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Carbohydrate Receptors of Bacterial Adhesins: Implications and Reflections

K. Ohlsen, T. A. Oelschlaeger, J. Hacker, and A. S. Khan

Abstract Bacteria entering a host depend on adhesins to achieve colonization. Adhesins are bacterial surface structures mediating binding to host surficial areas. Most adhesins are composed of one or several proteins. Usually a single bacterial strain is able to express various adhesins. The adhesion type expressed may influence host-, tissue or even cell tropism of Gram-negative and of Gram-positive bacteria. The binding of fimbrial as well as of afimbrial adhesins of Gram-negative bacteria to host carbohydrate structures (=receptors) has been elucidated in great detail. In contrast, in Gram-positives, most well studied adhesins bind to proteinaceous partners. Nevertheless, for both bacterial groups the binding of bacterial adhesins to eukaryotic carbohydrate receptors is essential for establishing colonization or infection. The characterization of this interaction down to the submolecular level provides the basis for strategies to interfere with this early step of infection which should lead to the prevention of subsequent disease. However, this goal will not be achieved easily because bacterial adherence is not a monocausal event but rather mediated by a variety of adhesins.

Keywords Adhesins, (A)fimbrial, Pili, Receptors, Anti-adhesion strategies

Contents

K. Ohlsen, T.A. Oelschlaeger (✉), J. Hacker, and A.S. Khan
Institut für Molekulare Infektionsbiologie, Röntgenring 11, 97070 Würzburg
e-mail: t.oelschlaeger@mail.uni-wuerzburg.de

1 Introduction

Microorganisms, such as the bacteria which colonize the gut, are known to be beneficial for host fitness (commensal). However, under certain conditions some of them acquire virulence-associated genes by horizontal gene transfer, become pathogenic and cause disease [1, 2]. In order to cause disease, bacteria must gain access into the host body and must be able to colonize the appropriate niche [3]. To colonize host mucosal surfaces, microorganisms have developed the capacity to produce surface molecules which enable them to adhere to the host cells and tissues [4]. Adhesion protects bacteria against natural cleaning mechanisms of the host, such as peristalsis of the intestine, coughing, airflow in the respiratory tract or the flow of urine through the urinary tract, and provides better access to the sources of nutrition [5]. It also facilitates the delivery of toxic agents and invasion of the bacteria into host tissues and cells. Many of the adhesive surface molecules expressed by bacteria are carbohydrate-binding proteins (lectins) called adhesins. Adhesins bind to the complementary carbohydrate receptors of the host cell membrane glycoproteins or glycolipids and determine the species specificity of pathogens [6, 7] and their preference for certain host cell or tissue types (tropism). For example, 987P and K99 fimbriated strains of enterotoxigenic *E. coli* can cause diarrhea in piglets, but not in adult pigs or humans [8–10]. Alternatively, host cells also express various cell surface molecules (lectins) that bind carbohydrates present on the surface of other cells or bacteria. The specific interactions between adhesins (lectins) and glycans are also crucial in cell–cell and cell–matrix interactions, signaling, differentiation and development [11]. Several other types of infectious agents such as viruses [12], fungi, e.g. *Candida albicans* [13] and amoebal parasite, e.g. *Acanthamoeba* [14] also require carbohydrate-mediated adherence for infection.

2 Bacterial Adhesins and Carbohydrate Host Receptors

Bacteria are capable to avoid successfully the mechanical defences of the host by specifically adhering to host cell surface carbohydrates linked to glycoproteins or to glycolipids. Adhesion is mediated either by hair-like hetero- or homopolymeric bacterial surface appendages called fimbriae, fibrils or pili, or by nonfimbrial adhesins. The adhesive subunit of heteropolymeric adhesins is in most cases located at the tip of these hair like structures [15, 16]. The expression of these adhesion determinants is not constitutive but dependent on, e.g. growth conditions. Thus, the bacteria may shift periodically back and forth between a fimbriated and nonfimbriated state. This phenomenon is known as phase variation. Moreover, an individual bacterium is capable to express either various types of fimbrial adhesins or different alleles of the same adhesin with different carbohydrate receptor specificities or affinities. For example, uropathogenic *E. coli* strain 536 (O6:K15:H31] has been shown to produce various types of fimbrial adhesins, including type 1,

Table 1 Carbohydrates as attachment sites for bacterial pathogens on animal tissues (Adapted from [19])

Organism	Target tissue	Carbohydrate	Structure
E. coli Type 1	Urinary	Manα3Manα6Man	GP
E. coli P	Urinary	Galα4Gal	GL
E. coli S	Neural	NeuAc (α2-3)Galβ3GalNAc	GL
E. coli CFA/1	Intestinal	NeuAc (α2-8)	GP
E. coli F1C	Urinary	GalNAcβ4Galβ	GL
E. coli F17	Urinary	GlcNAc	GP
E. coli K1	Endothelial	GlcNAcβ4GlcNAc	GP
E. coli K99	Intestinal	NeuAc(α2-3)Galβ4Glc	GL
C. jejuni	Intestinal	Fucα2GalβGlcNAc	GP
H. pylori	Stomach	NeuAc(α2-3)Galβ4GlcNAc	GP
		Fucα2Galβ3(Fucα4)Gal	GP
K. pneumoniae	Respiratory	Man	GP
N. gonorrhoea	Genital	Galβ4Glc(NAc)	GL
N. meningitidis	Respiratory	[NeuAc(α2–3)] Galβ4GlcNAcβ3Galβ4GlcNAc	GL
P. aeruginosa	Respiratory	L-Fuc	GP
	Respiratory	Galβ3Glc(NAc)β3Galβ4Glc	GL
S. typhimurium	Intestinal	Man	GP
S. pneumoniae	Respiratory	NeuAcα2-3Galβ1-4GlcNAcβ1-3Galβ1-4Glc	GL
S. suis	Respiratory	Galα4Galβ4Glc	GL

GP = glycoprotein, GL = glycolipids

P-related (Prf) and S-fimbriae [17]. P fimbriae of uropathogenic *E. coli* strains present three known classes of adhesin variants namely PapGI, PapGII, and PapGIII with different binding properties [18].

Although various adhesins of pathogenic bacteria have been identified (Table 1), only a small number of bacterial adhesins together with their host carbohydrate receptors has been well studied at the molecular level. For example, two fimbrial adhesins namely FimH and PapG of uropathogenic *E. coli* (UPEC) strains and adhesin F17-G of enterotoxigenic *E. coli* [20] have been crystallized and their three-dimensional structures have been elucidated [15, 21, 22]. Several other frequently expressed fimbrial adhesins of UPEC such as members of the S-fimbrial family which includes among others S-fimbria subtypes SfaI and SfaII and F1C fimbriae have also been well characterized and their host receptors were identified [23].

3 Type 1 Pili

FimH is the mannose-specific adhesive subunit of type 1 fimbriae and located at the tip of this organelle [24]. However, its presence in the fimbrial shaft has also been described which only becomes active upon fragmentation of the fimbrial shaft which in turn leads to the exposure of the binding site [25]. In addition to UPEC strains, type 1 fimbriae are expressed by a large number of other *E. coli* isolates,

e.g. from intestinal infections [4, 18]. They are also produced by other enterobacterial species such as *K. pneumoniae, Salmonella typhimurium* and *S. enteritidis*. On the basis of different affinities towards its natural receptor mannose or methyl α-mannoside, phenotypes of *E. coli* type 1 can be functionally subdivided into either high mannose-binding (MIH) or low mannose-binding (MIL) phenotypes [26]. Most isolates from the large intestine of healthy humans (around 80%) express a distinct MIL phenotype, whereas most isolates from urinary tract infections (more than 70%) express MIH variants [19]. Minor sequence variation in the FimH protein from different clinical isolates has been shown to be responsible for this altered carbohydrate-binding profile of the fimbriae [26].

Although the monosaccharide mannose linked to glycoproteins is the receptor for type 1 fimbriae of *E. coli* these fimbriae show a 40-fold higher affinity for oligosaccharides such as Manα3Manβ4GlcNAc or Manα6(Manα3) Manα6(Manα3)Man which are constituents of cell surface glycoproteins [27]. Similarly, the FimH subunits of *E. coli* and *K. pneumoniae* while being 88% homologous differ in their relative affinity for Manα3Manβ4GlcNAc and *p*-nitrophenyl α-mannosides [28, 29]. In addition, type 1 fimbriae of *Salmonella* species do not exhibit an enhanced affinity for mannose with hydrophobic substituents or for Manα3Manβ4GlcNAc [19].

X-ray analysis of the three-dimensional structure of FimC (this is the chaperon)–FimH (the adhesin) in complex with C-HEGA an analog of α-mannoside [15], with α-mannoside [30] and with α-butyl-mannoside [31] showed that a large portion of mannose surface is buried in the negatively charged binding cavity of the FimH lectin and it is involved in hydrogen bonding with combining site residues. The binding cavity is surrounded by a hydrophobic ridge which is responsible for the enhanced binding of hydrophobic mannose conjugates [30, 31]. It could be that the binding site of *Salmonella* FimH is smaller than that of *E. coli* and *K. pneumoniae* and is devoid of the hydrophobic ridge and hence does not exhibit an enhanced affinity for mannose with hydrophobic substituents or for Manα3Manβ4GlcNAc. Furthermore, recent studies involving the type 1 fimbriae of *E. coli, K. pneumoniae* and *Salmonella* showed that the fimbrial shaft imposes conformational constraints and thus modulates the binding specificity of fimbriae [32]. FimH adhesin alone is capable of binding to a broad range of mannosides. This observation may be responsible for the tissue tropism observed for the various type 1 fimbriated pathogens [33].

4 P Fimbriae

P-fimbriated uropathogenic *E. coli* strains are linked to the more serious urinary tract infections. The adhesin PapG of P-fimbriated uropathogenic *E. coli* strains in contrast to the adhesin FimH of type 1 fimbriae is specific for glycosphingolipids of the globo series namely globotriaosylceramide (GbO3), globotetraosylceramide (GbO4) and Forssman antigen (GbO5). These bacteria bind to the galabiose Galα4Gal disaccharide when it is present either at the nonreducing position or at an internal one of such glycolipids. There are three different alleles of PapG

(PapGI, II and III) which bind with different specificities to different receptor isotypes. PapG1 binds favourably to the human urinary bladder whereas PapGII and GIII favour colonization of the human and dog kidney, respectively [18, 21]. The recently determined crystal structure of PapGII adhesin bound to a galabiose-containing ligand not only reveals the molecular basis for the tropism conferred by the PapGII adhesin but also suggests a plausible model that accounts for the tropism conferred by PapGII [21].

5 S Fimbriae

The members of the S-fimbrial family differ in their receptor specificities. S-fimbrial adhesin Sfa-S recognize α-sialyl-2-3-β-lactose-containing receptors and are predominantly expressed by strains which cause sepsis and meningitis but also by urinary tract infection (UTI) isolates [34, 35]. Their binding to brain glycolipids has also been demonstrated [36]. In contrast, the F1C-fimbrial adhesin binds with a high affinity to β-GalNAc-1, 4-β-Gal containing glycolipid and is preferentially expressed by urinary tract infection (UTI) isolates [23].

6 Other Adhesins of Gram-Negative Bacteria

Furthermore, bacteria specifically binding to other carbohydrate receptors have also been described (Table 1). For example, *Neisseria gonorrhoeae*, a genital pathogen binds to *N*-acetyllactosamine (Galβ4GlcNAc, LacNAc). *Helicobacter pylori*, the causative agent of peptic ulcer, expresses several lectins with distinct binding specificities [37, 38]. Some of them recognize NeuAc(α2–3)Galβ4Glc(Sia3Lac) and its *N*-acetylglucosamine analog (Sia3LacNAc) while others are specific for the Le^b determinant Fucα2Galβ3[Fucα4]GlcNAc. The adhesins of enterotoxigenic *E. coli* K99 and F17G of F17 fimbriae bind to glycolipids containing *N*-glycolylneuraminic acid (NeuGc) and *N*-acetylglucosamine receptors on the microvilli of the intestine of ruminants, respectively. The high resolution crystal structure of the lectin domain of F17-G in complex with *N*-acetylglucosamine revealed that the monosaccharide is bound on the side of the ellipsoid-shaped protein in a site conserved in all natural variations of F17-G [20].

7 Adhesins of Gram-Positive Bacteria

Similar to the Gram-negative bacteria, Gram-positive bacteria also express a great variety of factors that enable these micro-organisms to adhere to host cell structures on cell surfaces. Most of these are proteins binding to proteinacous partners.

Prominent examples are matrix-binding proteins called MSCRAMMS (microbial surface components recognizing adhesive matrix molecules). These proteins bind to extracellular matrix proteins such as fibronectin, collagen, vitronectin, laminin and others [39]. Many of these adhesins play an important role in pathogenesis of Gram-positive pathogens. In contrast to the extensive work on protein–protein interactions between adhesins of Gram-positive bacteria and host surfaces, less is known about binding of Gram-positive bacterial adhesins to carbohydrate structures.

8 Adhesins of Streptococcus

One of the best studied carbohydrate binding adhesins of Gram-positive bacteria is expressed by *Streptococcus suis* strains. This bacterium causes meningitis, septicemia, and pneumonia in pigs and also in humans [40]. *S. suis* recognizes galactose containing glycolipids with specificity to the disaccharide Galα1–4Gal sequences present, e.g. in P blood group antigens. Moreover, experimental binding to pharyngeal tissue of pigs could be inhibited by trihexosylceramide (GbO3) indicating that the glycolipid may function as a receptor for galactose-binding strains of *S. suis* in pig pharyngeal epithelium [41, 42]. Two variant adhesins, inhibitable by galactose and *N*-acetylgalactosamine (type PN) or galactose only (type Po) have been described. Both prefer binding of the disaccharide in a terminal position [43, 44]. Surprisingly, on *S. suis*, no fimbriae have been observed, so it is likely that the adhesins of *S. suis* are afimbrial ones.

Streptococcus gordonii and related species of the viridans group are major components of the human oral microflora. These organisms play prominent roles as pioneer colonizers in the development of dental plaque [45]. In addition to colonizing surfaces in the human oral cavity, viridans streptococci cause infective endocarditis. The sialic acid-binding adhesins Hsa and GspB of *S. gordonii* have been shown to bind sialoglycoproteins on the platelet surface. The sialoglycoprotein receptors were identified as platelet glycoprotein Ib α (GPIbα) and glycoprotein IIb (GPIIb) [46, 47]. GspB and Hsa are serine-rich surface glycoproteins that consist of an *N*-terminal putative signal peptide, a short basic amino acid-rich region, a longer serine-rich region and a *C*-terminal cell wall anchoring domain. Binding assays with fusion proteins of the basic amino acid-rich region to a panel of oligosaccharides revealed that the basic amino acid-rich region BR of Hsa can bind both α(2-3) sialyllactosamine [NeuAcα(2-3)Galβ(1-4)GlcNAc] and sialyl-T antigen [NeuAcα(2-3)Galβ(1-3)GalNAc], whereas the BR of GspB only binds sialyl-T antigen [47]. GspB facilitates binding to carbohydrates bearing sialic acid in either α[2–3) or α(2–6) linkages, with a slight preference for α(2–3) linkages [46].

Another member of the viridans streptococci, *S. mutans*, plays an important role in the formation of dental caries and binds tightly to tooth surfaces. The bacterium is capable of binding salivary components such as salivary agglutinin. It has been shown that *S. mutans* can bind to Lewis antigen carbohydrate epitopes containing fucose residues that are present on salivary agglutinin [48].

Streptococcus pneumoniae is a major cause of pneumonia, otitis media, meningitis, and septicemia resulting in the death of more than 1 million people every year. Various virulence determinants of pneumococci have been described including the highly variable polysaccharide capsule, pneumolysin toxin, and carbohydrate binding proteins. For example, binding of *S. pneumoniae* to respiratory cells can be inhibited by sialyted oligosaccharides containing the pentasaccharide NeuAc(α-3) Galβ4GlcNAcβ3Galβ4Glc, as well as with the corresponding internal tetra- and trisaccharides Galβ4GlcNAcβ3Galβ4Glc and GlcNAcβ3Galβ4Glc, respectively [49]. Interestingly, sialylated oligosaccharides and glycoproteins at concentrations in the millimolar range block adherence of *S. pneumoniae* to epithelial cells of the upper respiratory tract, thereby reducing the load of colonizing organisms and diminishing the risk of infection. Moreover, in a rabbit model of pneumonia, NeuAcα2-3Galβ1-4GlcNAcβ1-3Galβ1-4Glc protected against infection by *S. pneumoniae*, and in an infant rat model, also reduced nasopharyngeal colonization by *S. pneumoniae* [50]. Thus, the use of orally or nasally administered oligosaccharides as prophylactic and/or therapeutic agents to promote clearance of *S. pneumoniae* from the nasopharyngeal mucosa may be applied as a strategy of reducing the risk of developing otitis media, meningitis or pneumonia.

Older reports deal with the binding of Gram-positive and Gram-negative pathogens involved in lung infections of cystic fibrosis patients and pneumonia such as *Staphylococcus aureus*, *Pseudomonas aeruginosa, Haemophilus influenzae, Streptococcus pneumoniae*, and *Klebsiella pneumoniae.* These pathogens bind specifically to fucosylasialo-GM1 (Fucα1-2Galβ1-3GalNAcβ1-4Galβ1-1Cer), asialo-GM1 (Galβ1-3GalNAcβ1-4Galβ1-4Glcβ1-1Cer), and asialo-GM2 (GalNAcβ1-4Galβ1-4Glcβ1-1Cer) present on the surface of lung tissues [51]. The investigated pathogens do not bind to galactosylceramide, glucosylceramide, lactosylceramide, trihexosylceramide, globoside, paragloboside, or glycosphingolipids including the gangliosides GM1, GM2, GM3, GD1a, GD1b, GT1b, and Cad. The authors concluded that the tested bacteria require at least terminal or internal asialo GalNAcβ1–4Gal sequences. This observation may be of biological relevance as substantial amounts of asialo-GM1 occur in human lung tissue [51]. However, additional work has to be done to characterize the significance of these binding properties for the pathogenesis of lung infections. Furthermore, it is not known which adhesive proteins are involved in the described Gram-positive pathogen–carbohydrate interaction.

9 Adhesins of *Staphylococcus*

Gram-positive opportunistic pathogens such as *Staphylococcus epidermidis, S. aureus, E. faecalis and E. faecium* have the capacity to form biofilms on foreign medical devices such as catheters, and surgical implants [52, 53]. These microorganisms are normal inhabitants of healthy humans, in recent years, however, the bacteria emerged as a common cause of nosocomial infections [54]. Interestingly,

the capacity of staphylococci to form thick multilayered biofilms on polymer and metal surfaces is associated mostly with the synthesis of an extracellular polysaccharide the so-called polysaccharide intercellular adhesin (PIA) [55]. The enzymes involved in PIA production are encoded by the *icaADBC* operon [56]. The *icaADBC* genes are more prevalent in *S. epidermidis* strains from device-associated infections than in commensal isolates suggesting an important role of polysaccharide interactions in pathogenic *S. epidermidis* strains [57]. Biofilm-positive bacteria are less susceptible against the action of antibiotics and are shielded from the host immune system. The polysaccharide PIA is a linear β-1,6-linked glucosaminoglycan that is essential for intercellular adhesin and biofilm accumulation of many *S. epidermidis* clinical isolates [58]. That PIA mediates also adherence to host structures is not known, however, it is tempting to speculate about this.

10 Implication in Antimicrobial Activity

The examples discussed above impressively show the diversity and importance of interaction between bacterial adhesion determinants and carbohydrate-containing receptor molecules. Pathogenic bacteria use binding to carbohydrates in different disease stages. However, many questions remain to be answered to unravel the full spectrum of bacteria–host interactions via carbohydrate binding.

Nevertheless, anti-adhesion strategies based on interference of pathogen–host interaction by carbohydrates represents an attractive approach in antimicrobial therapy. This concept may especially be promising as antimicrobial resistance is becoming a global health problem. Specific inhibition of adhesion properties should apply less selective pressure on pathogens therefore avoiding rapid resistance development. However, microorganisms use multiple adhesion factors, thus several structures have to be targeted for efficient inhibition of adhesion to host tissues. Moreover, many inhibitors of protein–carbohydrate interaction show only relatively low affinity, this is true at least for monovalent inhibitors. The development of improved multivalent ligands with higher affinity is one principle to increase the efficacy of anti-adhesion therapy. For in vivo application the size and polarity of such ligands may be problematic, therefore topical applications such as in the intestine or lung may have the highest potential for therapeutical use.

11 Final Reflections

Fimbrial adhesins may be visualized by electron microscopy. However, the processing for analysis by electron microscopy might cause alterations of the specimens, e.g. by dehydration. This might result in the collapse of certain fimbriae. Therefore, despite no fimbriae are visible by electron microscopy the “afimbrial” adhesins of the Dr family, e.g. AfaE of diarrheagenic and uropathogenic *E. coli* in fact assemble

into flexible fibers with the AfaD at the tip, which is an invasin [59]. This example also shows that fimbriae are often multi purpose tools. Obviously, they not only mediate adherence but function also as invasins for uptake into host cells and activate host proteases in order to cross host barriers, i.e. the blood-brain-barrier [60]. The later might be achieved by immobilization of plasminogen and tissue-type plasminogen activator on S and type 1 fimbriae [61].

Other adhesins of *E. coli* as antigen 43, AIDA-I, TibA and intimin of enteropathogenic and enterohemorrhagic *E. coli* are true afimbrial adhesins i.e. they are integral outer membrane proteins. However, also intimin seems to be involved in invasion of host cells [62, 63]. Intimin, which is actually a whole family of adhesins, is the only example of an adhesion that uses a protein (Tir: translocated intimin receptor) in the host cell membrane, that is a bacterial protein inserted into the host by the bacterial type 3 protein secretion system [64].

At least some adhesins bind to more than one receptor. Intimin might not only bind to Tir but also to β1 containing integrins as well as to nucleolin [65]. The Dr adhesin recognizes not just the short consensus repeat domain as all members of the Dr family of adhesins but also type IV collagen, which is a critical step in renal persistence [66].

Besides fimbrial and afimbrial adhesins, there are other surface structures that act as adhesins. For example, in *Pseudomonas aeruginosa* the major flagellar protein flagellin was identified as the adhesin responsible for binding to Muc 1 mucin [67].

In summary, bacterial adherence is not just mediated by one bacterial surface structure interacting with one host receptor. Rather, adherence is a process involving several bacterial and host cell components which interact in a temporal and special order. Interference with these processes in order to block infection will not be an easy task [68].

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