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Full Length Research Paper

Adhesion molecules; A potent surface marker of Mycobacterium play key role in Host-pathogen interaction and pathogenesis

Ruchi Rawat; Monu and *Laxman S. Meena

CSIR-Institute of Genomics and Integrative Biology, Council of Scientific and Industrial Research, Mall Road, Delhi-110007

Corresponding Author's E-mail: meena@igib.res.in, Laxmansm72@yahoo.com

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Host-pathogen interaction is a different and complex type of association. Some Host-pathogen interaction does not cause clinically evident disease, while some of them lead to mortality. This interaction is mediated through special type of biomolecules called adhesion molecule. These adhesion molecule shows high affinity towards their specific receptor which present on the host cell surface. Adhesion molecule considered as potent virulence factor, that facilitate the infection, during the time of host cell invasion which mean Host-pathogen interaction. The accentuation of this session is to encompass the concept of Host-pathogen interaction that causes disease. Moreover to understand how adhesion molecules damage host immunity and pathogen survives in host body.

Key word: *M. tuberculosis*, Adhesion molecules, Fibronectin, Fibronectin binding proteins.

INTRODUCTION

Tuberculosis (TB) is one of the major cause of mortality, it is a disease of antiquity (Gagneux, 2012 and Smith, 2003). The recent global TB report shows that there are 9.0 million new TB cases in 2013 and around 1.5 million TB deaths (1.1 million among HIV-negative people and 0.4 million among HIV-positive people) (WHO, Global tuberculosis report (2014), TB India (2013). The completion of the genome sequence of the *Mycobacterium tuberculosis* (*M. tuberculosis)* and analysis revealed that, the presence of highly specific gene that express adhesion molecules on the pathogen's surface or host surface respectively that contributes in host-pathogen interaction. Every disease symptoms and their infection are based on their interaction, which mean host-pathogen interaction. In case of TB we mainly focused on two aspect mycobacterium regard the proximal physiology interface between the bacteria and host (Rajni et al., 2011). *The cell wall of M. tuberculosis contains complex type of lipids* i.e mycolic acid, lipoarmanon, arbinogalacton, glycoproteins etc. which having capability to cause tissue damage, before going to depth of disease firstly it is more important. to find out how the *M. tuberculosis* circumvent host defense and cause disease. In particular organ *M. tuberculosis* having potential to replicate within phagocytic cell i.e macrophage, which are pathogen killer cells (Stanley et al., 2013). In *M. tuberculosis* pathogenesis, the cell membrane perforation occurs that provide intracellular survival niche to mycobacterium in the host (Rapanoel et al., 2011). Recently identified that *M. tuberculosis* regulates their infection in mainly persistent phase, it is a highly dynamic interaction of *M. tuberculosis* with their host. If we studied proteins-proteins interaction mechanism then we analysed properties of specific system (Monu et al., 2015). It is suggest that identification of proteins-proteins interaction between host and pathogen helping to identify to new drug designing.

History

From the ancient time microbes were considered as a pathogenic and some are non pathogenic for their host. *M. tuberculosis* and *Mycobacterium avium* (*M. avium*) are pathogenic while microbes may be *Mycobacterium smegmatis* (*M. smegmatis*) are non-pathogenic species of mycobacterium (Casadevall et al., 2000). Since microbes may be present in specialized setting and

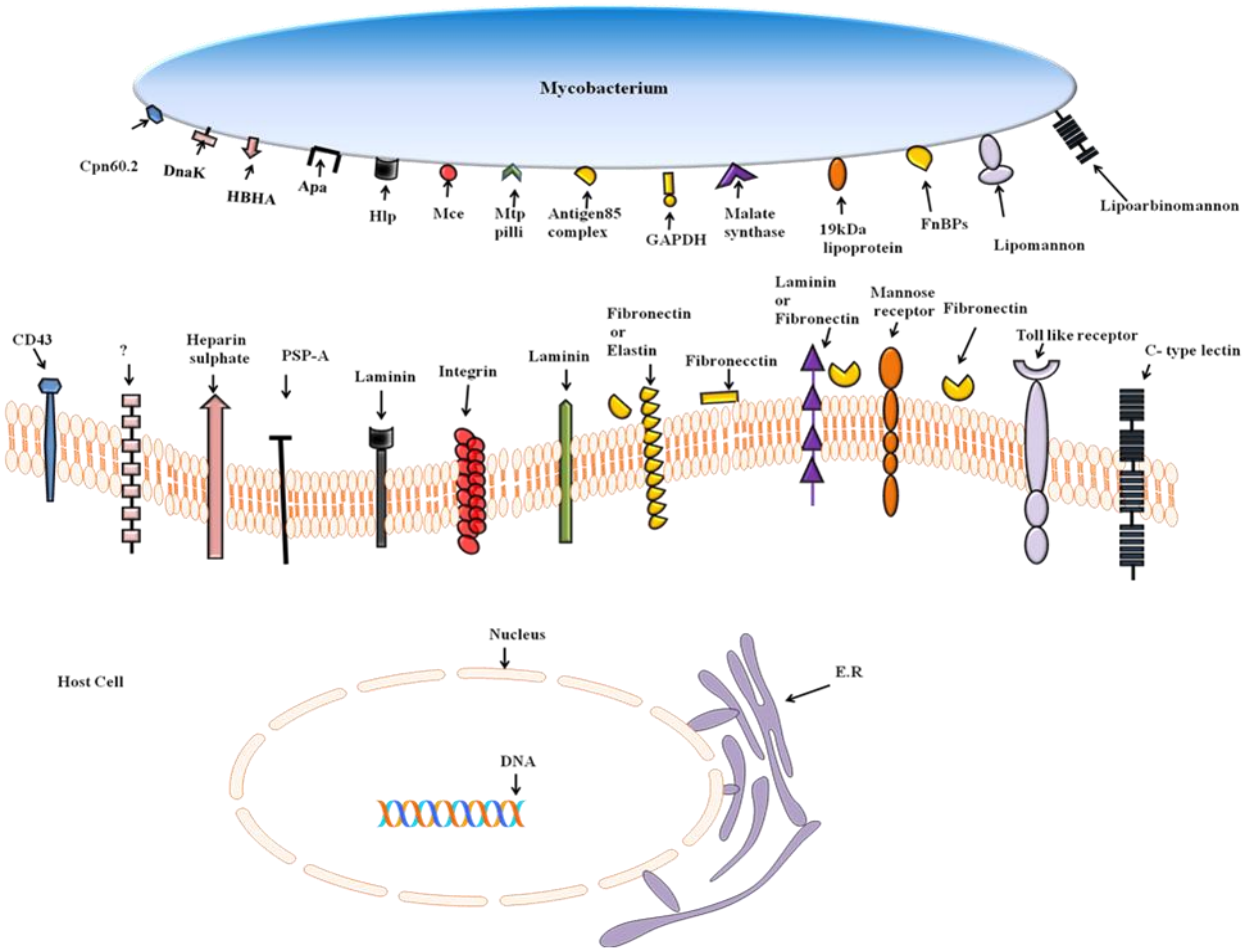

Figure 1: Schematic representation of the mycobacterium's adhesion molecules including their receptors; The different mycobacterium adhesion molecules are having strong affinity to contribute in host-pathogen interaction which described in the text. The structures depicted do not necessarily reflect the real receptors structure.

infection is a result of Host-pathogen interaction, moreover though many interactions likely still await discovery. Microbial pathogenesis is defined in two words virulence and pathogenicity. Virulence is expressed by quantitative measure while pathogenicity is a qualitative measure (Shapiro-Ilan et al., 2005). *M. tuberculosis* interacts with host by the phenomenon of proteins-proteins interactions which occur in molecular level, at this molecular level gene of pathogen is alter and acquired dormancy state. In *M. tuberculosis* pathogenesis is a role of host cell membrane perforation in intracellular survival of pathogen and host response (Meena LS et al., 2010). In future prospects which proteins encoded by *M. tuberculosis* genes should help in creating new vaccine. It is cleared that type of pathogen is most important factor which take part in host disease which affect host through secreted proteins (toxin), allergen molecule, inflammatory molecules etc (Danilchanka et al., 2014). Now days main prospects of TB control in global level, *M. tuberculosis* has evolved wide range of molecule term as adhesion, with having capability to bind with specific host receptor. The adhesion molecules are proteinss therefore they mainly bind with their specific target such as extracellular matrix proteins (ECM), Proteoglycans, laminin, fibronectin which present on the surface of host cell (Jaglic *et al.,* 2014).

Adhesion Molecules

Adhesion molecules are the group of proteins present on surface of the microbe's cell which involves in binding to cells one another and binding cells to extracellular matrix adhesion molecules which are specific for each cell as depict in (Figure 1) Mycobacterium that requires few selected adhesion molecules to binds with specific receptors as given in table (1) it may be an efficient inducer for interaction between host-pathogen.

Table 1: Showing the several examples of adhesion molecules of the Mycobacterium with their respective receptors on the host cell surface.

S. No.	Adhesion molecules.	Mycobacterium Species	Receptors	Reference
1	Cpn60.2	*M. tuberculosis*	CD43	[14]
2	DnaK	*M. tuberculosis*	Unknown	[18]
3	HBHA	*M. leprae*	Heparin Sulphate	[19]
4	Apa	*M. tuberculosis*	PSP-A	[29]
5	Hlp	*M. leprae*	Laminin	[24]
6	Mce	*M. tuberculosis*	Integrin	[15]
7	Mtp pilli	*M. tuberculosis*	Laminin	[28]
8	Antigen85 complex	*M. tuberculosis*	Elastin, precursor (tropoelastin)	[36]
9	GAPDH	*M. tuberculosis*	Laminin/actin/fibronectin	[31]
10	Malate synthase	*M. leprae*	Laminin/fibronectin	[34]
11	19kDa lipoproteins	*M. tuberculosis*	Mannose receptor	[39]
12	FnBPs	*M. tuberculosis*	Fibronectin	[41]
13	Lipomannon	*M. tuberculosis*	Toll like receptor	[45]
14	Lipoarbinomannon	*M. tuberculosis*	C- type lectin	[45]

Cpn60.2

Chaperonin 60.2 (Cpn60.2) is the adhesion molecule where cpn indicate chaperon molecules. As In earlier study's demonstration suggested that mycobacterium's high level of cpn60.2 can inhibit approximately 57% of bacterial association with macrophage. When polyclonal F(ab')2 fragment of anticpn60.2 were used to mask the surface presentation of these molecule chaperone a binding reduction of approximately 34% was seen for anti-cpn 60.2 F(ab')2 that mean cpn60.2 adhesion functionally with regard to macrophage interaction (Hickey et al., 2010; Zhang et al., 2012; Yong et al., 1987 and Henderson et al., 2006).

DnaK

DnaK is a chaperone molecular proteins encoded by the heat shock proteins genes *groEL* and *groE.* Dnak is also surface proteins on *M. tuberculosis*. In previous studies it demonstrated that Dnak and DnaJ chaperone molecules helps in bacterial (*Salmonella rotein serovar typhimurium*) invasion of epithelial cell (Hickey et al., 2009).

HBHA

Heparin binding haemagglutinin adhesion (HBHA) is 28kDa proteins. This proteins contains high lysine motifs present on the c-terminal region that bind to heparin sulfate mediating the adhesion *M. leprae* to epithelial cell. HBHA also plays role in the extra-pulmonary dissemination .This proteins used to investigate its adherence and antigenic property in leprosy (Silva-Carlos et al., 2013).

Hlp

Histone like proteins (Hlp) is a positively-charged, surface-exposed molecule of Mycobacterium which is much larger than other bacterial histone like proteins and is a highly conserved proteins present in all mycobacterium species (Lefrancois et al., 2011). This proteins was initially described as a laminin-binding proteins (LBP) that involved in *M. leprae* –Schwann cell (SC) interaction (Shimoji et al., 1999; Marques et al., 2000) a key role on bacterial attachment to respiratory epithelial cells (Aoki et al., 2004). This mycobacterium adhesion molecules play an important role in both leprosy and tuberculosis pathogenesis (Dias et al., 2012). It is hypothesized that the 'histone-like' proteins might likewise be involved in the stress response of *M. smegmatis* (Whiteford et al., 2011).

The Mtp pili

The Mtp pili are curli cell surface and structurally amyloids fibers composed of low molecular weight subunit proteins of pilin and produced by certain bacteria. It is suggested that pili consist adhesive property that have the binding ability with extracellular proteins laminin. Previous studies suggested that *M. tuberculosis* attack mostly in damaged tissue of human respiratory organs, in these instances ECM proteins highly exposed in damaged tissue than healthy tissue and these shown capability to bind with Mtp pili (Alteri et al., 2007). In other studies it also demonstrated that *Mycobacterium*

ulcerans (*M. ulcerans*) and *M. avium* pilis are important mediators in biofilm formation and have been implicated in biofilms formation leads to colonize the host tissue (Blanco et al., 2012; Ramsugit et al., 2013).

Apa

Alanine proline antigen (Apa) is a 45-47 kDa secretory alanine proline rich surface antigen proteins. It is suggested that an immune dominant Apa posses fibronectin binding activity. It is purposed that Apa work as a possible vaccine candidate for future vaccine against TB and it has been demonstrated in earlier study as an immunodominat antigen in mycobacterium species excluding *M. avium, M. marinum* and *M. smegmatis* (Ragas et al., 2007; Govender et al., 2014).

GAPDH

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is a family of proteins, use in glycolysis and also has functional activities (Seidler et al., 2013; Barbosa et al., 2006). In several studies elucidated that it a surface – associated proteins which interact to specific molecules such as fibronectin, fibrinogen, albumin, laminin and collagens etc (Govender et al*.,* 2014). It was also observed as a secreted and expressive proteins in gram positive and gram negative bacteria that are functionally complex proteins especially in interaction with other roteins during disease progression (Pancholi et al., 2011). In *M. tuberculosis* it participates in sequestration and internalization of human iron transport proteins through transferrin. In conclusion GAPDH molecules are multifunctional proteins rather than simple component.

Malate synthase

Malate synthase is an enzyme of glyoxalate pathway in *M. tuberculosis* single malate synthase secreted by glcB gene and plays a key role in pathogenesis and virulency. It is suggested that this is a secretory proteins in growth media culture (mid-exponential phase). Laminin and fibronectin are the binding site of malate synthase that shown the adherence capacity to the lung epithelial cells. This binding is achieved via unique c-terminal region of the *M. tuberculosis* (Kinhikar et al*.,* 2006).

Antigen 85 complex

An antigen 85 complex (ag85a, ag85b, ag85c) is a secretory proteins of mycobacterium that has been described as the potential cell surface marker of pathogen which contributes in host-pathogen interaction (Tang et al., 2012). Most likely these are the former protein recognizes as the first interacted antigenic molecules with host immune system during *M. tuberculosis* infection. Moreover, this protein plays key role in Adherence, invasion, dissemination and implicated in disease pathogenesis through fibronectin binding capacity in Mycobacterium (Kuo et al*.,* 2013; Belisle et al*.,* 1997). addition, this protein reported that it also binds with ECM to facilitate *M. tuberculosis* infection. Elastin and its precursor (tropoelastin) is a binding receptor of this protein. In the earlier study also described that ag85 mycobacterium proteins binds with the specific domain of fibronectin, which play a key role in host-pathogen interaction and might serve as virulence factor (Henderson et al*.*, 2011).

19kDa lipoproteins

The numerous bacterial adhesion molecules have already been described, on these grounds it would be of interest to identify the molecules of mycobacterium that are associated to the cell surface. So, in this context 19-kDa and 38-kDa antigens are glycosylated lipoproteins which anchored in lipid moiety of mycobacterium cell wall that elucidated by using anti-monoclonal antibody (Ciaramella et al., 2000). It induce interleukin and tumor necrosis factor, through Toll like receptor (TLR) signaling in macrophage, it studied that overexpression of this proteins on the immunoregulatory properties of *M. bovis* ,other report suggested that 19kDa proteins induced suppression of intracellular growth may involve apoptosis of infected cells (Stewart et al*.,* 2005).

FnBPs

Fibronectin binding proteins (Fnbp) antigens are prominent secretory proteins of mycobacterium tuberculosis. It is studied that bacterial fibronectin-binding proteinss (FnBPs) have actions other than adhesion. A key objective of the research in this area is to determine whether the utilization of different fibronectin-binding sites has different consequences for the overall biology of adhesion and virulence. Bacterial FnBPs is the complex form of the Fn proteins itself (and its physiological roles), which has to be understood to fully appreciate the nature of the interactions of FnBPs with fibronectin (Ahmad et al., 1996). The relationship between Fn with intgrin (receptor present on the host cell) is mediated by a bridge molecule known as Fn which is present on the extracellular matrix (ECM) in host. It is also noted that proteins function as autotransporters in *M. tuberculosis* (Henderson et al., 2011). Furthermore, in other mycobacterium species it

have been also reported that *M. bovis* contain gelatin binding domain (GBD) while *M. kansasii* contain heparin binding domain (HBD) which contributes in host-pathogen interaction (Peake et al., 1993; Naito et al., 2000).

13- lipomannon and lipoarbinomannon

The mycobacterium species have a unique lipid cell wall containing a vast repertoire of adhesion molecules such as 13-lipomannon and lipoarbinomannon both are immunomodulatory glycoconjugates molecules which possess highly variable chemical structure having ability to interact with different receptors and adhesion molecules in host-pathogen interaction (Rajni et al., 2011). Moreover, it also has been reported as an integral part of *M. tuberculosis* cell wall during infection. In continual research suggested that LAM inhibit the production of IL -12 and tumor necrosis factor (TNF), and increasing IL-21 production by dendritic cell. Whereas LAM consist different type of motifs which having the capability to interact with different pattern recognition receptor with pro or anti-inflammatory in *M. tuberculosis* pathogenesis (Mishra et al., 2011).

Abbreviation: Tuberculosis (TB); *Mycobacterium tuberculosis* (*M .tuberculosis); Mycobacterium avium* (*M. avium*); *Mycobacterium smegmatis* (*M. smegmatis*); *Mycobacterium ulcerans* (*M. ulcerans*);Extra-cellular matrix (ECM); Chaperonin 60.2 (Cpn60.2); Heparin binding haemagglutinin adhesion (HBHA); Histone like proteins (Hlp); laminin-binding proteins (LBP); Alanine proline antigen (Apa); Glyceraldehyde-3-phosphate dehydrogenase (GAPDH); Fibronectin binding proteins (Fnbp); Fibronectin (Fn); lipoarbinomannon (LM).

SUMMARY

Host-pathogen interaction process is carried out through specific biomolecules, identified as adhesion molecule. Adhesion molecules present on the cell surface of host and pathogen respectively, which expressed by some specific gene resulting host-pathogen interactions. All adhesion molecules are complementary to host receptor which present on the host cell surface. The emphasis of this session is how adhesion molecule interact with host receptor and facilitate infection, invasion of host cell that consequence disease occurs, and how host provide intracellular niche to pathogen survival mechanism, How pathogen damage our immune system. Each specific adhesion molecule binds with specific receptors. Now it is clear that host specificity of bacteria pathogen is determined by multiple molecule interaction between pathogen and their specificity. These results have implication in host-pathogen interaction control, developing new vaccine. *M. tuberculosis* survival mechanism does not have major influence alone; involvement of adhesion molecules may also shed light on host-pathogen interaction relationship and could open up new avenues for development of novel drug therapeutically useful approach by targeting mycobacterium adhesion molecules. Lastly, get an overview of host-pathogen interaction, adhesion molecule facilitate adherence, infection to pathogen invasion and epidemiology.

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