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Review Article

Prominent Role of FnBPs of *Mycobacterium Tuberculosis* in Cell Adhesion, Immune Invasion and Pathogenesis

Abstract

An asymmetrical sharing of adhesion molecules throughout the cell surface of the *M. tuberculosis* and their significant associative role in host-pathogen interaction remains elusive. The continual researches in host-pathogen interaction mechanism revealed certain potential adhesins that facilitates mycobacterium adherence to host cells surface. The adhesion proteins like fibronectin binding protein (fnbp) are expressed by PE_PGRS a polymorphic GC-repetitive sequence belong to subfamily in *M. tuberculosis* which have a potential role in cell-attachment, entry, and immune evasion. This review addresses the adhesion property of fnbp in *M. tuberculosis* and their role in cell-cell adhesion process. Additionally modulation of host's cells signaling to promotes adhesion and host-pathogen interaction events. Likewise, this study highlights the prominent role of fnbp that may further act as a potent source of antigenic variation lead to evoke immune response during mycobacterium infection. So, increasing in our current understanding in these selective fnbp (adhesion proteins) and by targeting these *M. tuberculosis* expressive genes could help us for development of novel drug that will further valuable for therapeutics.

Abbreviation

M. tuberculosis: Mycobacterium tuberculosis; PE_PGRS: Proline-Glutamic Polymorphic GC-rich Repetitive Sequence; fnbp: fibronectin binding protein; fn: fibronectin; *S. aureus*: *Staphylococcus aureus*; MSCRAMMs: Microbial Surface Component Recognize Adhesive Matrix Molecules; FAK: Focal Adhesion Kinase; PLC-γ: Phospholipase C-γ; IP3: Inositol Triphosphate- 3; Th1: T-helper cell 1; (MHC) class II (MHC-II): Major Histocompatibility Complex

Introduction

Tuberculosis (TB) one of the mortal disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) and, spreading the mortality rate throughout the world. It is estimated that, there were 9.0 million people infected with mycobacterium but only 10% of them break down with this disease, while 90% remains clinically latent followed by approximately 1.5 million TB deaths in worldwide [1]. In *M. tuberculosis* infection the virulence and molecular events are still largely unknown, and additionally the unique and chemical entity present in the cell envelope of this bacillus participate equally followed by disease succession [2]. *M. tuberculosis*'s cell envolpe contain complex lipids like mycolic acid (a long fatty acid and strong hydrophobic chain in nature), lipoarmanon, arbinogalacton and glycoproteins which have virulent potency into disease progression and tissue damaging. In particular, the greater understanding of adhesion molecules is required in host-pathogen interaction together with its potential role in cell-attachment, entry, and immune evasion. The adhesion of microorganisms to the host cell surface or tissue is a key constituent in initial stage of infection [3].

Previous studies explore different adhesion molecules which exhibits specific affinity toward particular host cell receptor that further influences disease progression [4]. Moreover, the entry of *M. tuberculosis* into the macrophage and its survival strategy within hostile environment are very specific for internalization [5]. The adherence of the pathogen with the host is highly dependent upon adhesions like cell adhesion molecules (CAMs), which are mycobacterium cell surface protein involved in binding with other cells and/or with the Extracellular Matrix (ECM) via adhesion specific receptor.

Interestingly, fibronectin binding protein (Fnbp) of *M. tuberculosis* exhibits binding with fibronectin (Fn) derived by the host. It has been demonstrated that, Fn is a versatile cell adhesive glycoprotein capable of interacting with macromolecule including fibrin, collagen, proteoglycan as well

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as cell bearing specific fibronectin receptor on their surfaces [6]. Fn exists as a protein dimer with identical monomer linked with disulfide bond. Fn present in two forms, one is soluble found in blood plasma and other found in extracellular matrix in insoluble forms. The RGD (Arginine, Glycine, Aspartate) sequence is the major binding site of cell attachment of Fn via $\alpha5\beta1$ integrin. Knowledge about the entry mechanism of *M. tuberculosis* into targeted cell via specific adhesion proteins are limited, thus exploration of these adhesion molecules in mycobacterium may provide new strategy to develop novel approaches that could help to reduce TB prevalence. Though intercalating with macromolecule and receptor armed cells, Fn also exhibits interaction with a large number of microorganism including bacteria, fungi, and protozoa. Additionally, in studies it has also shown that Fn binding antigens are the major secreted constituents in short term culture supernatants of *M. tuberculosis,* that exhibits high binding affinity to fnbp [7].

Our current study aim to summarize the significant role of multifunctional Fnbp that involve not only in adhesion event but also directly participate in host cell signaling alteration of the host that may further act as a potential source of antigenic variation. It was demonstrated that, ECM and cell-cell interaction play crucial role in many physiological and pathological events because matrix components also have the ability to alter cell functioning which is facilitated by cell adhesion molecule [8]. The extracellular matrix/region contains a variety of multi-functional collagen, super family molecule and non-collagen matrix molecule [9,10]. Furthermore, in past studies it has been reported that, the GC-repetitive sequence (PGRS) subfamily expresses Fnbp in *M. tuberculosis* which exhibits binding property with Fn. Mycobacterium expresses a range of fnbps proteins for instance, antigen 85 complex (The complex consists of three proteins termed 85A, 85B and 85C), which are known to be a major secreted proteins in *M. tuberculosis* infection. As in prior studies it was investigated that attachment of fnbp to Fn is considered to be important proteins involved in phagocytosis of various bacterium like *M. tuberculosis*, *Mycobacterium bovis* (*M. bovis*), *Mycobacterium kansasii* (*M. kansasii*), *Mycobacterium avium* (*M. avium*) and *Mycobacterium leprae* (*M. leprae*) in epithelial cells [11,12]. In support of this, it has been also recognized that, Fnbp are most prominent secreted antigen that alters macrophage cellular functions. *M. tuberculosis* infection brings macrophage activation that further developed a variety of inflammatory cytokines that mediate intracellular infection which causes apoptosis via Tumor Necrosis Factor (TNF-α) dependent mechanism [13,14]. It has also shown that, TNF-α additionally implicated in many of the immune-pathological features in TB infection.

Fibronectin binding proteins in cell adhesion

Microorganism infection begins with adherence, which is the most common phenomenon to invade the host tissue [15]. Both Gram positive and negative bacteria employ a number of adherence molecules like fnbps associated on their cell surface, which often exhibits binding to Fn and initiate colonization [3]. For instance *Staphylococcus aureus* (*S. aureus*) bacteria have evolved a wide range of adhesion proteins known as adhesin i.e. Fnbps, which binds to selected host molecules and facilitate internalization [16,17]. Moreover, evidence is emerging in signaling events for Fn and its proteolytic breakdown product, which are raising the possibilities that bacterial Fnbps have action other than adhesion [16].

In TB pathogenesis, the genomics study of *M. tuberculosis* exploring unique and multi-gene family of adhesion molecules, which are highly related to adhesion proteins that are still unknown in their function. In this aspect, the mycobacterium hold a large number of genes expressing proteins whose N-terminal contains characteristics motifs pro-glu (PE) or pro-pro-glu (PPE) (A subgroup of the PE proteins contain polymorphic GC- repetitive sequence PGRS). The PE_PGRS family proteins expressed in *M. tuberculosis* exhibit multiple Fnbps, which have specific sequence in motifs possessing binding property [18]. Similarly, in other study, PE_PGRS proteins were also analyzed by western blotting in similar mycobacterial species for their existence like in *M. bovis* BCG, *M. smegmatis*, *M. marinum* and *M. gordonae* [19]. Simultaneously, it was also imparted that immune-fluorescent labeling of mycobacterium species signifies some PE_PGRS proteins are localized and associated with the cell surface of BCG and *M. tuberculosis* during infection [20].

On this subject, our recent investigation proposed that *M. tuberculosis* PE_PGRS60 family protein fnbp possessed a novel adhering property with Fn receptor molecules [21]. It was established that, Fn is occurred in insoluble or and in soluble form in host cell as well in body fluids and multi-functional molecules were reported as an adherence factor that play important role during pathogenesis of *M. tuberculosis* [7,22]. This complex and multifunctional property of this protein classify its binding ability with other molecules and these were also noted as wound healing [23].

Adhesion proteins and *M. tuberculosis* infection

Pathogenesis of TB begins with the interaction between pathogen and mononuclear phagocytic cell. Here the bacteria are engulfed by alveolar macrophage, which presumably equipped with multiple microbicidal mechanism including respiratory burst, phagolysosome fusion etc. of infecting microorganism leads to establish infection successfully [24]. Mycobacterium infected alveolar macrophage stimulates local chemokine signals that further attract other macrophages from local lymphatic tissue. T-cells also migrate into these tissues and release interferon-gamma (IFN- γ) resulting in macrophage activation. In short, in other studies it was established that, *M. tuberculosis* contains divergent adhesion proteins for instance CD44, an adhesion molecule in hematopoietic cells and which is connected to the cytoskeletal constituent such as hyaluronic acid, , fibronectin, and collagen etc. further involved in inflammatory responses. Likewise, CD44 shows prominent role in macrophage recruitment leads to delayed type hypersensitivity and exhibits binding ability in *M. tuberculosis* infection [25]. Despite in mycobacterium, Fnbp proteins also significantly increased the phagocytic activity in macrophage against *S. aureus*, via alpha-5 (α-5) and beta-1 (β-1) chains which were associated with the cytoskeleton [26,27].

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Integrins are α-β heterodimer, family of transmembrane receptors. There are 18 α and 8 β varieties of heterodimer which involved in several signaling pathways. Alpha-5 (α-5) and beta-1 (β-1) chains of integrin is major fn receptor present on most of the cells [28].

In short, integrin are crucial for cell invasion and migration not only for physically tethering cell to the matrix but also for sending and receiving chemical signals [29]. In *M. tuberculosis* infection, these subunits of the integrin act as receptor for extra cellular proteins which attaches cells to ECM and mediates cell-cell adhesion events. The binding activity of integrin to the extracellular matrix is synchronized via intracellular environment of the cell by abruption in signaling events. Thus, it was reported that adhesions mediates signaling that further influences several critical cellular process including cell cycle, programmed cell death and continual gene expression [30,31]. Only limited information is available belonging to fnbps with Fn, while many of integrin signals covers some cell cycle regulation event that further involved in to the cell cycle and differentiation [32]. However, in earlier studies it has been reported that, Fn and integrin play a crucial roles in a variety of morphogenetic process includes adhesion, migration and signal transduction.

This review concern particularly in the effect of signaling events regulate the activities of numerous kinases occurred in cytoplasm, growth factor receptors and ion channels that further control the intracellular organization of the cells. Moreover, in past studies, it was postulated that, the focal adhesion kinase (FAK), protein-tyrosine kinase (PTK) links to the transmembrane integrin receptors involved in intracellular signaling pathway [33]. The triggering of FAK followed up nascent focal adhesion stimulation that further interact on activation either directly or via the talin and/or paxillin (cytoskeletal proteins) with the cytoplasmic tails of integrin β- subunit [32] (Figure 1).

In addition to FAK, some other PTK, adversely called proline-rich tyrosine kinase-2 (PYK-2) and proposed a connection between integrin receptors and paxillin. Moreover, another function comment to Fn-stimulated FAK and PYK2 lead to promote signal stimulation to other kinase extracellular regulated kinase (ERK2), followed up triggering of PTKS activity (belongs to non-receptor SRC family kinase) [34]. Thus, adherence to cell surface is to be essential for the activation and delivery of certain virulence factor and in *M. tuberculosis* expression Fnbps make up a diverse group of surface adhesin that binds to receptor protein Fn leads to promotes cell adhesion [27].

Macrophage's Response toward *M. tuberculosis* infection

In general, macrophage activation plays a significant role, not only in the activation of the inflammatory response but also in the resolution on this response. Potentially, *M. tuberculosis* has ability to manipulate host's intra-cellular pathways which further influence bactericidal action during infection. The intracellular parasites *M. tuberculosis* promote their survival rate within the host via inhibiting phagolysosome fusion thus further avoids exposure to the lysosomal hydrolases [35-36]. Thus, observation postulated that, *M. tuberculosis* could successfully parasitize macrophages by disrupting the phago-lysosome maturation and provide it an intracellular compartment with endosomal rather than lysosomal uniqueness [37]. After a certain extension of *M. tuberculosis* survival, its replication reaches to threshold and secretes a number of proteins like ESAT-6, which mediate the host cell necrotic cell death. Furthermore, additional inflammatory cells activation resulting in production of cytokine such as TGF-β by infected macrophage. These cytokines further add the resolution of inflammation and to the initiation of wound healing via ECM induction components [38]. Moreover, in the course of *M. tuberculosis* internalization, the bacillus are also opsonized via specific antibody, its ingestion brings in term via macrophage Fc-gamma receptors (Fc-γRS) [39]. It was also proposed that fn also involved in opsonization process by phagocytosis as non-antibody and noncomplement opsonin. The binding of fn to bacteria, collagen, fibrin and actin are important for the roles of circulatory fn as an opsonin protein [40,41].

Host immune regulation in response to *M. tuberculosis*

In TB, cellular immunity is considered to be more important for the suppression of infection, but also for damage of host tissue [42]. It was reported that, in TB cell-mediated immunity (CMI) is responsible for the eradication of mycobacterium. The major effectors' mechanism of CMI is through the activation of infected macrophage by activation of T-helper type-

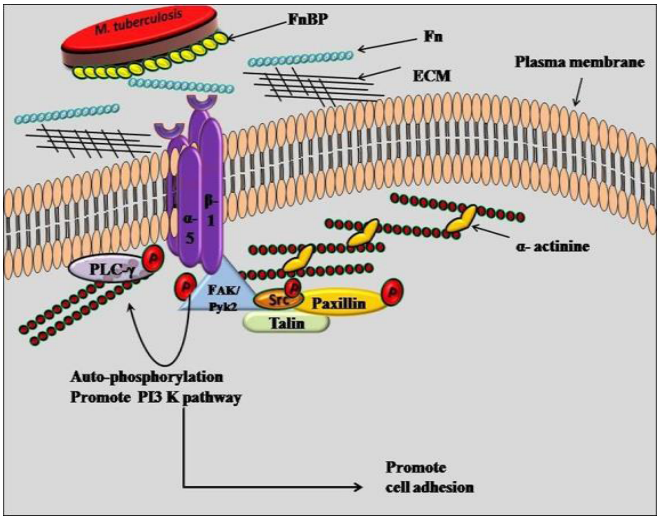

Figure 1: Representation of adhesion protein fibronectin binding protein (Fnbp) expressed in M. tuberculosis and involved in cell adhesion: In host-pathogen interaction Fnbp i.e. a PE_PGRS family protein has binding property, which provide a bridge to link up with the host's Fibronectin (Fn) receptor molecules [43] and brings stimulation of the Integrin receptor's α-subunit and β-subunit, which may further serve up a docking site for several kinases, like Focal Adhesion Kinase (FAK)/ Pyk2, Src, talins etc. Resulting, activation of kinases follows up effective binding with cytoskeletal proteins tails, and paxillin with the cytoplasmic tails of integrin's β- subunit. Thus, the ligand and receptor molecule interaction stimulates FAK tyrosin kinase phosphorylation that further promotes Phosphor-inositol 3-Kinase (PI3-Kinase) and phospholipase C-γ (PLC-γ) activities that may directly participate in catalytic metabolism and cell adhesion.

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1 (TH-1) produced cytokines, particularly IFN-γ. However, the balance between TH-1 type and TH-2 type cytokines responses in TB infection may influence mycobacterial growth as well as immune-pathological effect of host cells [43-44]. A major breakthrough has come, when a subset of $CD4^+$ T-cells constantly expressing the IL-2 receptor α-chain/CD25 (a high affinity, type-I trans-membrane protein present on activated T-cells) found to be increase in immunosuppressive activity during *M. tuberculosis* infection [45].

So, *M. tuberculosis* persists inside macrophage despite vigorous immune responses that is still obscure. Recently it is shown that Fnbp (major antigenic complex), which is a mycobacterial membrane's associated binding protein have immunomodulatory effect further follow up modulation in antigen presentation via MHC-II to $CD4^+$ T-cells [46]. In addition to this, the inhibitory action of IFN-γ in infected host cell also reported because of Fnbps proteins expression in *M. tuberculosis* [47]. Continual studies in immunopathology of TB, It has also been reported that, the host's immune system containing other ckemokines and chemokines like receptors like CCL3, CCL4, CCL5 and CXCLB which were equally contributed in macrophage proliferation as well as infection progression.

In support of this, the emerging literatures shown that, the inflammatory responses have generated after interacting with mycobacterium and macrophage/dendritic cells (DCs) in the lung mucosa and before their migration out of the inflamed tissues, they produced CCL3 and CCL5 further follow up to recruit immature DC to the site of infection [48]. Although we are having abundant knowledge of adhesion molecules in others bacterial species, but in mycobacterium infection it is still not well understood in terms of their effects in antigen presentation mechanism. Moreover, previous observation suggested that, during *M. tuberculosis* infection it expressed few of Intracellular Adhesion Molecule-I (ICAM-I) and macrophage adhesion ligand-1(MAC-I) marker on murine peritoneal macrophages, and reported that these adhesions possessing binding property with host cells [49,50]. In addition to enhance expression of ICAM-1 in response to *M. tuberculosis* was mediated in a paracrine or autocrine manner predominant via TNF-α that subsequently involves in the orchestrated production of chemokines and cytokines, further followed up granuloma formation (Figure 2). Thus, one hypothesis for the importance of the granuloma was postulated that the granuloma provides a wall of macrophage and lymphocytes surrounding infected cells that further help mycobacterium in survival [51,52].

Summary

The intimate connection between the infected cells and *M. tuberculosis* still not well understood. However it is well established that the mycobacterium have employed wide range of adherence molecules involved in evading host's immune mechanisms for its persistence and survival. The host-pathogen interaction via adhesion molecules and their adhering abilities specifically to ligands, receptors that relatively contribute in signaling events involved in phagocytosis mechanism during this bacilli infection, which is still remains to be fully understood. The ligands and receptor molecules interaction, specifically Fn binding to integrins receptor molecule of the host's cell via fnbp adhesion proteins that may offer a key possibilities in understanding the TB infection strategically caused by *M. tuberculosis*. So, targeting of these specific adhesion proteins could help us for development of novel drug that may further valuable in to reducing TB prevalence world widely.

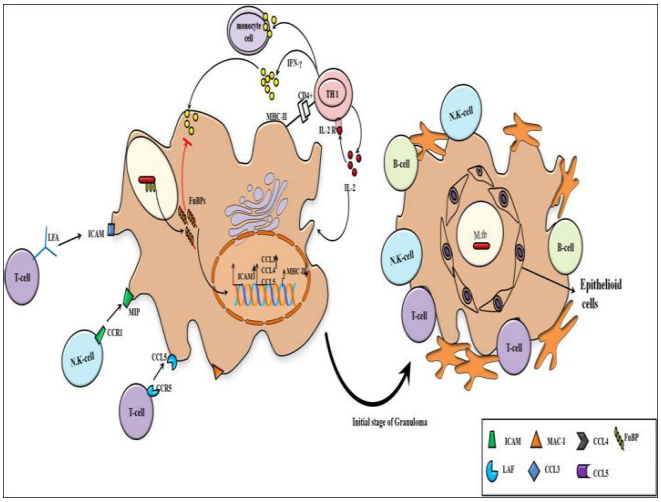

Figure 2: Schematic representations of the immune invasion of the host cell during M. tuberculosis infection: In M. tuberculosis infection, initially the bacilli internalized within macrophage via adhesions proteins (Fnbps) result in early phagosome formation. Emergence in virulence factors further follows up antigen presentation via MHC-II class protein pathway. The interaction of the processed antigen's peptide allocated to the T-helper cell 1 (Th1) via T-cell receptor (TCR), thus, interaction facilitate Th1 cell stimulation and macrophage induction secretes interleukin-2 (IL-2).
The essential cytokines production like IFN-γ may be inhibited through Fnbps expressed by M. tuberculosis. The defensive mechanism of the bacilli how it escape wisely from these bactericidal action and Fnbps act as a defensive molecules to inhibit IFN-γ stimulation with decline in MHC-II class protein expression remains elusive and up regulates the expression of Intracellular Adhesion Molecule-I (ICAM-I) and Macrophage adhesion ligand-1(MAC-I) marker proteins, Chemokines like Chemokine like ligand-3 (CCL-3), Chemokine like ligand- 4 (CCL-4) and Chemokine like ligand-5 (CCL-5). The secretion of certain chemokines through M. tuberculosis infection attracts on their respective receptors/moieties present on Natural Killer (N.K) cells contain CCR1, B-cells and T-cell (LFA) of the host and result in homotypic cellular adhesion may leads to granuloma formation.

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