protein targets	Host receptors	Binding sites	References
GroES	Plg	Unknown Lys residue	Xolalpa et al., 2007
Cnp60.1	DC-SIGN	Unknown	Carroll et al., 2010
GAPDH	DC-SIGN	Unknown	Carroll et al., 2010

Abreviations:
Ch Carbohydrates
Hs Heparan sulphate
Lm Laminin
Plg Plasminogen
MR Mannose Receptor

Table 1. Host-Mycobacteria proteins involved in interactions.

with native proteins reported before, that the interaction involved lysine residues. In addition Plg bound to recombinant mycobacterial proteins was activated to Plm tPA activator (Xolalpa et al., 2007).

Until now, our results show that *M. tuberculosis* possesses Plg binding and activating molecules present in the soluble protein extracts; based in these evidences works are in progress to identify potential PA in mycobacteria. Considering that interaction with the Plg system promotes damage of extracellular matrices as well as bacterial spread and organ invasion during infection, this suggests a common mechanism in migration of eukaryotic and prokaryotic cells that could be used by *M. tuberculosis* in disease process. *M. tuberculosis* possesses several Plg receptors suggesting that bound Plg to bacteria surface can be activated to Plg, endowing bacteria with the ability to degrade ECM and basal membranes proteins contributing to tissue injury in tuberculosis.

5. Influence of genetic variations in host-mycobacteria relationship

Human tuberculosis results from the interactions between host and bacteria, the degree to which genetic variations of both human and mycobacteria influence this relationship has become elucidated.

5.1 Mycobacterial genetic polymorphisms

Massively DNA sequencing and comparative genomic, together with in *vitro* and *in vivo* models of *M. tuberculosis* infection are contributing to define how different clinical genotypes of *M. tuberculosis* affect the innate immune response. There is now evidence that strain variation can lead to variable virulence phenotypes and can evoke or suppress host immune response (López et al., 2003).

Recently direct role for strain-variation-associated virulence in suppressing host immune response and inducing hyperlethality in mice documented in a subset of clinical isolates belonging to the W-Beijing family where the presence of a polyketide synthase-derived phenolic glycolipid endowed the strains with hypervirulent phenotype (Reed et al., 2004). A recent report also showed how the cyclopropane modification of trehalose dimycolate was critical to induce a pro-inflammatory response during the first week of infection in mice (Rao et al., 2005).

On the other wise, genetic polymorphism in *M. tuberculosis* genome is given by the presence of insertion sequence 6110 (IS*6110*). About 23 copies of this sequence are distributed along the genome. Molecular tipification based on number and localization of the IS*6110* in *M. tuberculosis* clinical isolates have been used for several molecular epidemiology studies.

However, the sequence can be inserted in promoter region of regulatory genes, modifying the expression the genes they regulate, an example is the presence of IS*6110* in the promoter region of *phoP* of *M. bovis* strain B, a multidrug resistant and hypervirulent strain that was responsible for a nosocomial outbreak of tuberculosis in Spain (Soto et al., 2004). Many copies of IS*6110* has been found in or near of *pe/ppe* genes of *M. tuberculosis* strain 210, responsible of several cases of tuberculosis in Los Angeles, California USA suggest the possibility that the insertions could be mediating recombination of these sequences that result in changes that endowed the bacteria with high capacity for transmission and/or replication (Barnes et al., 1997; Beggs et al., 2000).

PE/PPE family also showed important variation in their coded sequences. Analysis of mutations in PPE38 gene of *M. tuberculosis* clinical isolates representing all major evolutionary lineages, show hypervariability of the PPE38 region consequence of the combination of a high frequency of IS*6110* insertion events, IS*6110*-associated recombination/deletion events, homologous recombination and gene conversion events (McEvoy et al., 2009).

It is known that one of the most important sources of genetic variability in *M. tuberculosis* complex is given by PE/PPE gene family (Cole et al., 1998; Fleischmann et al., 2002). Sequence of *pe_pgrs33* gene from 123 *M. tuberculosis* clinical isolates showed variations relative to PE_PGRS33 sequence from H37Rv in 84 (68.3%) of the 123 isolates. Sequence variations included insertions, deletions and both as well as single nucleotide polymorphisms (SNPs). Variations were more frequently found in the C-terminal PGRS domain of PE_PGRS protein and affecting one or more of the glycine-alanine repeats. These variations could potentially account for some of the differences in their ability to evade the host immune system, and this idea contribute to support the role of the PE_PGRS family in antigenic variation (Talarico et al., 2005).

Furthermore, the study of variations in PE_PGRS33 gene from 649 *M. tuberculosis* clinical isolates showed a possible association of major changes (large insertions/deletions or frameshift mutations) in the PE_PGRS33 protein with clustering of tuberculosis cases and the absence of cavitations in the lungs, in contrast with patients infected with *M. tuberculosis* isolates having any or minimal changes in the protein (Talarico et al., 2007). Basu et al., 2007 also observed that deletions within the PGRS domain attenuate the induction of TNF-α-mediated by PE_PGRS33 through its TLR2. Also in this work was observed that the induction of TNF-α was specific of PE_PGRS33 and not a common feature of the PE_PGRS family, since PE_PGRS48 and PE_PGRS62 did not induced production of TNF-α at the same level of the PE_PGRS33. These results provide evidences that variations in the polymorphic repeats of the PGRS domain modulate the innate immune response (Basu et al., 2007).

It has been observed that the PE_PGRS genes are differentially expressed in different strains of *M. tuberculosis* during growth *in vitro* (Flores et al., 2003; Dheenadhayalan et al., 2006) and *in vivo* (Delogu et al., 2006). Interestingly, expression of many of these proteins seems to be widely regulated by several conditions (Voskuil et al., 2004; Vallecillo & Espitia, 2010). In addition to that, the extreme polymorphism found among the clinical isolates, suggests that they could be a major source of antigenic variation in *M. tuberculosis* (Talarico et al., 2005; Santillan et al., 2006). PE_PGRS16 and PE_PGRS26, genes are inversely regulated during persistent of *M. tuberculosis* infection, suggesting that differential expression of these two PE_PGRS genes may have a role in latency. The variations in these sequences were also studied in 200 strains, 102 (51%) and 100 (50%) showed variations within the PE_PGRS16 gene and the PE_PGRS26 gene, respectively. Variations consist in insertions and deletions, frameshifts, and SNPs. Frameshifts are predominant in PE_PGRS16 gene and in-frame deletions in PE_PGRS26 gene. The observed sequence variations could impact the function of these protein and could be asociated with different clinical manifestations of tuberculosis, but remains to be understood the specific role that these genes play in *M. tuberculosis*-host interaction (Talarico, et al., 2008).

Sequence analysis of the coded sequence of PPE18 a vaccine candidate in 225 clinical isolated of *M. tuberculosis* showed an important variability that must be considered when potential vaccine candidates are selected and evaluated. Evaluation of genetic variability could provide important information regarding the ability of the immune response induced by a vaccine candidate to recognize different field strains of *M. tuberculosis* (Hebert et al., 2007).

Differential gene expression also can contribute to modify the host-pathogen interactions. It has been demonstrated that HBHA, the heparin binding protein is differentially expressed during the infection with *M. tuberculosis*, showing a higher expression early infection when the bacteria spread from the primary site of infection. In addition, it was also found that *hbha* gene is up regulated in epithelial cells but not in macrophages (Delogu et al., 2006).

Mutation in *Rv0444* gene that codified for the anti-sigma factor K increased the expression of MB83 antigen in *M. bovis* BCG and *M. bovis* clinical isolates compare with the very low expression of this protein in *M. tuberculosis* (Charlet et al., 2005; Saïd-Salim et al., 2006).

In a recent work, genome sequences of 21 phylogeographically diverse strains of *M. tuberculosis* complex (16 *M. tuberculosis* and 4 *M. africanum* strains representative of the six human *M. tuberculosis* lineages, and one strain of *M. canettii*) were carried out. The presence of 491 human T cell epitopes experimentally determined was evaluated from the genome database. The result of the analysis showed that known human T cell epitopes are highly conserved suggesting these observations that the hyperconservation of T cell epitopes in *M. tuberculosis* is consequence of a strong selection pressure, perhaps because the immune response they elicit in humans, is essential for the survival of an infected individual, and might be partially beneficial to the pathogen. One potential mechanism by which the mycobacterium could benefit from human T cell recognition is that human T cell responses are essential for *M. tuberculosis* to establish latent infection and one effective transmission to new susceptible host (Comas et al., 2010). One important limitation of this study was the exclusion of PE/PPE genes, because as it has been commented that the sequence variations into some of these genes contributed in significant form to the dynamical parasite-host relation.

According to the observations of Comas *et al*. sequence analysis of genes encoding a major *M. tuberculosis* antigens ESAT-6, TB10.4, and antigen 85B from 88 clinical isolates of *M. tuberculosis* revealed no variability in the genes *esx*A and *esx*H in all isolates. In the case of *fbp*B (antigen 85B) only one synonymous SNP located at position 714 bp of the gene sequence, among 39 (44.3%) of the 88 strains sequenced (Davila et al., 2010).

5.2 Host genetic variability

The severity of tuberculosis disease is controlled not only by genetics variations at the level of the bacteria but also by host disparities. The presence of SNP (T597C) in TLR2 among 2 groups of Vietnamese adults with pulmonary or meningeal tuberculosis suggests a strong association of TLR2 variation with meningeal tuberculosis. The authors hypothesize that polymorphisms in genes of the innate immune response may influence the host response resulting in increased susceptibility to disease causing by some bacterial lineages but not others (Caws et al., 2008).

Crohn's disease itself resembles a chronic intestinal granulomatous infection seen in animals called Johne's disease, which appears to be caused by *Mycobacterium avium* spp. *paratuberculosis* trigger (Berrington & Hawn, 2007) a controversy exists as to whether Crohn's disease has an environmental or infectious trigger. Frameshift mutations in the N-terminal leucine-rich region of NOD2 have been associated with Crohn's disease in adults. More recently, NOD2 variants were found to be associated with susceptibility to tuberculosis in an African American population. In light of these findings, the importance of NOD2-mediated immunity during a chronic mycobacterial infection requires further study (Austin et al., 2008).

In a study from Mexico, several variants of Sp-A and Sp-D were associated with susceptibility to tuberculosis (Floros et al., 2000). These results have not been verified in an independent cohort, and the functional significance of the variants has not been reported. The continued identification of *M. tuberculosis* genes or host-encoded will ultimately enhance our knowledge of the complex and highly dynamic interaction between the pathogen and host (Zahrt et al., 2003).

6. Adhesins as therapeutic targets

The emergence of *M. tuberculosis* Multidrug-resistant strains is now a major public health problem all over the world. In this context, it is highly critical to develop a new strategy for the treatment of infected patients that supplements the conventional antimycobacterial chemotherapeutic drugs. More precise understanding of the host-bacteria interactions will pave the way for the development of an effective drug. In this way, targeting bacterial colonization through blockade of selective adhesins could be therapeutically useful (Ofek et al., 2003; Klemm et al., 2010). There are a number of examples where inactivation of FnBP genes or antibodies to FnBPs has resulted in decreased bacterial colonization/virulence (Rennermalm et al., 2001; Rivas et al., 2004). Clinically, most work has been carried out on the humanized monoclonal antibody tefibazumab, which selectively binds *S. aureus* ClfA (Hetherington et al., 2006). In tuberculosis, patient sera containing anti-HBHA antibodies neutralize the entry of *M. tuberculosis* to epithelial cells, suggest that antibody to HBHA may

play a role in protection against mycobacterial extrapulmonary dissemination (Shin et al., 2006).

Some important advances of the interaction of mycobacteria and host has been elucidated but there is more questions to answer. *M. tuberculosis* as has been shown in this chapter, posseses multiple and diverse molecules that targeting innate immune system, ECM and fibrinolytic system. The study of the molecular interactions to define, binding motifs, and specificity of these interactions is crucial in the search of new molecular targets. Bacteria receptors that result in colonization and invasion are likely to be targeted.

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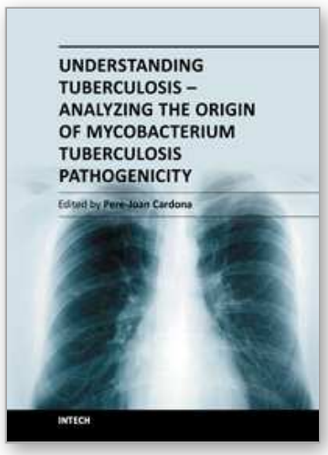
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Mycobacterium tuberculosis in an attempt to understand the extent to which the bacilli has adapted itself to the host and to its final target. On the other hand, there is a section in which other specialists discuss how to manipulate this immune response to obtain innovative prophylactic and therapeutic approaches to truncate the intimal co-evolution between Mycobacterium tuberculosis and the Homo sapiens.

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Phone: +86-21-62489820
Fax: +86-21-62489821

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