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Review

Bacterial adhesins, the pathogenic weapons to trick host defense arsenal

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ABSTRACT

Adhesins are bacterial proteins with host cell adhesive properties. These proteins occur in diverse architectures, ranging from capsules, vesicles, pili, fimbri, to enzymes. These proteins interact with host cell surface receptor proteins, for cross-membrane- trafficking and the invasion of host cells. Thus, they lead to inflammation and pathogenesis, of chronic as well as acute type. Inhibition of adhesin-mediated immune activation can be possible by mannose supplementation, assembly disruption, and host receptor blockage, among other approaches. Almost all bacterial pathogenesis is mediated by adhesins, yet when elaborated by normal flora, they might also be important for the exclusion of pathogens. For their ubiquity in bacterial pathogenesis, these lectin-like virulence proteins have been drug targets and vaccine components. Adhesins hold the clue for bacterial persistence and drug resistance as well, which can be detected through the annotation of hypothetical genes, the coding genes with sparsely-characterized functionality. This work takes a unique perspective on adhesins for better management of infectious diseases.

Contents

1. Introduction

Adhesins are the cell surface components of bacteria, associated with virulence [1,2]. Without the anchoring of adhesins, bacteria would be unable to tolerate the shear forces [3]. Types of adhesins vary depending on the Gram nature of the bacteria. Gram-positive bacteria have the adhesins in the form of protein or polysaccharide surface layer. Some of them are secreted in capsule or vesicle form, as in *Porphyromonas gingivalis* [4]. The soluble adhesin proteins aggregate to form biofilms [4]. The adhesin filaments can configure into fimbrial or nonfimbrial structures [5]. In the Gram-negative bacteria, adhesins are in fimbri (such as FimH) or pili form [5]. FimH is a bi-domain protein in which the N-terminal domain binds

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to host receptor, while the C-terminal domain is used for integration into the organelle [6]. Bacteria like *Escherichia coli*, and *Salmonella enterica* serovar Enteritidis have this fimbri [7,8]. Such aggregative fimbriae or adhesive amyloids are called curli. The major subunit protein CsgA of the curli is secreted across the membrans by the Sec and CsgG proteins. Some autotransporters also serve as adhesins, for example, the outer membrane proteins such as trimeric-autotransporter adhesins (TAA) [9,10]. TAAs can bind to host proteins like collagen, fibronectin, laminin, and others. In some instances, adhesin is part of a multi-purpose protein, occurring along with invasin [11]. Such adhesin/invasin proteins include TibA protein in enterotoxigenic *Escherichia coli* [11] and PagN in *Salmonella enterica* serovar Typhimurium [12]. Adhesins can be enzymes such as enolase [13], and pyruvate dehydrogenase [14]. Bacteria of genera *Lactobacillus*, *Weissella* and *Streptococcus* have several moonlighting proteins as GroEL, peptidase C1, enolase, formyl-CoA transferase, phosphoglyceromutase, triose-phosphate isomerase, phosphofructokinase, phosphoglycerate kinase etc., which act as adhesins as well [15]. Some adhesins rely on Ca^{2+} ion for their adhesion, as the cation offers rigidity to the protein [16]. Adhesins differ in their architecture and receptor specificities, for example, FimH binds to D-mannose on glycoproteins [7].

Bacterial adhesins play pleiotropic roles, encompassing offense and defense. Bacteria use their arsenal of adhesins to tackle competitors and find their ecological niche by adherence, invasion, survival within the eukaryotic cells, biofilm formation, serum resistance and cytotoxicity. The tropism determined by adhesins is diverse. Almost all parts of human body are prone to inflammation by adhesin-mediated immune activation. Dental canals, gut mucosa, bladder and lungs alveoli are some of the most-studied vulnerable sites. Adhesins attach to host extracellular matrix (ECM) components to enter the suitable niches. Adhesins are reported to be responsible for pathogen persistence as well [17]. Successful anchoring of bacteria via adhesin paves the way for host colonization, quorum sensing and biofilm formation [18]. Biofilms are crucial in drug resistance [19], a mammoth problem of current times.

These sticky appendages allow the bacteria to adhere to abiotic surfaces as well, which leads to contamination and infection, following surgeries. The adhesins like fimbriae are targets for antibodies. Antibodies are employed to disrupt physical properties of fimbriae and thus, they disarm the pathogens [20]. Passive immunization with anti FimH-antibodies is deemed an antidote against bacterial pathogens [21]. Thus, many vaccines are based on adhesins such as acellular pertussis vaccines [22]. *Neisseria meningitidis* lipoprotein GNA1870 or fHbp (factor H-binding protein) is being investigated as a vaccine against meningococcal diseases [23].

For their pathogenic as well as therapeutic significance, adhesins have been studied widely and deeply. Immense insights on adhesin's structure and functions have been accumulated over the years of investigations. However, adhesins undergo variation with changing host milieu, which begets an issue in tackling the pathogens. Many adhesins are masked by the bacteria to evade immune surveillance.

1.1. Adhesin versus human extracellular matrix (ECM) components

Extracellular space in human body is a complex meshwork of proteins and polysaccharides [24]. Inflammatory agents activate stromal fibroblasts, inducing them to secrete the extracellular matrix (ECM) components, which possess structural and adhesive attributes. Glycosaminoglycans (GAGs) like dermatan sulfate and hyaluronan, form the polysaccharide part, which are covalently linked with protein to form of proteoglycans [25]. The protein components of ECM include collagen, elastin, fibronectin, elastin, platelet-derived growth factors (PDGFs), transforming growth factor ß induced protein (TGFBIp) and laminin [26] etc. These proteins further occur in multiple isoforms. ECM plays critical role in cytoskeleton contractility, tensile strength, shock absorbance, cell proliferation, differentiation, adhesion, migration, gene expression, and tissue integrity (repairing tissue injury and healing). Diseases like fibrosis and cancer are the resultant of perturbed ECM [26]. TGFBIp mediates vascular inflammatory conditions like sepsis. Several host-derived extracellular RNA (eRNA) also occur in the ECM, which play role in pathogenesis, by adhering to pathogen surface proteins. ECM is dynamic as the proteins are remodeled by proteolytic enzymes as matrix metalloproteinases (MMPs) (*e.g.* collagenases, gelatinases (MMP-2 and MMP-9), stromelysins (MMP-3), and serine proteases (*e.g.*neutrophil elastase, urokinase-type plasminogen activator etc.) [27,28].

1.2. Immune evasion by the adhesins

Immune system is supposed to eliminate intruders and it strictly performs it, but it also enhances their ill-effects, by being hyper-stimulated. Several immune components can recognize the bacterial adhesins. Consequently, the infiltration of neutrophils and mast cells occur to the site of pathogenic entry. These immune cells elaborate proinflammatory cytokines like TNF-α (tumor necrosis factor), G-CSF (granulocyte-colony stimulating factor), interleukins as IL-1α, and IL-1β. Interleukin-8 (IL-8), a potent neutrophil-activating chemokine, induces the infiltration and migration of neutrophils into areas of bacterial infection. Adhesion molecules and chemoattractants on leukocytes and endothelial cells are the major interacting proteins [29,30]. The common chemokines involved in the immune response include chemokine (C-X-C motif) ligand (CXCL1, CXCL2), and chemokine ligand (CCL2, CCL3, CCL4, and CCL5) [31]. Monocytes are connected to ECM by the receptor integrins and are differentiated into macrophages, stimulated by serum growth factors (as vascular endothelial growth factor (VEGF)) and fibronectin [32]. Intercellular adhesion molecule 1 (ICAM-1) is one such host proteins that causes inflammation, inhibition of which using anti-ICAM-1 antibody has been protective against inflammation [33]. Vascular adhesion protein 1 (VAP-1), an amino oxidase, is another inflammation-inducible endothelial cell surface protein [34]. Other proteins interacting with pathogen adhesins include the prostaglandin E2, EP1/EP2 receptors, purinergic receptors ($P2\times2/P2\times3$), and neurokinin 1 receptor (NK1R) [35]. Solute carrier family 7 member 2 (SLC7A2), a cationic amino acid (L-Arg) transporter, is associated with adhesin crosstalk [36]. This protein on T cells is over-expressed by the adherence of pathogenic bacteria. SLC7A2 and talin-1, a focal adhesion protein, collaborate in bacterial attachment to human cells [36]. These high molecular weight cytoskeletal proteins – actin, talin, and ECM proteins are connected by integrins. Human CEACAM (carcinoembryonic antigen-related cell adhesion molecule) are signaling receptors on epithelial and immune cells [37]. These receptors have inhibitory ITIM/ITSM (immunoreceptor tyrosine-based inhibitory motif/immunoreceptor tyrosine-based switch motif) and activating ITAM (immunoreceptor tyrosine-based activation motif) –like motifs [38]. Bacterial pathogens bind to CEACAM isoforms for navigation into the host cells. Attachment to CEACAM1 leads to their internalization and suppression of host immune response, whereas attachment to the granulocyte-specific CEACAM3 leads to their internalization and destruction [39]. Platelet-activating factor receptor (PAFr) expression of pulmonary epithelium is up-regulated following stressors (*e.g.* smoking, pollutant inhalation) encounter, which results in chronic obstructive pulmonary disease (COPD) [40]. The high PAFr level favors the colonization of