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Imperative role of fibronectin binding proteins in cell adhesion and invasion: An overview

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The Cell adherence proteins are critical important as access of pathogens into the host cells depend upon the interaction between the host cell surface markers and the pathogen's surface ligands. The microbial pathogen entry initiate when it interact with host and that host-pathogen interaction assist by some host specific constituents such as Fibronectin (Fn) as well as pathogen's own cell surface adhesion molecules itself. The fibronectin has been known as adhesive glycoproteins that support binding to bacterial cell surface adhesions proteins; that proteins are known as Fibronectin Binding Proteins (FnBPs). Although Fn and FnBP association has been studied for more than decennium, these remarkably complex molecules are still the subject of exciting discoveries. Moreover, the roles of FnBPs during bacterial colonization and in pathogenesis still a major challenge in the host-pathogen interaction biology. In this review, we summarize the importance of FnBPs of both Gram-positive and Gram-negative bacteria in host-pathogen interaction and how these cell-specific adhesions protein contributes in cell invasion with their an imperative role in colonization, and establishment of infection. FnBP should be useful as a novel therapeutics, by targeting fibronectin binding genes or antibodies to FnBPs, that helpful in reducing bacterial colonization and pathogenesis.

Keywords: Fibronectin, Fibronectin binding protein, Gram -positive bacteria, Gram- negative bacteria, Extracellular membrane, Epithelium.

INTRODUCTION

The host-microbes interaction has been in use for nearly a century. The Gram-positive and Gram-negative bacteria's interactions trends emerge out that they have developed many strategies, some are specific to pathogens, to enable active interaction to host to gain access in internalization (Wilson M et al., 2002). Early in this period, the microbes were thought to be primary aggressors that governed the host-pathogen interaction, results in disease progression. In this reviewed, Both Gram-positive and Gram-negative bacteria display a multitude of adhesion proteins as Fibronectin binding proteins (FnBPs) on their cell surfaces (Kuusela P et al., 1978, Mongodin E et al., 2002) which are often used for adherence to Fibronectin (Fn) and initiate colonization and pathogenesis.(Henderson B et al., 2011, Peacock SJ et al., 1999).

Fibronectin (Fn), as it has been known a sticky extra-cellular multidomain glycoprotein that exists in soluble form in plasma as well as insoluble form in extracellular matrix (ECM) with cell adhesion regions independently in addition to several receptors specificities (Pankov et al., 2002). Fn mediated a wide verity of cellular adhesive activities to associates with bacterial Fibronectin Binding Protein (FnBP) (Vazquez V et al., 2011). Fibronectin has many biological functions and actions rather that of simple adhesion. As earlier studies described, it has reported that the Fn binding domains contain two regions; one is lying in C-terminal D-region and another in the N-terminal A-region (Henderson B et al., 2011). Fn can be a ligand for a dozen members of integrin receptors family that have defined specific binding domain site as heparin-binding domain (HBD), gelatin-binding domain (GBD), Fibronectin adhesion protein (FAP) that act as a bridge for bacterial FnBPs and leads

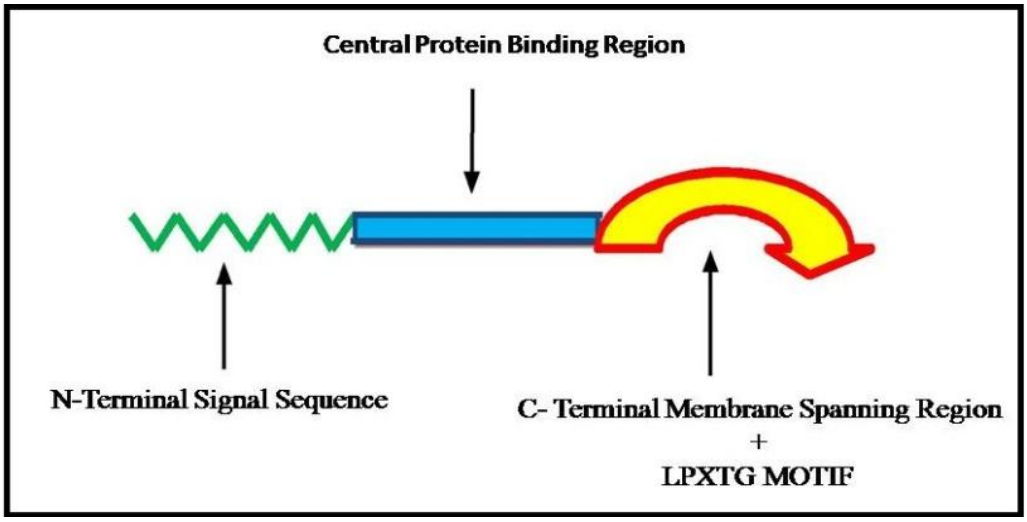

Figure. 1: Schematic representation showing: A MSCRAMM structure includes an N-terminal signal sequence that involved in secretion across the bacterial membrane and a central binding region a C-terminal membrane spanning region.

to contribute in internalization of bacteria into host cells (Katagiri Y et al., 2003). It is now recognized as a target for many bacterial proteins for instance FnBP, fibronectin adhesion protein (FAP) that functions generally in bacterial adhesins (Vazquez V et al., 2011). The bacterial close proximity to host cell, thus it gives a clear assumption to be made about its role in pathogenesis. The binding ability can be revealed by inactivating the gene encoding the FnBP followed by the testing of the isogenic mutant.

In several cases, such as gene of *Staphylococcus aureus* (*S. aureus*) showed that the inactivation of the genes lowers the cell invasiveness property and thereby lowers the bacterial binding to fibronectin and resulted in reduce adherence (Greene C et al., 1996). The isogenic mutant was found to be lesser virulent in animal models as compare by wild-type.

Another hand, the recurrent interaction of *Mycobacterium* to the host molecules is also gaining increasing significance with it adhesive properties. It also has been reported that Fn exhibits binding to specific FnBPs encoded by The PE_PGRS (Proline-glutamic polymorphic CG-repetitive sequences) family protein of *Mycobacterium tuberculosis* (Meena LS et al., 2014, Meena LS et al., 2010).

The following section dealt with the Gram-positive and Gram-negative bacteria that show some FnBPs importance in colonization and pathogenesis.

Fibronectin Binding proteins in Gram-positive bacteria

The adhesion of microbes to the host cell tissue is a key element in the initial stages of pathogenesis mechanism. These microbial adhesive components mediate adhesion to the host cell tissues that plays a major role in the host-pathogen interaction through specific fibronectin receptors etc. These cell surface adhesion molecules that interact with extracellular matrix components have been designated as MSCRAMMs (Microbial surface components recognizing adhesive matrix molecules). Particularly, MSCRAMMs including fibronectin, fibrinogen, collagen, heparin and in addition to several polysaccharides have been identified for binding ability (Patti JM et al., 1994). The MSCRAMM structure includes an N-terminal signal sequence involved in secretion across the bacterial membrane in a central binding region and a C-terminal membrane spanning region as depicted in (Figure1) (Wilson M et al 2002). The numbers of MSCRAMM expressed may vary from strain to strain, out of them the well studied fibronectin binding proteins are that of *Staphylococcus aureus* (*S. aureus*) and *Streptococcus pyogenes* (*S. pyogenes*).

Staphylococcus aureus

S. aureus is the leading overall cause of nosocomial infections that infects every tissue and organ system of the body. The members of microbial surface components recognizing adhesive matrix molecules MSCRAMMs are the family of adhesion proteins that have immense importance because of their ability to promote adhesion to ECM that surrounds and anchors cells in tissue, thus being liable for attractive targets for therapeutics and vaccination therapies (Katagiri Y et al., 2003) On *S. aureus* MSCRAMMs have multiple ligands, receptors, and additionally FnBPs are candidate participant in invasion and pathogenesis mechanism in

host cells. The host cell consist various surface expressed proteins that endorse and act as a bridge between bacterial surface expressed protein and host (Vazquez V et al., 2011). It was reported by Kuusela that *S. aureus* binds to fibronectin and a staphylococcal FnBP has been isolated (Kuusela P et al., 1978). For depth studies, the gene was cloned for this protein and was designated as fnb (Jonsson K et al., 1991). Moreover, a gene downstream of fnb encoding a second FnBP was discovered and the genes were renamed as fnbA and fnbB and that proteins encoded by genes were named as FnBPA and FnBPB respectively (Katagiri Y et al., 2003). *S. aureus* was previously being considered as an exclusive extracellular pathogen, but it's now clear that this bacterium is a facultative intracellular microorganism that can gain access to cytoplasm of mammalian cells that are not professional phagocytes, including endothelial cells, epithelial cells, keratinocytes, osteoblasts and cytokines expression etc (Lowy FD et al., 1988, Almeida RA et al., 1996, Jevon M et al., 1999, Yao L et al., 1996).

Adherence to human endothelial cells

A remarkable feature of *S. aureus* is its ability with which it seeds from the bloodstream to other body sites. Once the adhesion occurs, the *S. aureus* cells undergo a process similar to phagocytosis which results in changes in cytokine and interleukins expression (IL-1, IL-6 etc) [Lowy FD et al., 1988, Tekstra J et al 1999]. Moreover, hyper adhesiveness is induced for monocytes and granulocytes (Soell M et al., 1995)]. The bacterial determinants that promote adhesion of *S. aureus* to endothelium have not been elucidated yet. The clinical isolates have been reported of producing capsular polysaccharide serotypes 5 or 8 that after purification have been shown to bind the endothelial cells resulting in secretion of interleukin-6 and interleukin-8 (Yao L et al., 1996, Raja RH et al., 1990). *S. aureus* also expresses a large range of cell wall-associated proteins that promote adherence to extracellular matrix proteins and soluble plasma components. The fibronectin and FnBPs of *S. aureus* promote bacterial attachment to plasma clots (Peacock SJ et al., 1999). In this study, the role of many bacterial surface structures in adherence of *S. aureus* to endothelial cells was studied in vitro. Isogenic mutants defective in expression of FnBPs showed reduction in adhesion to endothelial cells. Adhesion was inhibited by anti-fibronectin polyclonal or monoclonal antibodies and by recombinant fibronectin binding domain from the FnBP of *Streptococcus dysgalactiae* (*S. dysgalactiae*) (Huesca M et al., 2000). These findings can cast light on a key interaction in the pathogenesis of metastatic *S. aureus* infection, the adherence to endothelial cells. The observation that *S. aureus* 8325-4 has two FnBPs, FnBPA and FnBPB underscores the importance of interactions with fibronectin in the biology of the organism (Grundmeier M et al., 2004). Adhesion of S. aureus to live endothelial cells is rapidly followed by internalization, a process which requires the presence of bacterial FnBPs. Many other invasive pathogens use integrins as cellular receptors. Plasma proteins are also an important component of these interactions. Finally, it noted that the FnBPs are not unique to *S. aureus* but are widely distributed among the streptococci (Heilmann C et al., 2004, Johnson KJ et al., 1999).

Others FnBPs like activities of *Staphylococcus aureus*

S. aureus possesses numerous other FnBPs such as Autolysin, Aaa (autolysin/adhesion of S. aureus) binds fibrinogen, fibronectin and mediates bacterial adherence to these host proteins (Heilmann C et al., 2005). Additionally, collagen binding protein (Can) and Clf A from *S. aureus* also have been reported for binding properties. An ECM binding filamentous protein homolog (Ebh) has also been found to be involved in bacterial cell wall stabilization and it has been explain that it binds to Fibronectin (Clarke SR et al., 2002). Ebh contains large tandem arrays that form large α-helical bundles. Furthermore, Eap has been found that is a small protein consisting of a single copy of MAP domain, its structure consists of a single α-helix packed against a small β-sheet. MAP domains have significant structural similarity to the part of the *S. aureus* superantigen and Eap itself has immunomodulatory activity that results in the inhibition of leucocytes adhesion to endothelial cells and neutrophil recruitment (Henderson B et al., 2011, Harraghy N et al., 2003, Qoronfleh MW et al., 1990). Moreover, stress response proteins as heat shock protein 60 (Hsp60) roles in infection still has not been established well. GroEL and DnaK proteins were identified previously (Dziewanowska K et al., 2000). These are immunogenic proteins distributed throughout the cytoplasm and associated with membrane proteins showed interaction with FnBP (Massey RC et al., 2001).

Candidate role of FnBP's in invasion of *S. aureus*

The large range of virulence factors that are produced by *S. aureus* and these contribute effectively in pathogenesis. The FnBPs are required by *S. aureus* to invade host cell machinery and invasions are carried out strategically. Several studies depict that antisera to the D1-D4 FnBP binding sites blocked the binding of bacteria to Fibronectin (Henderson B et al., 2011). The fibronectin-binding protein A (FnbA), an adhesion

molecule of *S. aureus* that is closely homologous to Fnbp of *S. pyogenes* that allow bacterial adhesion to endothelial cells of the host. It was demonstrated that FnBP has multiple binding repeats or sites in an unfolded region of the protein each confirming capable to adherence to host fibronectin and endothelial cell leads to invasion through tandom β-zipper in presence of specific receptor-like integrin (α5β1 etc.) enabling the tethering of *S. aureus* to host cell and induce disease (Schwarz-Linek U et al., 2003, Lemichez E et al., 2010, Powers ME et al., 2014). These virulence factors modulate host cell signaling and affects immune mechanism as a strong Potent stimulant cause inflammatory response by producing TNF-α, IL-1β and IL-6 etc, alter coagulation, deform vascular integrity leads to dysregulation of metabolism and host cell injury (Fournier B et al., 2005, Molinari G et al., 2000).

Streptococcus pyogenes

S. pyogenes or group A *streptococcus* is a pathogen whose binding to mucosal surfaces and epithelial cells in the host is crucial for disease induction (Nobbs AH et al., 2009). In previous studies, *S. aureus* had been shown to bind fibronectin which is an interaction that is important in bacterial attachment and opsonization. Recently, some strains of streptococci of serological groups A, C and G were also found to bind fibronectin (Mongodin E et al., 2002). It has been evaluated that group A *streptococcus* binds to the N-terminal region of fibronectin and it has also been suggested that the bacterial receptor was a protein (Speziale P et al., 1984). Fibronectin binding proteins in *streptococci* and *staphylococci* have been described as important mediators for adherence to eukaryotic cells (Donskey CJ et al 2004). So, developing a better understanding towards the role of bacterial surface proteins plays in the interaction of group A *streptococci* with epithelial cells is an important step towards the development of new strategies to fight infections.

Identification of some FnBP on the surface of Group A Streptococci

The pfbp gene is transcribed during cell growth and was present in class I and II *streptococcal* strains tested. Two distinct genotypes of prtf 2 exist such as FbaB and PFBP (Rocha CL et al., 1999). PrtF2 contains two Fibronectin binding domains and mediates attachment and internalization via different pathways (Tang YW et al., 2014). A new *S. pyogenes* fibronectin-binding protein (PFBP) has been elucidated. The largest surface PFBP protein (pfbp) cell wall associated molecules contains LPXTGX motif described for group A *streptococci* was identified from an M12 strain genomic library. Moreover, The PFBP repeated region expressed on the surface of other strain as *S. gordonii* which showed binding with Fibronectin (Dinkla K et al., 2003).

Protein F, an adhesive of group A *streptococci*

In this study, it has been demonstrated that the fibronectin binding property of *S. pyogenes* is mediated by protein F, also known as group A *Streptococcus* (GAS). Protein F1/SfbI is a bacterial surface protein that binds fibronectin with a high affinity (Okada N et al., 1998). However, the molecular and surface events during colonization of GAS to the human epithelial cell remain limited. Moreover, ECM-binding proteins have diverse Fibronectin molecules participate in invasion (Hanski E et al., 1992). The gene encoding protein F (prtF) produced a functional fibronectin binding protein in E. coli. Insertional mutagenesis of the cloned gene generated a mutation that resulted in the loss of fibronectin binding ability. When this mutation was introduced into the *S. pyrogenes* chromosome by homologous recombination with the wild-type allele, the resulting strains no longer produced protein F and lost their ability to bind to fibronectin. The mutation could be complemented by prtF introduced on a plasmid. Mutants lacking protein F had a much lower capacity to adhere to respiratory epithelial cells. These results depict that protein F is an important adhesion of *S. pyogenes* (Hanski E et al., 1992). During interaction of GAS to pattern recognition receptors (PRRs) roots to innate immune activation results in cytokines induction (TNF, INF,IL-1β), (Harder J et al., 2009, Kurupati P et al., 2010) activation of macrophages, DC through the TLR and MyD88 signaling cascades (Fieber C et al., 2014). The molecular interaction still undefined in response to surface proteins of these bacteria.

Virulence of Group A *Streptococci* FnBPs

The virulence and invasion of GAS FnBPs have been investigated for its significant role in the pathogenesis and the surface structures that is responsible for binding to fibronectin has not been clearly identified. The inactivation of Group A streptococci FnBP genes, (Greene C et al., 1996, Greeff A et al., 2002) or vaccination with these proteins is generally reported to diminish virulence in mice, suggesting that most of these FnBPs are vaccine candidates. Immunization of mice against PrtF1and PrtF2 induces a protective immune response (Ramachandran V et al., 2004, Rohde M et al., 2013). Inactivation of the fbaA gene significantly reduced cell adherence and invasiveness with Hep-2 cells and demonstrated decreased mortality in contrast to the wild-type FbaA bearing group A Streptococci in a

murine skin infection model (Henderson B et al., 2011, Kreikemeyer B et al., 2004). Inactivation of the gene encoding FbaB resulted in the reduction of attachment and invasion rates of Hep-2 cells and mortality in mice injected intraperitoneally with the strains of group A *Streptococci.* Inactivation of the shr gene resulted in a 40% decline in bacterial binding to Hep-2 cells and decreased virulence in a Zebrafish intramuscular infection model (Fisher M et al., 2008, Flier M et al., 1995). Thus, we can conclude that binding to fibronectin is a crucial part of the virulence behavior of group A *Streptococci*.

Streptococcus pneumonia

It was firstly reported by the Tuomanen's group that *Streptococcus pneumonia* (*S. pneumonia*) bound to immobilized fibronectin which is time, dose and temperature dependent (Fisher M et al., 2008). *S. pneumoniae* is a leading cause of sepsis, meningitis and middle ear infections in children, and of pneumonia and sepsis in the elderly or immune compromised (Wardlaw TM et al., 2006, WHO & UNICEF ,2009). It has been previously demonstrated that fibronectin mediates the streptococcal adhesion to host cells and that *streptococci* interact primarily with the N-terminal domain of Fibronectin. FBP54 is a 54-kDa protein from group A *streptococci* that binds to the N-terminal domain of fibronectin reacts with FBP54 (Holmes AR et al., 2001) and preferentially blocks *streptococcal* adhesion by approximately 80% in a dose-related fashion to buccal epithelial cells but did not block adhesion to Hep-2 cells. The fibronectin-binding domain of FBP54 has been localized to the first 89 N-terminal residues of the protein and exposed on the surface of *streptococci* that preferentially mediates adhesion to certain types of human cells (Courtney HS et al., 1996). Trypsin treatment of the bacteria resulted in decreased binding, suggesting that the bacterial adhesive component was a protein. It was also reported in several studies that a novel pneumococcal protein PavA with 67% identical amino acid sequence to Fbp54 protein in *S. pyogenes* (Holmes AR et al., 2001, Courtney HS et al., 1996, Pracht D et al., 2005). Isogenic mutants of *S. pneumoniae* both abrogated in PavA expression and reduced binding to immobilized Fibronectin. In additionally, PavA deficient results in a less efficient activation of the adaptive immune response (Noske N et al., 2009). Furthermore, the experiments also had been showed that induction of competence for genetic transformation has a role in virulence.

Fibronectin Binding Proteins from Gram-negative Bacteria

Since, more than 20 Gram-negative bacteria are known to be possessing fibronectin binding Proteins those involved in pathogenesis mechanisms. For intense Many Gram-negative species have a PavA/FBP54 homologue. Although, different types of FnBPs were identified in Gram-negative organisms, but the exact composition and molecular weight varies among different splice variants. A large number of such proteins of them also functions as auto transporters within the host cell. Here, brief descriptions of fibronectin binding proteins of some Gram-negative bacteria are discussed.

Borrelia burgdorferi

Borrelia burgdorferi (*B. burgdorferi*) is the causative agent of Lyme disease, which makes use of multiple adhesions for interaction with both the vector and colonizing hosts (Raibaud S et al., 2005). The cellular attachment and entry of pathogenic micro-organisms *B. burgdorferi* can be facilitated by the expression of adhesions such as FnBPs that binds with host Fibronectin. For instance, BBK32 gene that encodes a fibronectin binding protein which has been recognized as binding with host fibronectin and the biochemical mechanism of these binding proteins has been elucidated (He M et al., 2007, Probert WS et al., 2001). In addition to, the ligand-binding region of BBK32 was also found to be contributes in sequence homology for protein F1 of *S. pyogenes* which suggests a common adhesion mechanism like *B. burgdorferi* and can bind to the mammalian extracellular matrix they all were categorized as MSCRAMMS (Seshu J et al., 2006).

Many investigators also have been found adhesive proteins like p66 and Bgp, surface-exposed lipoprotein that bind decorin (DbpA and DbpB) and outer surface protein C (OspC) etc (Kenedy MR et al., 2012, Antonara S et al., 2007, Medrano MS et al., 2010). MSCRAMM significantly play a role in lyme pathogenesis likewise in Gram-positive bacteria. So, In conclusion, the involvement of BBK32 is necessary to the infection of mice by *B. burgdorferi*. In another study, Li .et al, used homologous recombination and replaced BBK32 gene by a kanamycin resistance cassette and failed to complement the mutant (Li X et al., 2006). However, the molecular invasion and the presence of multiple MSCRAMMs as FnBPs in *B. burgdorferi* are widely unclear and their candidate role in pathogenesis mechanism required an investigation on interaction to host cells and alteration in *Borrelia* specific interferon IFN-γ, IL-4, and IL-17 etc, in addition to upregulation or downregulation of immune regulatory molecules during invasion.

Campylobacter jejuni

Campylobacter jejuni (*C. jejuni*) is a curved rod-shaped

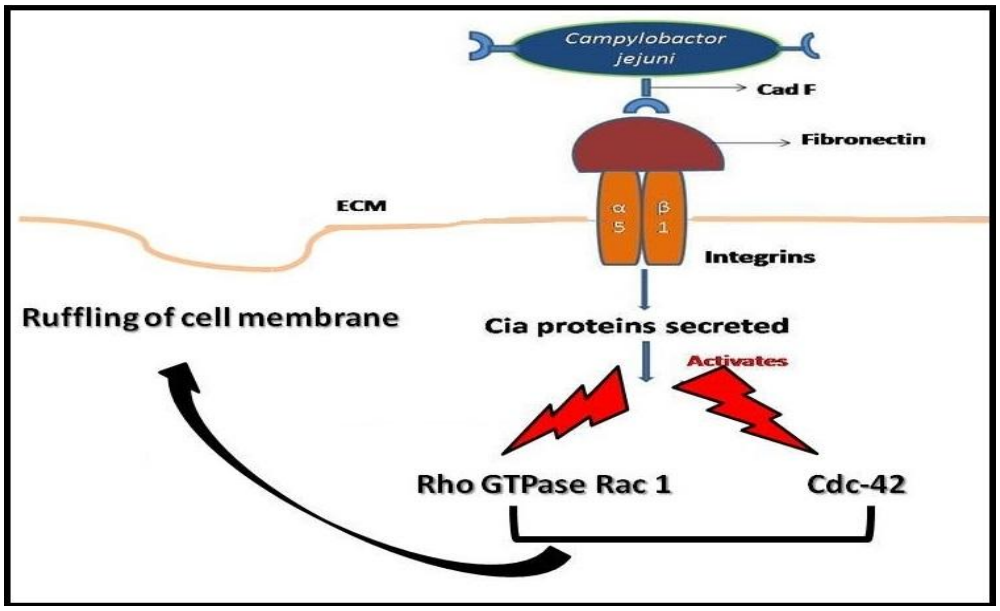

Figure 2: Schematic representation showing the Campylobactor jejuni cell invasion, the binding of Campylobactor jejuni bacteria to fibronectin via FnBP Cad F bring results in the secretion of Cia proteins that further activate the Rho GTPase Rac 1 and Cdc 42 (GTPase family signaling protein that regulates many aspects of intracellular actin dynamics) resulting in ruffling of host cell membrane and bacterial uptake.

flagellated and food-born gram-negative bacterium that leads to cause of bacterial-mediated diarrhoea and gastroenteritis disease worldwide (Allos BM et al., 2001). Outer membrane protein of *C. jejuni* such as CadF and FlpA are the two adhesions proteins that adhere and promotes binding of the pathogen to host epithelial cells by stimulates signal transduction that leads to full internalization (Konkel ME et al., 1999, Charles LL et al., 2013). CadF and FlpA proteins are used by *C. jejuni* results bind to host cells that activate or phosphorylate the epidermal growth factor (EGF) along with PI3-Kinase, c-Src results in requirement of focal adhesion kinase (FAK) for maximal invasion (Konkel ME et al., 2004). In addition, Virulence proteins secretion are required for the maximal invasion of cells, those are termed as Campylobacter invasion antigens (Cia). Cia are the proteins secreted from flagellar export apparatus and its export requires at least one of the two filament proteins. It was also observed that *C. jejuni* Cia proteins are responsible for Rho GTPase, Rac1 and Cdc42 (Eucker TP et al., 2012) activation that affects rearrangement of actin filament that cause membrane ruffling (Figure 2). The cooperative action of these bacterial CadF proteins constitutes 2 domains; one is N-terminal transmembrane which forms β barrel pore in other proteins and another one is C-terminal domain which cause α/β mixed fold (Henderson B et al., 2011). Examination was done with FlpA, a Fnbp of *C. jejuni* composed of 3 FN III-like repeats D1 D2 and D3 for identifying the host cell signaling induced by pathogen (Neal-McKinney JM et al., 2014). These interactions results in a massive pro-inflammatory response and increase in cytokines levels and adhesion protein expression like FnBP, FAP in an addition association others PE_PGRS family proteins of *Mycobacterium* etc still need to be focused.

FlpA and FlpA domain 2 a binding domain of Fibronectin

Fn is composed of type I (FNI), type II (FNII) and type III (FNIII) repeats and one of them the FlpA amino acid sequence contains three domains that resemble with FNIII repeats FlpA-D1, FlpA-D2 and FlpA-D3 (Flanagan RC et al., 2009). To check whether the three FlpA FNIII like domains possess Fn-binding activity, each FlpA domain was expressed as an N-terminal fusion with GST:GST-FlpA-D1 (aa 35-132) (Konkel ME et al., 2010), purified by GST tag and detection was done by using Ab against GST. On other hand, the alignments of amino acid sequence of FlpA-D2 with the FNIII repeats revealed that FlpA-D2 most closely aligned with FNIII. FlpA may also bind the N-terminus suggested by FNIII is involved in intramolecular interactions with the FNI and FNII repeats within the N-terminus of Fn.

Haemophilus influenzae

Haemophilus influenzae (*H. influenzae*) is a small gram-negative pleomorphic coccobacillus. Which involve the

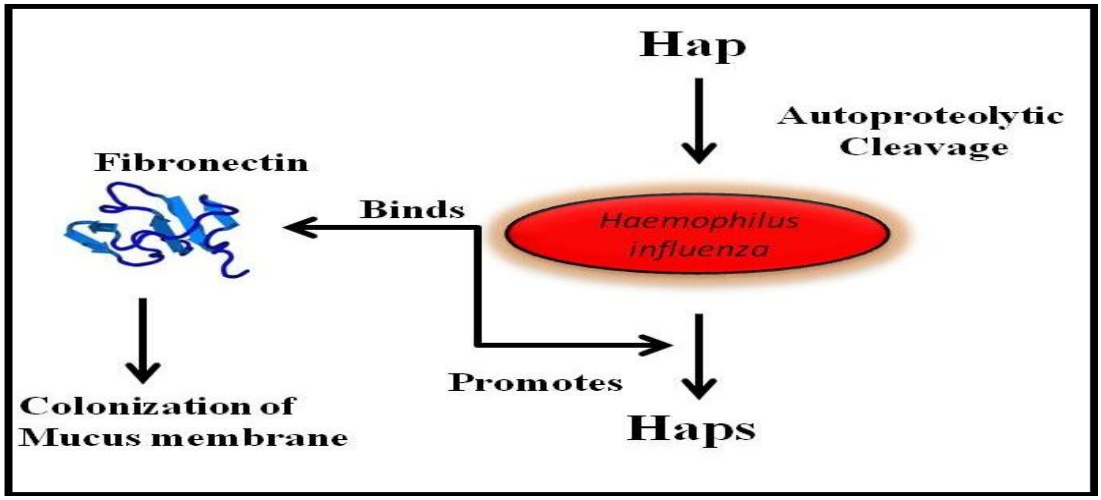

Figure.3: Schematic representation showing: The Hap adhesin of *Haemophilus influenza* that is an autotransporter protein undergo autoproteolytic cleavage and releases adhesive passenger domain Haps, from the cell surface of bacteria leads to promote bacterial binding to fibronectin and result in colonize the mucous membrane of upper respiratory tract.

most Virulent strain which is H. influenza type b (Hib). Some strains have no capsule and are termed as non-encapsulated *H. influenzae* or non-type able *H. influenzae* (NTHI). Most of the studies showed that Hap promotes bacterial adherence to purified fibronectin and Interactions between Hap-extracellular matrix protein that may play an important role in colonization and with NTHI initiates leads infection with colonizing the mucosa of upper respiratory tract (Fink DL et al., 2002). In this infection, the organisms encounter damaged epithelium and exposed basement membrane. *H. influenzae* has many adhesins from the monomeric to trimeric auto-transporter families. Out of them, only one monomeric auto-transporter Hap is involved in binding to host fibronectin. Many studies were done to examine the interactions between the Hap adhesin and selected extracellular matrix proteins (Virkola R et al., 1996). The pilus from this organism was shown to bind to the N-terminal 30 kDa and the C-terminal 40 kDa heparin binding fragments (Henderson B et al., 2011). Additionally, Hap found to promote adherence of bacteria to purified fibronectin, laminin and collagen IV and this adherence is enhanced by inhibition of autoproteolysis as the Hap protein undergo autoproteolytic cleavage, releasing adhesive passenger domain, Haps, from the cell surface of bacteria as shown in Figure 3. Pretreatment of bacteria was done to inhibit adherence with a polyclonal antiserum recognizing Haps (Fink DL et al., 2001). The portion of Haps containing serine protease at its end attached to a pertactin-like domain before the membrane pore found to bind to the GBD of fibronectin. So, by targeting this binding sequence shed light on adherence features have become an effective tool for drug designing to reduce pandemic effect all over the world.

SUMMARY

Fibronectin is a glycoprotein having adhesive properties that binds to fibronectin binding proteins of microorganism. Which act as a bridge between cells and their ECM also recognized as a target for a large number of gram-negative and positive-bacteria proteins, that function as bacterial adhesions and direct contribution in pathogenesis still unclear? In few last test periods, FnBPs has been identified in both gram-positive and gram-negative bacteria and their roles in colonization, virulence, and host-bacterial interactions. Many bacterial FnBPs of gram-positive and gram-negative are described that were noted for FAP activities, in our earlier studies *M. tuberculosis* PE_PGRS family protein (FnBP) reveals binding to Fn during *M. tuberculosis* pathological process. These proteins are categorized on the basis of sequence homology of proteins, on the sites of targeted fibronectin protein deposition and biological function of the proteins. In the current status of FnBPs categorization, relies on sequence conservation. These approaches use protein sequences to identify regions where similarity of sequences exists between proteins from that may have common function and can be deduced to understand the molecular line of attack of fibronectin to identify an eminence binding property of numerous fibronectin binding bacteria. With that goal, the researches on pathogen cell surface proteins as FnBP binding specific domain site could be targeted and that have the potential

to bind disease target's cellular markers to shed light on surface features have become an effective tool for drug designing and epitope modeling in genomic medicine emanate.

Future Direction

Fibronectin binding protein was shown to be required for pathogenesis by misusing the host fibronectin glycoprotein as adhesions to initiates the infections by modulating host defensive mechanism that leads to cause diseases. So, by targeting this fibronectin binding proteins we may overcome the pandemic burden of pathogenesis all over the world. Moreover, the treatment and survival strategy could also be improved.

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Abbreviations: FnBPs (Fibronectin binding proteins), MSCRAMMs (Microbial surface components recognizing adhesive matrix molecules), NTD (N-terminal domain), GBD (Gelatin-binding domain), HBD (Heparin-binding domain).

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