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Short Communication

FnBPs: An effective adhesion molecule in *Mycobacterium tuberculosis* pathogenesis

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Abstract

A significant step during infection is the attachment of pathogen with the host cell surface. *Mycobacterium tuberculosis* is a major human pathogenic strain that invades host cell by using several successful mechanisms. FnBPs are important protein present on microorganism which specifically binds with the Fn protein of host. Antigen85 complex and PE_PGRS family shows fibronectin binding properties that has evidenced important role in many bacterial adherence including species of mycobacterium. FnBPs plays a vital role in adhesion with the host surface as well as in various signalling pathway.

Keyword: Ag85, Fibronectin, Fibronectin binding protein, *M. tuberculosis*, PE_PGRS

INTRODUCTION

Mycobacterium tuberculosis (*M. tuberculosis)* is one of the major diseases causing pathogen prevailing in today's world resulting in victim's high mortality rate. According to global report by WHO in 2015 it has been stated that about 9.6 million population all over the world has been affected with TB and there was an estimated 1.2 million death in year 2014 (http://apps.who.int/iris /bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1).

M. tuberculosis is a facultative pathogenic bacterial strain that causes tuberculosis. It consists of mycolic acid in its cell wall that makes the organism impervious to gram's staining. It is one of the oldest and deadliest reported diseases prevailing in today's world. Any pathogen requires a specific adapter on the host surface at which it can result in firm attachment with the host, so that it may cause potent infection. In order to colonize on the host surface, bacteria require some adhesive molecules; generally, these adhesive molecules are protein in nature and are termed as "adhesion" (Henderson et al., 2011). Fibronectin (Fn) is an adhesive molecule which have high molecular weight, dimeric glycoprotein of 450kDa (Xu and Mosher, 2011) existing in two different forms: - soluble form in plasma and insoluble form in extracellular matrix (ECM) (Monu et al., 2015). Fn is a hetrodimer with two protein variant chain and each monomer consisting of three distinct types of domains (Xu and Mosher, 2011). It consists of multiple binding sites for collagen, heparin, and fibrin, and it has been shown to enhance the attachment of several pathogens both gram positive and gram negative, including mycobacteria to the host cells (Hall-Stoodley et al., 2006).

More than 100 Fibronectin binding proteins (FnBPs) have been studied till date in bacteria/prokaryotes. Role of FnBPs have been well established in different gram positive and gram negative bacteria such as *Staphylococcus aureus, Streptococcus pneumonia, Streptococcus pyogenes, Borrelia burgdorferi, Campylobacter jejuni, Haemophilus influenza*, etc. In case of all these pathogens FnBPs plays a vital role in adhesion with the host surface as well as in various signalling pathway (Henderson et al., 2011; Monu et al., 2015).

In case of *M. tuberculosis* it has been reported that it secretes various Fibronectin binding protein (FnBPs) in which Antigen85 complex is a potent molecule (Pasula et al., 2000) that aids in adherence with host Fn protein. Antigen85 (Ag85) complex is combination of three proteins namely 85A, 85B, 85C which is encoded by three different genes (Henderson et al., 2011; Monu et al., 2015) Rv3804, Rv1886 and Rv0129 respectively, that

plays a major role in virulence of mycobacterium. The proteins enclose a single peptide at N terminus followed by carboxyltransferase domain (Ramulu et al., 2006). These three proteins differ slightly in their molecular weight ranging from 30kDa-33kDa and are valuable immunomodulators (Henderson et al., 2011; Wiker and Harboe, 1992). Ag85 acts as mycolyl transferases (Pasula et al., 2000) that aids in cell wall biosynthesis of mycobacteria (Pasula et al., 2000; Sundar et al., 2015). Inspite of structural similarities in substrate binding site and active site in case of three mycolyl transferases as reported earlier, the surface residue varies at the active site which indicates that all three Ag85 enzymes in *M. tuberculosis* can evoke the host immune system (Ramulu et al., 2006). The three isoforms of Antigen85 complex synthesize mycolated arabinogalactan, trehalose monomycolate (TMM), and trehalose dimycolate (TDM) (Backus et al., 2014) which are important component of cellular envelop of mycobacterium. It has been reported that Ag85 enzyme catalyses the transfer of mycolyl residue from one molecule of α, α' TMM (trehalose monomycolate) to another leading to the formation of α, α' TDM (trehalose dimycolate). The virulent structure consists of α/β hydrolase fold and a catalytic triad is formed which is responsible for the mycolyl-transferase activity that comprises the amino acid residues S126, E230 and H262 (Ramulu et al., 2006).

The sites of interaction for different mycobacterial species has been reported differently. As in case of *M. bovis* protein it's GTPase protein binding domain (GBD) (Henderson et al., 2011; Peake et al., 1993), and in *Mycobacterium kansasii* protein it is Hemoglobin subunit delta (HBD) and cell-wall-binding regions (Henderson et al., 2011; Naito et al., 2000).

Another FnBP reported is Polymorphic GC-rich repetitive sequence (PGRS) in *M. tuberculosis* $H_{37}Rv$, Rv1759c gene that encodes fibronectin adhesion protein (FAP) as FnBP (Meena et al., 2015). The initial mode of infection is that FnBP secreted by the PGRS family protein binds to hosts Fn molecule. The binding site of FAP with Fn is GXRQRWFVVWLG. According to a study it has been reported that PE_PGRS60 is a potential macromolecule that is expressed on surface of Mycobacterial strain $H_{37}Rv$ that aids in pathogenesis of *M. tuberculosis* (Meena and Meena, 2015). In one experimental assay, it has been reported that disruption of gene encoded by Antigen85A has retrenched the growth of mycobacterium (Pasula et al., 2000).

In conclusion, we would like to state that cell adherence proteins are critically important for access of pathogen into host cell depending on the interaction of host cell surface markers and ligands present in pathogen's surface. Ag85 is major secretary product by *M. tuberculosis* and *Mycobacterium bovis*. Another potential family of FnBPs is PE_PGRS family gene that plays an important role in bacterial colonization, bacterial virulence and host-bacterial interaction by enhancing adhesion with host. These proteins also have ability to alter immune system of the host. So in deadly pathogen like *M. tuberculosis* targeting FnBPs protein by inactivating their gene would hinder the formation of effective adhesion molecules to the host which in turn will directly affect the virulence of the bacteria. This would lead us to an effective way to deal with pathogenesis of *M. tuberculosis* which gives an important approach in therapeutics.

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