

Review Article

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Adhesion molecules facilitate host-pathogen interaction & mediate *Mycobacterium tuberculosis* pathogenesis

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Most of the microorganisms display adhesion molecules on their surface which help them to bind and interact with the host cell during infection. Adhesion molecules help mycobacteria to colonize and invade immune system of the host, and also trigger immune response explicated by the host against the infection. Hence, understanding the signalling pathways illustrated by these molecules to enhance our knowledge on mycobacterial survival and persistence inside the host cell is required. Hence, this review was focussed on the role of adhesion molecules and their receptor molecules. The various mechanisms adopted by adhesion molecules to bind with the specific receptors on the host cell and their role in invasion and persistence of mycobacterium inside the host cell are explained.

Key words Adhesion - fibronectin - fibronectin-binding protein - lipoarabinomannan - macrophages - *Mycobacterium tuberculosis* - proline glutamic polymorphic CG repetitive sequence

Introduction

Tuberculosis (TB) remains a worldwide cause of increasing morbidity and mortality despite major advances in anti-TB drug administration and treatment^{1,2}. Increasing cases of multidrug resistance and extensive drug resistance with co-infection of HIV has further added to the prevalence of the active disease³. According to the WHO Report 2017, 6.3 million new TB cases were reported in 2016⁴. However, TB motility rate fell by 37 per cent in between 2000 to 2016. In spite of that, the Report has shown an increasing prevalence of the disease worldwide⁴.

An understanding of interaction between host cell surface receptors with pathogen's surface-

associated adhesion molecules is required to gain access to the mechanism involved in host-pathogen interactions. In reference to this, the bacterial strategy to countervail the host defence and how it persists for a longer time within the host can be further analyzed^{5,6}. Identification of functioning and unified system of molecules present in host pathogenesis is well identified through studying protein-protein interactions, which contributes to cellular mechanism. On these grounds, it would be interesting to elaborate functions of adhesion molecules which are majorly involved in mediating interaction between the pathogen and the host cell⁵⁻⁸ (Fig. 1 and Table). Adhesion molecules are cell surface molecules, which bind to receptors or with soluble macromolecules present in extracellular membrane of host to promote

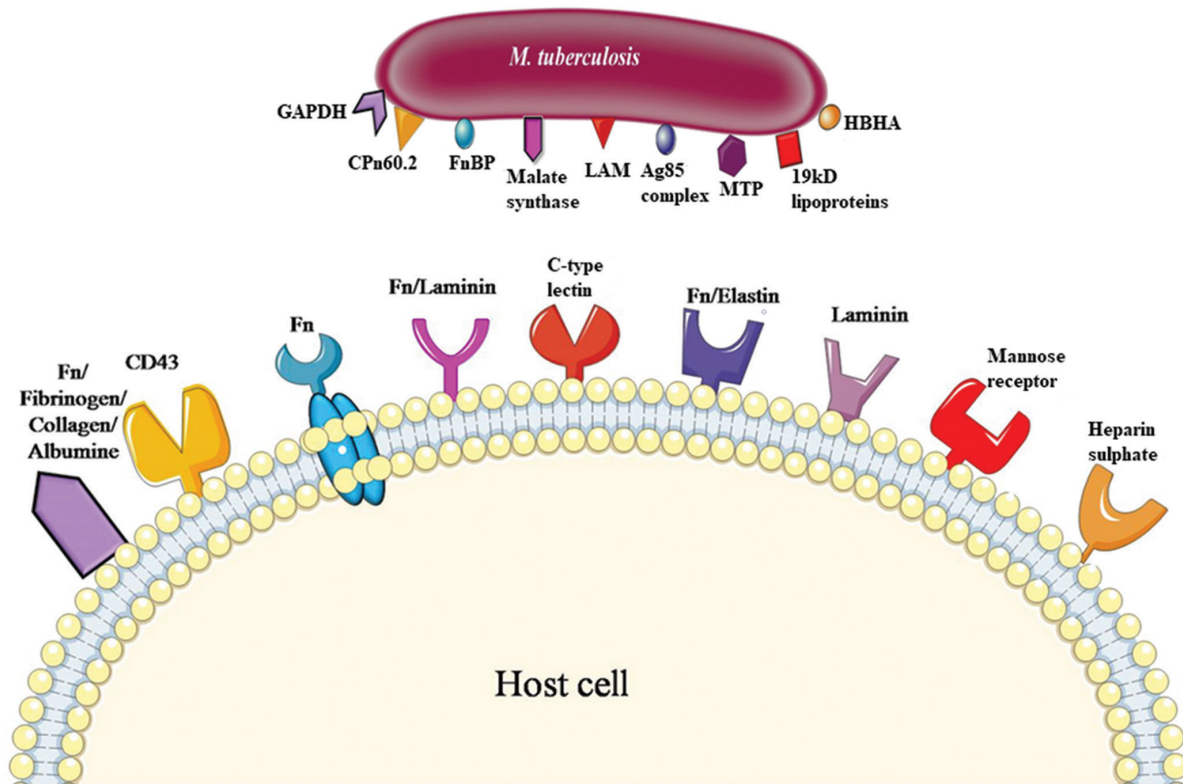


Fig. 1. Illustrative representation of mycobacterial adhesions and their respective receptors on host cell (Structures portrayed here do not necessarily imitate the actual receptor structure). GAPDH, glyceraldehyde 3-phosphate dehydrogenase; CPn60.2, chaperonin 60.2; FnBP, fibronectin binding protein; LAM, lipoarabinomannan; Ag 85, antigen 85 complex; MTP, *Mycobacterium tuberculosis* pili; HBHA, heparin-binding hemagglutinin A; Fn, fibronectin.

Table. List of adhesion molecules with their receptors present on host cell surface and their interaction facilitates pathogenesis

Adhesins present in pathogen's surface	Receptors present in host cell	Pathogenesis	References
Man-LAM	TLRs, C-type lectin	Interference with calcium signalling, blocks signalling of DC	6,15, 19-20
FnBP	Fn	Reorganization of actin cytoskeleton, stimulates coronin/TACO which inhibits phagosome lysosome fusion	22,28
Cpn60.2	CD43	Stimulates production of TNF α , interferes in antigen presentation	29,31
HBHA	Sulphated surface receptors such as heparin sulphate	Mycobacterial dissemination	33,37-40,42
Antigen 85 complex	Fn	Maintains cell wall integrity of mycobacteria	45,46,49
19 kDa protein	Mannose receptor	Decreases antigen presentation by inhibiting HLA-DR protein	53,57
Malate synthase	Laminin, Fn, A549 lung epithelial cells	Helps mycobacteria to survive under hypoxic condition	59,60
MTP	Laminin, epithelial cells	Mainly promotes adhesion	66,67
GAPDH	Fn, fibrinogen, albumin, collagen	Helps to uptake iron from host cell	68,73

Man-LAM, mannose lipoarabinomannan; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; MTP, *Mycobacterium tuberculosis* pili; HLA-DR, human leukocyte antigen-antigen D-related; HBHA, heparin binding haemagglutinin; TACO, tryptophan aspartate containing coat protein; TLRs, Toll-like receptors; Fn, fibronectin; FnBP, fibronectin binding protein; TNF α , tumour necrosis factor alpha; DC, dendritic cells

cell adhesion and are involved in host pathogenesis^{7,8}. Several adhesion molecules found in mycobacteria such as fibronectin-binding proteins (FnBPs) and heparin-binding haemagglutinin (HBHA), which are involved in adherence and promote internalization of the *Mycobacterium tuberculosis* into the host cells, facilitate bacterial colonization⁹. Interaction of these adhesions with host cell surface receptors not only helps in attachment and invasion but further exhibiting a cascade of signalling such as interferon

(IFN)- γ response and activation of mitogen-activated protein kinases (MAPKs) pathway, which promotes pro- and/or anti-inflammatory events by stimulating an immune response⁸. Further, adhesion molecules not only trigger the immune response but also interfere with the host signalling and modulate its intracellular mechanism (Fig. 2). Hence, exploiting the role of adhesion molecules is important to understand host pathogenesis induced by *M. tuberculosis*.

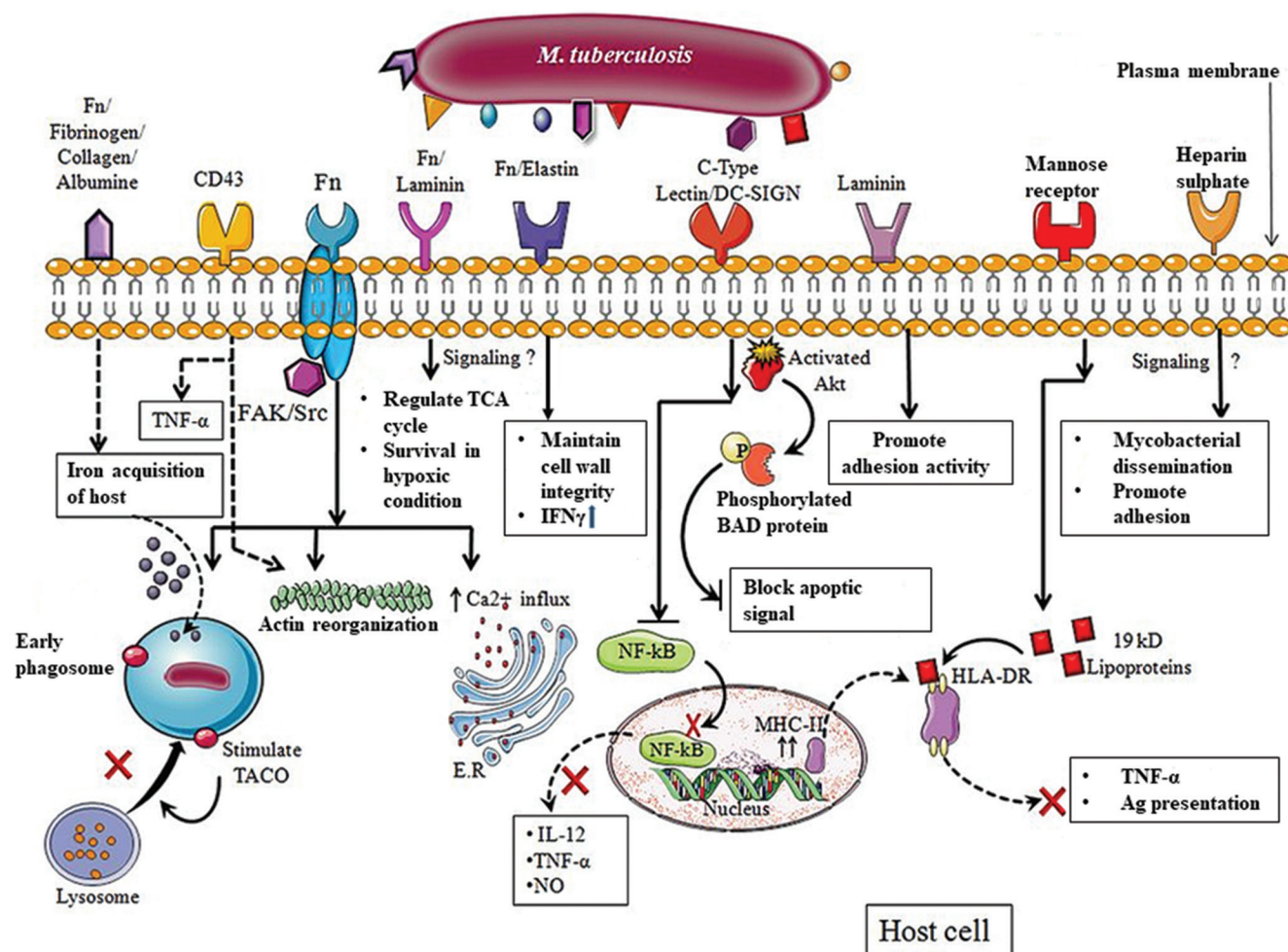


Fig. 2. Schematic representation of signalling induced by adhesion molecules inside the host cell. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) binding to fibrinogen (Fn) on the host cell induces the uptake of iron which is to be acquired by the host cell for its own use. Cpn60.2 binding to CD43 induces interferon- γ (IFN- γ) production and also leads to actin reorganization. Adhesion of fibronectin-binding protein (FnBP) to fibronectin stimulates FAK/Src kinase which also leads to actin reorganization and also recruits tryptophan aspartate containing coat protein to early phagosome and prevents its fusion with lysosome. It also triggers calcium upregulation. Malate synthase binding with fibronectin or laminin has been shown. It mainly helps bacteria to survive under hypoxic conditions inside the host cell. Antigen-85 complex binding with fibronectin/elastin induces interferon- γ (IFN- γ) which indicates that it also participates in host cell signalling mechanism. Binding of lipoarabinomannan to C-type lectin/DC-SIGN stimulates Akt protein which phosphorylates Bad protein, and hence, the intrinsic apoptotic pathway is blocked. *Mycobacterium tuberculosis* pili binding to laminin promotes strong adhesion activity; 19 kDa protein binds with mannose receptor and blocks human leukocyte antigen-antigen D-related (HLA-DR) protein present on major histocompatibility complex II (MHC-II) and leads to delayed antigen presentation. Heparin-binding haemagglutinin binds to heparin present on host cell and triggers mycobacterial dissemination which is important for its survival inside the host cell.

Synergetic effect of adhesion and host cell signalling in TB infection

Lipoarabinomannan (LAM): Lipoarabinomannan (LAM) is a cell wall active polysaccharide of *M. tuberculosis*, which constitutes arabinose and mannose moieties. Multiple branched arabinofuranosyl (Ara) side chain modified with mannose residue encompasses LAM¹⁰⁻¹⁴. Mannose-lipoarabinomannan (Man-LAM) is abundant in pathogenic mycobacteria such as *M. tuberculosis* and *M. ulcerans* while Ara-LAM is more excessive in non-pathogenic bacteria such as *M. fortuitum* and *M. smegmatis*^{11,12}. The phosphatidylinositol moiety in LAM helps the pathogen to anchor to the cell wall of the host cell¹⁴. It has been proposed that LAM, along with 13 lipomannans, is an immunomodulatory glycoconjugate molecule, which constitutes several chemical structures involved in *M. tuberculosis* disease progression¹⁵⁻¹⁷. These structures have an ability to interact with their respective receptors on the host cell surface.

LAM interferes with calcium signalling: In the host cell an increase in the amount of calcium modifies calmodulin, which in turn activates Ca²⁺/Calmodulin-dependent protein kinase II (CaMKII)¹⁸. CaMKII is required to recruit early endosome antigen I (EEA1) to the phagosomal membrane which helps in vesicle fusion. LAM decreases Ca²⁺ concentration by either chelating Ca²⁺ or inhibiting CaMKII and phagosome maturation^{15,19}. Furthermore, the intracellular survival of mycobacteria has also been maintained by Man-LAM which takes part in blocking apoptotic signals. Man-LAM stimulates phosphorylation of apoptic protein Bad (pro-apoptotic protein), which in turn stimulates Akt protein kinase activity and interferes with apoptotic signals²⁰. These illustrations clearly establish that Man-LAM helps mycobacteria to invade and persist for longer time inside the host cell and hence is involved in pathogenesis.

LAM blocks signalling of dendritic cells: In addition to macrophages, other cells such as dendritic cells (DCs) also display Toll-like receptors (TLRs) and C-type lectins on their surface²¹. TLRs are conserved receptors that can perceive pathogen-associated molecular patterns (PAMPs) and actuate innate as well as adaptive immunity against these pathogens. Man-LAM binds to C-type lectins which are involved in recognizing a wide variety of pathogens through their diverse carbohydrate structures that induce host-pathogen interaction. This also suggests that LAM interferes in lipopolysaccharide signalling exhibited by

TLRs and inhibits production of interleukin (IL)-12 by DCs and suppresses the immune response^{6,20}.

Fibronectin-binding protein (FnBP): It is a secretory adhesion protein on the mycobacterial surface, which proves to be a potent immunomodulator^{22,23}. FnBP complex constitutes antigen-85A, -85B, -85C (Ag85a, Ag85B, Ag85C) and FnBP A, B, C which play a crucial role in *M. tuberculosis* pathogenesis and also illustrate cell wall mycolyl transferase activity²³. FnBPs mainly belong to proline glutamic polymorphic CG repetitive sequence family of genes present in mycobacteria²⁴⁻²⁶. Previous studies have validated its binding to fibronectin (Fn), a multidomain glycoprotein on host surface²². Fn can act as a ligand to a number of integrin receptors. Hence, one can presume that the connection of FnBPs with integrin present on host surface is mediated by Fn receptor molecule. Moreover, in other bacterial species, such as *Staphylococcus aureus*, it has been established that Fn executes adhesion to live endothelial cells²⁷ which leads to phagocytosis and activation of cytokines, *i.e.* a suitable immune response, is generated²⁸ (Table). This supports the idea of Fn being an adhesion molecule involved in pathogenesis. FnBPs have been identified as members of microbial surface components recognizing adhesive matrix molecules in *M. tuberculosis* infection²². These are considered to constitute LPXTG motif in their C-terminal region which covalently attaches FnBP to the extracellular matrix (ECM)²⁹. In other studies, it has also been demonstrated that Fn plays crucial role in matrix assembly. Fn binding leads to interaction of the virulent factor with integrin on the host cell, thus resulting in reorganization of actin cytoskeleton associated with tyrosine kinase activation. For example, stimulation of focal adhesion kinase (FAK) and Src kinases signalling has been shown to promote phospholipase activity which helps stimulate coronin/tryptophan aspartate-containing coat protein (TACO). TACO recruited to phagosomal surface will inhibit phagosomal maturation²⁸. This exemplifies as to how Fn, an adhesion molecule, modulates host cell signalling and helps in survival of mycobacteria inside the granuloma for a longer period of time.

Cpn60.2: Molecular chaperones are proteins that play a vital role in maintaining cellular functions by facilitating protein folding. These are potentially involved in entry of mycobacteria inside the host cell and facilitate pathogenesis. There are two types of chaperone molecules found on *M. tuberculosis* cell surface, *i.e.* Cpn60.2 (also known as Hsp65) and Hsp70, which belongs to the family of heat

shock proteins. Molecular chaperones can act like 'moonlighting proteins', suggesting that these can serve for varied functions³⁰. Experiments have proved that almost 57 per cent of the bacterial association with macrophages is hindered by recombinant Cpn60.2³¹. Hence, one can say that Cpn60.2 is a major adhesion molecule found on the surface of *M. tuberculosis*. Previous studies have proved that it helps in binding to the host cell through its attachment to a large sialylated glycoprotein present on the surface of the macrophage known as CD43³¹. Cpn60.2 plays a major role in cell survival mechanism inside the host and can act as a potent immunomodulator³². It has also been found that Cpn60.2 can activate human peripheral blood macrophages followed by stimulation and secretion of cytokines that brings B- and T-cell activation³⁰. Furthermore, CD43 interaction with the pathogen regulates tumour necrosis factor (TNF)- α production by *M. tuberculosis*-infected macrophages cell³³. Hence, CD43 is shown to be related with cell signalling events along with cytoskeleton rearrangement and other intracellular as well as extracellular functions³⁰. According to evidences, Cpn60.2 has been unable to show anti-inflammatory activity³⁴. Binding of Cpn60.2 with macrophages does not reveal enhanced expression of major histocompatibility complex II (MHC-II), Fc- γ receptors or any other free radicals. This suggests that these will interfere in antigen presentation and stimulation of T-lymphocytes, thus ensuring the survival of *M. tuberculosis* inside the host cell³⁵. As a heat shock protein, Cpn60.2 is also involved in the survival of mycobacteria inside the host cell during stress conditions³⁶. In *M. leprae* infection also, it plays a vital role in coordination with T-cells that help establish its role in *M. tuberculosis*. It stimulates monocyte cytokines which guides the formulation of TNF, IL-6 and IL-2, thus effectively mediating host immunity. It also constitutes highly conserved sequence due to which it is also involved in progression of autoimmune response.

Heparin-binding haemagglutinin (HBHA): This is a surface exposed 28 kDa molecule with 199 amino acid residues which can act as an adhesion molecule. Adherence property of mycobacteria to epithelial cells is specifically inhibited by heparin and other sulphated carbohydrates. This proves that HBHA is involved in adherence by binding to sulphated surface receptors³⁷⁻⁴⁰. It also acts as a methylated antigen that helps in HBHA-specific T-cell response⁴¹. According to Pethe *et al*⁴², HBHA disrupted mutant strain of

BCG shows no difference in invading phagocytic cells in comparison to wild type, while these show 60 per cent reduction in adherence to pneumocytes. Hence, it is concluded that HBHA-mediated adherence is specific to non-phagocytic cells and that it is involved in mycobacterial dissemination which is essential for the pathogen to spread its infection^{33,39}. HBHA acts as a multifunctional adhesion molecule which is involved in auto-aggregation as well as bacterial-eukaryotic cell interaction³⁹. Potential of HBHA in the detection of latent infection of TB has also been evaluated.

Antigen-85 (Ag85) complex: Ag85 complex serves as a major secretory product released by *M. tuberculosis*, which possesses Fn-binding property⁴³. It constitutes three abundantly secreted proteins 85A (fbpA), 85B (fbpB) and 85C (fbpC) encoded by Rv3804c, Rv1886c and Rv0129c, respectively, in *M. tuberculosis*⁴⁴. These have been shown to be involved in disease pathogenesis as these stimulate uptake of *M. tuberculosis* via their interaction with Fn receptor molecules present on host cell^{45,46}. Armitige *et al*⁴⁷ have demonstrated that disrupting genes of Ag85 complex from *M. tuberculosis* strains affects cell wall synthesis. Besides having role in cell wall biosynthesis, the surface Ag85 complex has also been found to exhibit cell wall mycolyl transferase activity during infection⁴⁵.

Studies have shown that transfer of mycolylates is catalyzed by the mycolyl transferase⁴⁸. It directs the formation of two products: α,α -trehalose monomycolate and α,α -trehalose dimycolate (a cord factor), which are useful in maintaining cell wall integrity in *M. tuberculosis* infection⁴⁹. A significant proliferation and IFN- γ secretion in the peripheral blood leukocytes have been found to be induced by 32 kDa protein (Ag85) isolated from *M. bovis*⁵⁰. Hence, it is suggested that Ag85 complex acts as a prominent marker in diagnosis of TB as it can be detected in blood and sputum of pulmonary TB patients⁵¹.

19 kDa protein: The 19 kDa lipoprotein is expressed by *M. tuberculosis* and other slow-growing pathogenic bacteria such as *M. vaccae* and not by fast-growing bacteria such as *M. smegmatis*⁵². It is a surface exposed glycolipoprotein, which acts as pathogen associated molecular patterns (PAMPs) that can be recognized by pattern recognition receptors such as TLRs. Hence, it is involved in the production of pro-inflammatory cytokines such as ILs and TNF- α , which further generate a significant immune response. It has been found to bind with

mannose receptor present on host cell surface and promote adhesion of mycobacteria to host cell⁵³. A structural motif of triacyl head group is attached to amino terminal cysteine which is expressed by these lipoproteins. Its interaction to host cell via TLR2 has been shown in previous studies⁵⁴, indicating its participation in host cell signalling. In addition, Neufert *et al*⁵⁵ have demonstrated that 19 kDa protein also acts as a priming agent in neutrophil activation. Further, these lipoproteins have been found to induce humoral as well as cellular immune responses by host cell towards *M. tuberculosis* which demonstrates its role in pathogenesis. It also confers TLR2-dependent inhibition of MHC-II expression and antigen processing⁵⁶. Gehring *et al*⁵⁷ have demonstrated that 19 kDa lipoprotein interferes in IFN- γ signalling by inhibiting IFN- γ -regulated human leukocyte antigen-antigen D-related (HLA-DR)⁵⁷ protein which in turn inhibits IFN- γ induced expression of fc γ -R1 and decreases bacilli antigen processing and presentation on MHC-II to CD4⁺ T-cells. This evolves a mechanism for *M. tuberculosis* to survive and persist for a long time inside the cell. It is also described that this inhibitory effect shown by 19 kDa protein is restricted to MHC-II expression instead of MHC-I. In addition, 19 kDa protein also contributes in transport of nutrients through mycobacterial cell wall which helps in its survival. Ciaramella *et al*⁵⁸ have reported that 19 kDa proteins majorly induce apoptosis in monocytes/macrophages by LpqH activation which in turn triggers TLR2 activation which upregulates the death receptor and signalling molecule, thus beginning death receptor signalling cascade. They demonstrated this using anti-19 kDa monoclonal antibodies and high amounts of *M. tuberculosis* H₃₇Rv. This protein needs to be studied further to track mycobacterial strategy to invade and persist inside the host cell.

Malate synthase: Malate synthase is a multifunctional protein found in mycobacteria encoded by the gene *glcB*⁵⁹. It is an extracellular protein which serves as an adhesin and has a significant role in host pathogenesis. This enzyme has been shown to bind with laminin, Fn and A549 lung epithelial cells, which is acquired by a unique C-terminal region⁶⁰. As bacterial persistence inside the host undergoes low oxygen tension, the changes in malate synthase help bacteria to survive. The involvement of malate synthase in glyoxylate pathway has been also suggested. Assimilation of the carbon compound into

tri carboxylic acid (TCA)⁶¹ cycle is accompanied by malate synthase, which can be utilized for the bacterial replication in macrophages⁶². Malate synthase serves to play vital role for growth of oxidizing co-factors involved in energy production and perseverance of carbon moieties during *M. tuberculosis* survival inside the host cells under hypoxic conditions⁵⁹. It has also been demonstrated that malate synthase is recognized by serum antibodies easily; hence, it can be used in serodiagnostic assay⁶³. Thus, malate synthase not only serves as an adhesion molecule but also helps bacteria to survive inside the host cell under stress conditions.

Mycobacterium tuberculosis pili (MTP): *M. tuberculosis* pili (MTP) are fine adhesion molecules, which belong to bacterial amyloid family called pili or curli. Using electron microscopy, Alteri *et al*⁶⁴ have demonstrated that mycobacterium produces two distinct types of pili morphotypes, type IV and curli pili. In terms of adhesion property, MTPs have shown adherence properties that help them to bind with laminin present in the ECM of the host cell. Previously, it was also established that pili were involved in mediating specific recognition of receptors present in host cells⁶⁴. Several studies have demonstrated that it is encoded by the gene, Rv3312A, which is further involved in tissue colonization and reported as potential virulence factor associated to *M. tuberculosis* pathogenesis⁶⁴. Pili are also involved in bacterial aggregation, host cell interaction and biofilm formation which lead to colonization of mucosal surface. Ramsugit and Pillay⁶⁵ demonstrated that MTP mutant-type mycobacterial strain was not able to adhere and invade THP-1 macrophages to that extent as compared to wild-type strain which further confirmed their adherence property⁶⁵. They also found that MTP did not extensively influence the whole cytokine response of *M. tuberculosis* infected epithelial cells⁶⁶. Alteri *et al*⁶⁴, using immunofluorescence-based assay, analyzed the presence of interaction of MTP with A549 epithelial cells. Further, it was reported that adhesion between bacteria and epithelial cells was mediated by the hydrophobicity of pilian adhesion⁶⁷. Earlier studies also show the role of MTP in biofilm formation. Hence, MTP is a major adhesion molecule which helps to invade the host cell and is involved in pathogenesis.

Glyceraldehyde 3-phosphate dehydrogenase (GAPDH): Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is known to be a surface associated multifunctional protein^{68,69}. The adhesion property of

the enzyme is exhibited towards Fn, fibrinogen, albumin and collagen⁶⁸. It is also a vital moonlighting protein, *i.e.* it exhibits multiple functions⁶⁹. It is demonstrated that the highly conserved enzyme converts glyceraldehyde-3-phosphate in the presence of inorganic phosphate and nicotinamide adenine dinucleotide (NAD⁺) to 1,3-bisphosphoglycerate. Meanwhile, NAD⁺ is reduced to NAD hydrogenase^{70,71}. Studies have shown that GAPDH is also involved in cellular signalling network; for example, phosphorylation of Siah-I by apoptosis signal regulating kinase I (ASKI). It is a stress kinase which triggers GAPDH-Siah-I stress signalling, thus suggesting that it is involved in stress signalling networks^{70,72}.

Uptake of iron from the host cell

Overexpression of GAPDH helps *M. tuberculosis* to uptake iron from host cells via its increased binding to transferrin, which is a host iron transport protein evolved during infection⁷³. Past demonstration suggests that iron is important for persistence of the pathogen inside the host. Transferrin bound iron is utilized by transferrin receptor-1 (TFR-1) expressed in macrophages. *Mycobacterium avium* has been studied to interfere with TFR-1 and utilize transferrin bound protein for its own use which helps us to hypothesize similar roles in *M. tuberculosis* pathogenesis. GAPDH has also been reported to be involved in apoptosis induction and transcription regulation⁷⁴. Hence, by targeting GAPDH and signalling cascade, we could probably open up distinct channels for the evaluation of novel TB drugs to eradicate tuberculosis.

Conclusion

The pathogenic effects of adhesion molecules in TB pathogenesis and its intimate relation with host cellular signalling require more researches in this direction to be clearly interpreted. According to previous studies, the current status is that the factual role of these adhesion molecules remains elusive. Adhesion molecules are the initiation mediators of mycobacterial interaction with the host cell. Hence, gaining access to the overall structural and functional aspects of adhesion molecules involved in host-pathogen interaction is essential. Further elucidation of their importance in host signalling can be accessed via methods such as RNA interference and knock-out techniques which can find their actual role and mechanism of action inside the host cell. The involvement of a cooperative mechanism in host invasion can also be studied. This information

is essential in targeting these adhesion molecules to develop new TB vaccines and treatment strategies, which can help to cope up with the epidemiology of the disease and thus fulfil our ultimate goal to control this pandemic disease throughout the world.

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Conflicts of Interest: None.

References

1. Glaziou P, Floyd K, Raviglione MC. Global Epidemiology of Tuberculosis. *Semin Respir Crit Care Med* 2018; 39 : 271-85.
2. Godebo A, Woldi A, Toma A. Recent advances in the development of anti-tuberculosis drugs acting on multidrug-resistant strains: A review. *Int J Res Pharm Biosci* 2015; 2 : 1-18.
3. Meena LS, Rajni. Survival mechanisms of pathogenic *Mycobacterium tuberculosis* H37Rv. *FEBS J* 2010; 277 : 2416-27.
4. World Health Organization. Global Tuberculosis Report 2017. Available from: https://www.who.int/publications/global_report/MainText_13Nov2017; accessed on December 2, 2016.
5. Espitia C, Rodriguez E, Ramon-Luing L, Echeverria-Valencia G, Vallecillo AJ. Host-pathogen interactions in tuberculosis. In: Cardona PJ, editor. *Understanding tuberculosis – Analyzing the origin of Mycobacterium tuberculosis pathogenicity*. Vienna: Intech; 2012. p. 43-76.
6. Rawat R, Monu, Meena LS. Adhesion molecules A potent surface marker of *Mycobacterium* play key role in host-pathogen interaction and pathogenesis. *Adv Res J Biochem Biotechnol* 2015; 2 : 41-6.
7. Kline KA, Fälker S, Dahlberg S, Normark S, Henriques-Normark B. Bacterial adhesins in host-microbe interactions. *Cell Host Microbe* 2009; 5 : 580-92.
8. Govender VS, Ramsugit S, Pillay M. *Mycobacterium tuberculosis* adhesins: Potential biomarkers as anti-tuberculosis therapeutic and diagnostic targets. *Microbiology* 2014; 160 : 1821-31.
9. García B, Merayo-Llodes J, Martín C, Alcalde I, Quirós LM, Vazquez F. Surface Proteoglycans as Mediators in Bacterial Pathogens Infections. *Front Microbiol* 2016; 7 : 220.
10. Jankute M, Cox JA, Harrison J, Besra GS. Assembly of the mycobacterial cell wall. *Annu Rev Microbiol* 2015; 69 : 405-23.
11. Chatterjee D, Khoo KH. Mycobacterial lipoarabinomannan: An extraordinary lipoheteroglycan with profound physiological effects. *Glycobiology* 1998; 8 : 113-20.

12. Rajni, Rao N, Meena LS. Biosynthesis and virulent behavior of lipids produced by *Mycobacterium tuberculosis*: LAM and cord factor: An overview. *Biotechnol Res Int* 2011; 2011 : 274693.
13. Fukuda T, Matsumura T, Ato M, Hamasaki M, Nishiuchi Y, Murakami Y, *et al.* Critical roles for lipomannan and lipoarabinomannan in cell wall integrity of mycobacteria and pathogenesis of tuberculosis. *MBio* 2013; 4 : e00472-12.
14. Brennan PJ, Nikaido H. The envelope of mycobacteria. *Annu Rev Biochem* 1995; 64 : 29-63.
15. Koul A, Herget T, Klebl B, Ullrich A. Interplay between mycobacteria and host signalling pathways. *Nat Rev Microbiol* 2004; 2 : 189-202.
16. Meena LS, Kolattukudy PE. Expression and characterization of Rv0447c product, potentially the methyltransferase involved in tuberculostearic acid biosynthesis in *Mycobacterium tuberculosis*. *Biotechnol Appl Biochem* 2013; 60 : 412-6.
17. Meena LS, Chopra P, Vishwakarma RA, Singh Y. Biochemical characterization of an S-adenosyl-l-methionine-dependent methyltransferase (Rv0469) of *Mycobacterium tuberculosis*. *Biol Chem* 2013; 394 : 871-7.
18. Rich RC, Schulman H. Substrate-directed function of calmodulin in autophosphorylation of Ca²⁺/calmodulin-dependent protein kinase II. *J Biol Chem* 1998; 273 : 28424-9.
19. Malik ZA, Iyer SS, Kusner DJ. *Mycobacterium tuberculosis* phagosomes exhibit altered calmodulin-dependent signal transduction: Contribution to inhibition of phagosome-lysosome fusion and intracellular survival in human macrophages. *J Immunol* 2001; 166 : 3392-401.
20. Nigou J, Gilleron M, Rojas M, García LF, Thurnher M, Puzo G. Mycobacterial lipoarabinomannans: Modulators of dendritic cell function and the apoptotic response. *Microbes Infect* 2002; 4 : 945-53.
21. Diebold SS. Activation of dendritic cells by toll-like receptors and C-type lectins. *Handb Exp Pharmacol* 2009; 188 : 3-30.
22. Henderson B, Nair S, Pallas J, Williams MA. Fibronectin: A multidomain host adhesin targeted by bacterial fibronectin-binding proteins. *FEMS Microbiol Rev* 2011; 35 : 147-200.
23. Abou-Zeid C, Garbe T, Lathigra R, Wiker HG, Harboe M, Rook GA, *et al.* Genetic and immunological analysis of *Mycobacterium tuberculosis* fibronectin-binding proteins. *Infect Immun* 1991; 59 : 2712-8.
24. Cole ST, Brosch R, Parkhill J, Garnier T, Churcher C, Harris D, *et al.* Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature* 1998; 393 : 537-44.
25. Meena LS. An overview to understand the role of PE_PGRS family proteins in *Mycobacterium tuberculosis* H37 Rv and their potential as new drug targets. *Biotechnol Appl Biochem* 2015; 62 : 145-53.
26. Meena LS, Meena J. Cloning and characterization of a novel PE_PGRS60 protein (Rv3652) of *Mycobacterium tuberculosis* H37 Rv exhibit fibronectin-binding property. *Biotechnol Appl Biochem* 2016; 63 : 525-31.
27. Monu, Meena P, Meena A, Meena LS. Imperative role of fibronectin binding proteins in cell adhesion and invasion. *Adv Res J Biochem Biotechnol* 2015; 2 : 31-40.
28. Meena PR, Monu, Meena LS. Fibronectin binding protein and Ca²⁺ play an access key role to mediate pathogenesis in *Mycobacterium tuberculosis*: An overview. *Biotechnol Appl Biochem* 2016; 63 : 820-6.
29. Naito M, Ohara N, Matsumoto S, Yamada T. The novel fibronectin-binding motif and key residues of mycobacteria. *J Biol Chem* 1998; 273 : 2905-9.
30. Henderson B, Lund PA, Coates AR. Multiple moonlighting functions of mycobacterial molecular chaperones. *Tuberculosis (Edinb)* 2010; 90 : 119-24.
31. Hickey TB, Ziltener HJ, Speert DP, Stokes RW. *Mycobacterium tuberculosis* employs cpn60.2 as an adhesin that binds CD43 on the macrophage surface. *Cell Microbiol* 2010; 12 : 1634-47.
32. Henderson B, Allan E, Coates AR. Stress wars: The direct role of host and bacterial molecular chaperones in bacterial infection. *Infect Immun* 2006; 74 : 3693-706.
33. Randhawa AK, Ziltener HJ, Merzaban JS, Stokes RW. CD43 is required for optimal growth inhibition of *Mycobacterium tuberculosis* in macrophages and in mice. *J Immunol* 2005; 175 : 1805-12.
34. Joseph S, Yuen A, Singh V, Hmama Z. *Mycobacterium tuberculosis* Cpn60.2 (GroEL2) blocks macrophage apoptosis via interaction with mitochondrial mortalin. *Biol Open* 2017; 6 : 481-8.
35. Peetermans WE, Raats CJ, Langermans JA, van Furth R. Mycobacterial heat-shock protein 65 induces proinflammatory cytokines but does not activate human mononuclear phagocytes. *Scand J Immunol* 1994; 39 : 613-7.
36. Sharma A, Rustad T, Mahajan G, Kumar A, Rao KV, Banerjee S, *et al.* Towards understanding the biological function of the unusual chaperonin cpn60.1 (GroEL1) of *Mycobacterium tuberculosis*. *Tuberculosis (Edinb)* 2016; 97 : 137-46.
37. Pethe K, Aumercier M, Fort E, Gatot C, Loch C, Menozzi FD. Characterization of the heparin-binding site of the mycobacterial heparin-binding hemagglutinin adhesin. *J Biol Chem* 2000; 275 : 14273-80.
38. Menozzi FD, Rouse JH, Alavi M, Laude-Sharp M, Muller J, Bischoff R, *et al.* Identification of a heparin-binding hemagglutinin present in mycobacteria. *J Exp Med* 1996; 184 : 993-1001.
39. Menozzi FD, Bischoff R, Fort E, Brennan MJ, Loch C. Molecular characterization of the mycobacterial heparin-binding hemagglutinin, a mycobacterial adhesin. *Proc Natl Acad Sci U S A* 1998; 95 : 12625-30.
40. Lomino JV, Tripathy A, Redinbo MR. Triggered *Mycobacterium tuberculosis* heparin-binding hemagglutinin adhesin folding and dimerization. *J Bacteriol* 2011; 193 : 2089-96.

41. Temmerman S, Pethe K, Parra M, Alonso S, Rouanet C, Pickett T, *et al.* Methylation-dependent T cell immunity to *Mycobacterium tuberculosis* heparin-binding hemagglutinin. *Nat Med* 2004; 10 : 935-41.
42. Pethe K, Alonso S, Biet F, Delogu G, Brennan MJ, Loch C, *et al.* The heparin-binding haemagglutinin of *M. tuberculosis* is required for extrapulmonary dissemination. *Nature* 2001; 412 : 190-4.
43. Abou-Zeid C, Ratliff TL, Wiker HG, Harboe M, Bennedsen J, Rook GA. Characterization of fibronectin-binding antigens released by *Mycobacterium tuberculosis* and *Mycobacterium bovis* BCG. *Infect Immun* 1988; 56 : 3046-51.
44. Wiker HG, Sletten K, Nagai S, Harboe M. Evidence for three separate genes encoding the proteins of the mycobacterial antigen 85 complex. *Infect Immun* 1990; 58 : 272-4.
45. Belisle JT, Vissa VD, Sievert T, Takayama K, Brennan PJ, Besra GS. Role of the major antigen of *Mycobacterium tuberculosis* in cell wall biogenesis. *Science* 1997; 276 : 1420-2.
46. Borremans M, de Wit L, Volckaert G, Ooms J, de Bruyn J, Huygen K, *et al.* Cloning, sequence determination, and expression of a 32-kilodalton-protein gene of *Mycobacterium tuberculosis*. *Infect Immun* 1989; 57 : 3123-30.
47. Armitige LY, Jagannath C, Wanger AR, Norris SJ. Disruption of the genes encoding antigen 85A and antigen 85B of *Mycobacterium tuberculosis* H₃Rv: Effect on growth in culture and in macrophages. *Infect Immun* 2000; 68 : 767-78.
48. Matsunaga I, Naka T, Talekar RS, McConnell MJ, Katoh K, Nakao H, *et al.* Mycolyltransferase-mediated glycolipid exchange in Mycobacteria. *J Biol Chem* 2008; 283 : 28835-41.
49. Kremer L, Maughan WN, Wilson RA, Dover LG, Besra GS. The *M. tuberculosis* antigen 85 complex and mycolyltransferase activity. *Lett Appl Microbiol* 2002; 34 : 233-7.
50. Launois P, Huygen K, De Bruyn J, N'Diaye M, Diouf B, Sarthouj L, *et al.* T cell response to purified filtrate antigen 85 from *Mycobacterium bovis* bacilli calmette-guérin (BCG) in leprosy patients. *Clin Exp Immunol* 1991; 86 : 286-90.
51. Wallis RS, Perkins M, Phillips M, Joloba M, Demchuk B, Namale A, *et al.* Induction of the antigen 85 complex of *Mycobacterium tuberculosis* in sputum: A determinant of outcome in pulmonary tuberculosis treatment. *J Infect Dis* 1998; 178 : 1115-21.
52. Yeremeev VV, Lyadova IV, Nikonenko BV, Apt AS, Abou-Zeid C, Inwald J, *et al.* The 19-kD antigen and protective immunity in a murine model of tuberculosis. *Clin Exp Immunol* 2000; 120 : 274-9.
53. Diaz-Silvestre H, Espinosa-Cueto P, Sanchez-Gonzalez A, Esparza-Ceron MA, Pereira-Suarez AL, Bernal-Fernandez G, *et al.* The 19-kDa antigen of *Mycobacterium tuberculosis* is a major adhesin that binds the mannose receptor of THP-1 monocytic cells and promotes phagocytosis of mycobacteria. *Microb Pathog* 2005; 39 : 97-107.
54. Basu J, Shin DM, Jo EK. Mycobacterial signaling through toll-like receptors. *Front Cell Infect Microbiol* 2012; 2 : 145.
55. Neufert C, Pai RK, Noss EH, Berger M, Boom WH, Harding CV, *et al.* *Mycobacterium tuberculosis* 19-kDa lipoprotein promotes neutrophil activation. *J Immunol* 2001; 167 : 1542-9.
56. Noss EH, Pai RK, Sellati TJ, Radolf JD, Belisle J, Golenbock DT, *et al.* Toll-like receptor 2-dependent inhibition of macrophage class II MHC expression and antigen processing by 19-kDa lipoprotein of *Mycobacterium tuberculosis*. *J Immunol* 2001; 167 : 910-8.
57. Gehring AJ, Rojas RE, Canaday DH, Lakey DL, Harding CV, Boom WH, *et al.* The *Mycobacterium tuberculosis* 19-kilodalton lipoprotein inhibits gamma interferon-regulated HLA-DR and fc gamma R1 on human macrophages through toll-like receptor 2. *Infect Immun* 2003; 71 : 4487-97.
58. Ciaramella A, Martino A, Cicconi R, Colizzi V, Fraziano M. Mycobacterial 19-kDa lipoprotein mediates *Mycobacterium tuberculosis*-induced apoptosis in monocytes/macrophages at early stages of infection. *Cell Death Differ* 2000; 7 : 1270-2.
59. May EE, Leitão A, Tropsha A, Oprea TI. A systems chemical biology study of malate synthase and isocitrate lyase inhibition in *Mycobacterium tuberculosis* during active and NRP growth. *Comput Biol Chem* 2013; 47 : 167-80.
60. Kinhikar AG, Vargas D, Li H, Mahaffey SB, Hinds L, Belisle JT, *et al.* *Mycobacterium tuberculosis* malate synthase is a laminin-binding adhesin. *Mol Microbiol* 2006; 60 : 999-1013.
61. Ahn S, Jung J, Jang IA, Madsen EL, Park W. Role of glyoxylate shunt in oxidative stress response. *J Biol Chem* 2016; 291 : 11928-38.
62. Wayne LG, Lin KY. Glyoxylate metabolism and adaptation of *Mycobacterium tuberculosis* to survival under anaerobic conditions. *Infect Immun* 1982; 37 : 1042-9.
63. Achkar JM, Dong Y, Holzman RS, Belisle J, Kourbeti IS, Sherpa T, *et al.* *Mycobacterium tuberculosis* malate synthase- and MPT51-based serodiagnostic assay as an adjunct to rapid identification of pulmonary tuberculosis. *Clin Vaccine Immunol* 2006; 13 : 1291-3.
64. Alteri CJ, Xicohténcatl-Cortes J, Hess S, Caballero-Olin G, Girón JA, Friedman RL, *et al.* *Mycobacterium tuberculosis* produces pili during human infection. *Proc Natl Acad Sci USA* 2007; 104 : 5145-50.
65. Ramsugit S, Pillay M. *Mycobacterium tuberculosis* pili promote adhesion to and invasion of THP-1 macrophages. *Jpn J Infect Dis* 2014; 67 : 476-8.
66. Ramsugit S, Pillay B, Pillay M. Evaluation of the role of *Mycobacterium tuberculosis* pili (MTP) as an adhesin, invasin, and cytokine inducer of epithelial cells. *Braz J Infect Dis* 2016; 20 : 160-5.
67. Klemm P, Schembri MA. Bacterial adhesins: Function and structure. *Int J Med Microbiol* 2000; 290 : 27-35.
68. Barbosa MS, Bão SN, Andreotti PF, de Faria FP, Felipe MS, dos Santos Feitosa L, *et al.* Glyceraldehyde-3-phosphate dehydrogenase of *Paracoccidioides brasiliensis* is a cell surface protein involved in fungal adhesion to extracellular

- matrix proteins and interaction with cells. *Infect Immun* 2006; 74 : 382-9.
69. Boradia VM, Malhotra H, Thakkar JS, Tillu VA, Vuppala B, Patil P, *et al.* *Mycobacterium tuberculosis* acquires iron by cell-surface sequestration and internalization of human holo-transferrin. *Nat Commun* 2014; 5 : 4730.
70. Seidler KA, Seidler NW. Role of extracellular GAPDH in *Streptococcus pyogenes* virulence. *Mo Med* 2013; 110 : 236-40.
71. Wolfson-Stofko B, Hadi T, Blanchard JS. Kinetic and mechanistic characterization of the glyceraldehyde 3-phosphate dehydrogenase from *Mycobacterium tuberculosis*. *Arch Biochem Biophys* 2013; 540 : 53-61.
72. Tristan CA, Ramos A, Shahani N, Emiliani FE, Nakajima H, Noeh CC, *et al.* Role of apoptosis signal-regulating kinase 1 (ASK1) as an activator of the GAPDH-siah1 stress-signaling cascade. *J Biol Chem* 2015; 290 : 56-64.
73. Monfeli RR, Beeson C. Targeting iron acquisition by *Mycobacterium tuberculosis*. *Infect Disord Drug Targets* 2007; 7 : 213-20.
74. Tajima H, Tsuchiya K, Yamada M, Kondo K, Katsube N, Ishitani R. Over-expression of GAPDH induces apoptosis in COS-7 cells transfected with cloned GAPDH cDNAs. *Neuroreport* 1999; 10 : 2029-33.

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