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Targeting the bacteria-host interface
Strategies in anti-adhesion therapy

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Abbreviations: ClfA, clumping factor A; CAN, collagen-binding protein; EHEC, enterohemorrhagic *E. coli*; EPEC, enteropathogenic *E. coli*; ETEC, enterotoxigenic *E. coli*; FnbpA, fibronectin binding protein A; Gal, galactose; Glc, glucose; GSL, glycosphingolipid; LPS, lipopolysaccharide; LT, heat-labile toxin; MAM, multivalent adhesion molecule; PAK, *P. aeruginosa* strain K; SA, streptococcal antigen; Srt, Sortase; STa, shiga toxin subunit A; STEC, shiga toxin producing *E. coli*; UPEC, uropathogenic *E. coli*; UTI, urinary tract infection

Bacterial infections are a major cause of morbidity and mortality worldwide and are increasingly problematic to treat due to the rise in antibiotic-resistant strains. It becomes more and more challenging to develop new antimicrobials that are able to withstand the ever-increasing repertoire of bacterial resistance mechanisms. This necessitates the development of alternative approaches to prevent and treat bacterial infections. One of the first steps during bacterial infection is adhesion of the pathogen to host cells. A pathogen's ability to colonize and invade host tissues strictly depends on this process. Thus, interference with adhesion (anti-adhesion therapy) is an efficient way to prevent or treat bacterial infections. As a basis to present different strategies to interfere with pathogen adhesion, this review briefly introduces general concepts of bacterial attachment to host cells. We further discuss advantages and disadvantages of anti-adhesion treatments and issues that are in need of improvement so as to make anti-adhesion compounds a more broadly applicable alternative to conventional antimicrobials.

Concepts of Bacterial Adhesion

A bacterium's ability to colonize its host highly depends on the mechanisms it has in place to withstand the host's mechanical and immunological clearance mechanisms. To avoid being removed from the organism, bacteria have to be able to quickly and effectively attach to host cells. Adhesion is also a universal prerequisite for pathogens to efficiently deploy their repertoire of virulence factors and exert effects on host cells, no matter if they are effector-mediated or toxin-mediated. For example, a wide range of gram-negative pathogens employ type III, type IV, or type VI secretion systems to inject effector proteins into host cells where they biochemically tune the host's cellular machinery to facilitate infection. Translocation of effector proteins from the bacterial cytoplasm into the host cell's cytoplasm requires direct contact between bacterium and host.[1] Binding needs to be tight such that the interaction is long enough to allow the correct sequence of proteins to be injected over time. Several studies have shown that different effector proteins are not all injected simultaneously but follow a sequence depending on their initial concentrations and affinity for the translocation machinery.[2,3] This makes sense since, in some cases, effectors injected by the same pathogen at different time points during infection can have opposing activities.[4,5] Hence, if bacteria are removed from host cells prematurely, infection is not productive.[6] In the case of autotransporter-toxins, which are secreted by bacteria into the extracellular medium prior to entering host cells, local toxin concentration is critical to their activity.[7] For example, in the case of pore-forming toxins, subunits have to be co-localized to be able to form a pore in the host cell membrane. Hence, their mechanism of action also depends on close proximity between pathogen and host cell to avoid a dip in local protein concentration through diffusive loss. Because attachment is so crucial to the fate of infection, bacterial pathogens have devised a vast repertoire of attachment mechanisms for initial contact with host cells.

Upon encountering the host cell, bacteria first attach via weak non-specific interactions with the host cell surface. This is not mediated by specific adhesin-receptor pairing, but rather by overall physicochemical properties of the bacterial and host surfaces, such as charge and hydrophobicity.[8] This reversible adsorption process is followed by initial adhesion, which can be mediated by specific interactions, but still gives the bacteria enough freedom of movement to sample the host cell surface through a rolling or gliding motion.[9] These initial, transient interactions are then reinforced by high affinity bacterial–host cell interactions, which rely on specific interactions between bacterial surface molecules and host cell receptors (**Fig. 1**). The binding moiety on both the bacterial and host side can vary in terms of their chemical identity to be a sugar, a protein or a lipid. All these pair-wise combinations can be involved in mediating specific bacterial–host cell interactions.

All steps of this multi-stage process can potentially be targeted in anti-adhesion therapy (**Fig. 2**). Changing the surface properties

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of either bacteria or host cell can discourage non-specific interactions. The biogenesis of bacterial adhesins or host receptors can be inhibited, either by interfering with biosynthesis of subunits or by blocking translocation and surface assembly. Specific interactions between bacterial adhesins and host cell receptors can be targeted in several ways: Anti-adhesion compounds can competitively inhibit attachment by mimicking bacterial or host cell binding partners and alternatively, antibodies recognizing bacterial surface epitopes can be used to either actively or passively immunize the host (**Fig. 2**).

Disrupting Surface Receptor Biogenesis

Impairing pathogen receptor biogenesis. Several studies have described that sub-inhibitory concentrations of certain antibiotics; in particular the fluoroquinolone ciprofloxacine and the aminoglycoside amikacin, can lead to altered physicochemical properties of the bacterial surface and decreased bacterial adhesion to host cells (**Fig. 2A and B**). This is thought to be caused by aberrant protein synthesis leading to the production of partially or incorrectly folded proteins and thus impaired surface display of outer membrane proteins and assembly of fimbrial adhesins. The resulting change in surface charge as well as inhibition of specific interactions with host receptors both act synergistically in preventing adhesion.[10-12]

Chaperone–usher (C/U) pili are large, multi-subunit organelles mediating host cell adhesion and are important virulence factors in a range of bacterial pathogens, including *Escherichia coli* and species of *Salmonella*, *Yersinia*, *Pseudomonas*, *Klebsiella*, and *Haemophilus*. Although Type 1 and P pili are the two most prominent examples of C/U pili, a further 17 putative chaperone–usher operons are encoded in the genomes of sequenced *E. coli* strains.[13] Consequently, inhibition of pilus assembly is a promising strategy for preventing infection. C/U pilus biogenesis is accomplished by translocation of pilin subunits via the Sec pathway and subsequent association with a periplasmic chaperone. The chaperone delivers subunits to an outer membrane usher complex, which secretes them and simultaneously acts as an assembly platform. The structure of the complex between the P pilus chaperone PapD and a synthetic peptide mimicking the C-terminus of the pilus protein PapG was solved and used as a basis to rationally design small molecule inhibitors to prevent pilus assembly (pilicides) by disrupting the chaperon–pilin complex.[14] Another study reported the design of small compounds interfering with association of the chaperone–pilin–usher complex.[15,16] As key structural features responsible for mediating the chaperone–pilin–usher interactions are conserved, pilicides are effective against a range of chaperone–usher pili. More recent studies have aimed at improving the efficacy of pilicides by varying substituents on the main peptidomimetic pilicide fragment and at extending the approach to generate inhibitors of curli assembly (curlicides).[17,18]

Inhibition of host receptor biogenesis. Many bacterial adhesins and toxins rely on host glycosphingolipids (GSLs) for host cell binding and membrane translocation[19,20] and depletion of GSLs from the host cell membrane has been proposed as an efficient strategy to prevent or treat infections (**Fig. 2C**).[21] GSL depletion can be accomplished by administering inhibitors specific for enzymes in the GSL biosynthetic pathway. For example, inhibitors blocking the ceramide-specific glycosyltransferase which catalyzes the formation of glucosyl ceramide, the precursor for GSLs, have successfully been used to diminish bacterial colonization of cultivated human uroepithelial cells and in a murine model of urinary tract infection (UTI).[22] Glycosylation inhibitors have been shown to be safe and effective in patients with lipid storage diseases and thus their off-label use for treatment of bacterial infections may be a viable option.[23,24] Alternatively, GSL depletion can be accomplished by enzyme replacement therapy with human glucosyl ceramide glucosidase, and this has been successfully used to treat a patient suffering from Gaucher disease and systemic salmonellosis.[25]

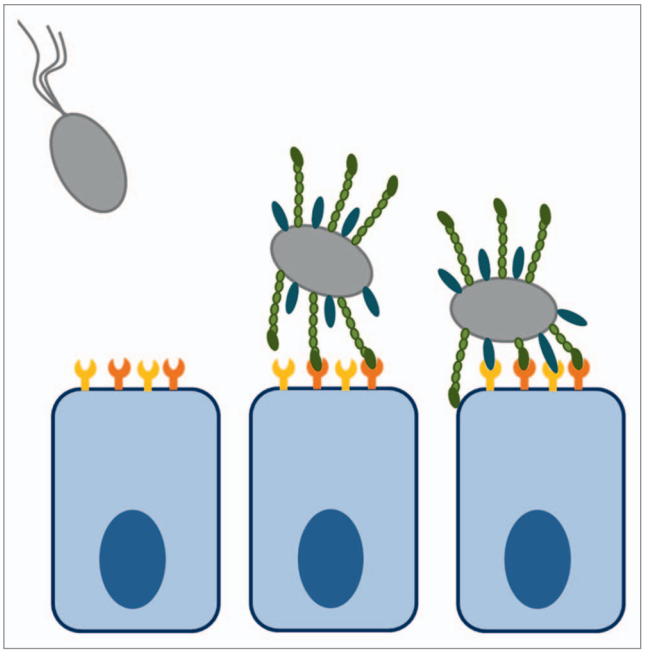

Figure 1. Bacterial attachment to host cells. Upon encountering host cells, bacteria are attracted by weak, non-specific forces, which are driven by physicochemical properties of bacterial and host surface. Initial low-affinity attachment is driven by specific surface receptors but still allows the bacterium to sample the host cell surface. Initial interactions are reinforced by additional receptor pairing, leading to overall high affinity of binding.

Use of Receptor Analogs in Competition-Based Strategies

Sugar-based inhibitors and glycomimetics. Specific bacterial host interactions are frequently mediated by carbohydrates, which are present in large numbers both on the bacterial surface (in the form of capsules, lipopolysaccharides, and glycoproteins) and the host surface (as glycoproteins and glycosphingolipids) (**Fig. 2D**). It is thus unsurprising that a large body of research has focused on the use of glycomimetics and synthetic glycosides that would act as anti-adhesives by competitively inhibiting pathogen

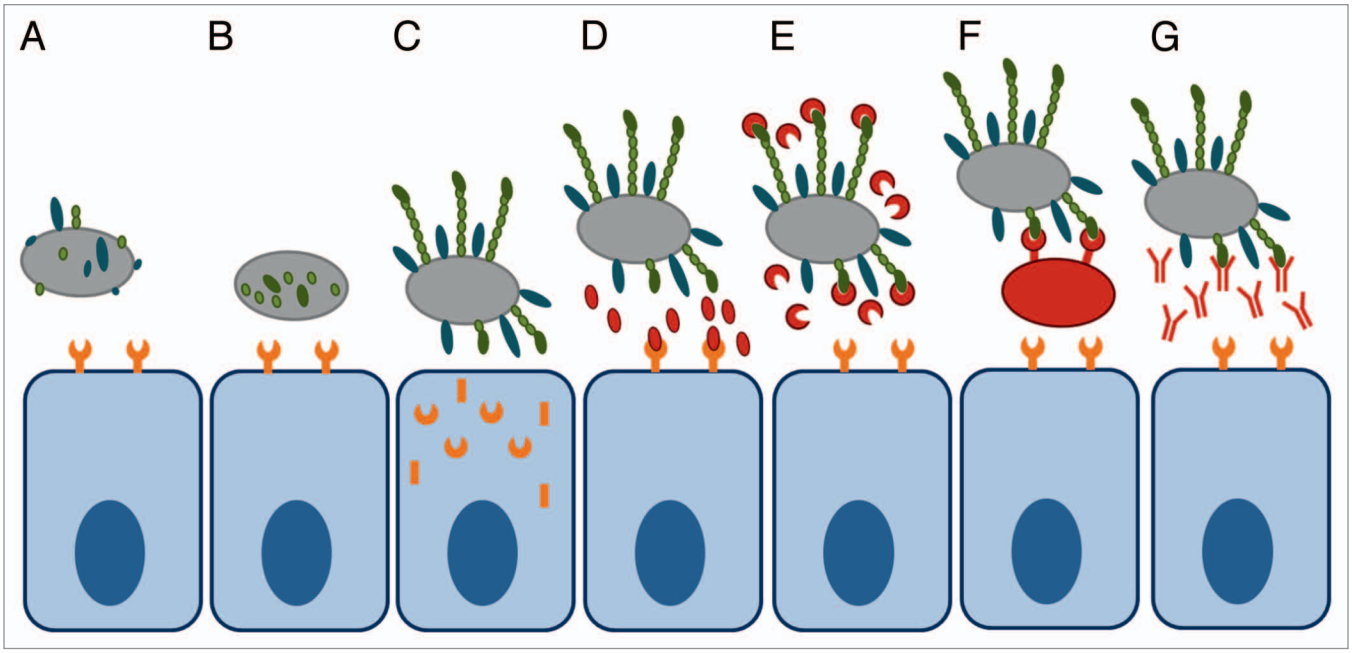

Figure 2. Strategies for anti-adhesion therapy. Bacterial attachment can be inhibited by interfering with adhesin biosynthesis (**A**), adhesin assembly (**B**), or host receptor assembly (**C**). Binding can be inhibited by competitive replacement of the adhesin from the host (**D**) or of the host receptor from the adhesin (**E**) using soluble molecules or by using designer microbes (**F**). Antibodies against bacterial adhesins can block surface epitopes required for binding (**G**).

binding. A number of excellent reviews have been published over the past few years discussing various aspects of carbohydrate-mediated adhesion and the use of sugar-based inhibitors[26-29] so we will only discuss key concepts and present recent developments here.

Some of the most promising anti-adhesive compounds made in recent years are targeted at preventing infections of the urogenital tract caused by fimbriated uropathogenic *E. coli* (UPEC). FimH, the adhesive subunit at the tip of type 1 pili, is a bacterial lectin recognizing mannosylated uroplakins and N-linked oligosaccharides on β1 and α3 integrins located on the luminal surface of the bladder. FimH is a key virulence factor in UTIs and is crucial for multiple stages of infection, such as colonization and invasion of bladder tissue as well as formation of intracellular bacterial communities which are responsible for disease recurrence. The interaction of FimH with host cells has thus long been a target for the development of anti-adhesives. The first study demonstrating the anti-adhesive effect of mannoside-based host receptor analogs in a murine model of UTI goes back to the 1970s.[30] However, monovalent mannose derivatives displayed comparatively weak inhibition and it proved difficult to maintain them at an effective dose over a prolonged period.[31] Since then, two strategies were pursued to improve the efficacy of FimH inhibitors: Synthesis of multivalent compounds with increased binding avidity and rational design of monovalent inhibitors with novel aglucan moieties to increase affinity. To generate multivalent inhibitors, monovalent FimH antagonists are coupled to a multivalent scaffold, such as a synthetic polymer, sugar core or peptide backbone.[32-34] The resulting inhibitors are not only potent anti-adhesives, they also cause cross-linking of bacteria.[32] Structural studies of FimH bound to mannosides revealed that the key determinant for their interaction was a carbohydrate binding pocket with a hydrophobic entrance (tyrosine gate). It was rationalized that compounds containing a mannoside glucan moiety and large aglucan moieties that would be excluded from the pocket and engage in stacking interactions with tyrosine (out-docking mode) would display higher affinities for FimH than those with an aglucan entering the gate (in-docking mode).[35] Thus, the aglucan moiety can be systematically varied to achieve improved affinity, solubility and metabolic stability. The most recent generation of FimH antagonists are biphenyl mannosides, which are approximately 200 000-fold more potent than D-mannose and are orally bioavailable.[36] FimH antagonists have been demonstrated to have low cytotoxicity and despite being based on mannose, they are not cross-reactive with human mannose receptors.[37,38] In murine models, they have proven to decrease bacterial colonization to levels similar to those achieved with the antibiotic ciprofloxacine, making them viable alternatives to antimicrobials.[39,40]

Many food components have long been known to have a protective effect against bacterial infection but in many cases this was based only on anecdotal evidence. More recently, the active compounds for some of these foods have been isolated and demonstrated to have anti-adhesive properties in vitro, underlining their effectiveness as anti-infective compounds. A good example for this is cranberry juice, which has long been described to protect against bacterial infections, in particular UTIs. This protective effect was later shown to be due to anti-adhesive properties of cranberry compounds, and eventually a family of high molecular weight polyphenols, proanthocyanidins, proved to be the bioactive compounds contained in cranberries.[41,42] Proanthocyanidins

inhibit the adhesion and co-aggregation of UPEC, *Helicobacter pylori* and the oral pathogen *Porphyromonas gingivalis*, among others.[42-44] Their mechanism of action seems to be binding to flagella and pili, thus inhibiting bacterial surface attachment, swarming motility and aggregation into biofilms.[42,45,46] Clinical studies evaluating the effects of consumption of both cranberry juice and cranberry extracts on the incidence of UTIs had mixed outcomes, with some reporting no significant benefit and others reporting significant decreases in the rate of infection upon consumption.[47-50] The outcome of these studies seems to strongly depend on whether or not patients had preexisting, recurring UTIs or received prophylaxis (in which case the effect was more significant), and on how much of and for how long the active compound was consumed. Many more foods such as plantains, tea, coffee, and wine, to name a few, contain compounds with anti-adhesive properties and this topic has recently been reviewed comprehensively.[51]

Many of the body's endogenous defense mechanisms against bacterial infection are based on sugars, which act as decoys for bacterial surface receptors. For example, mucus is secreted by the intestinal epithelium and acts as a physical barrier against colonization by enteropathogens. Mucus contains a variety of mucin glycoproteins and the glycosylation pattern of mucins mimics the pattern found in epithelial surface receptors. Mucins act by binding and immobilizing bacteria, which are subsequently cleared from the gastrointestinal tract by shedding of the mucus layer.[52-54] This strategy has been adapted for therapeutic use, for example by using purified mucins as anti-adhesives. Purified bovine Muc1, a highly glycosylated mucin derived from cow milk, efficiently prevents bacterial infection of cultured intestinal epithelial cells. Muc1 selectively inhibits the attachment of gram-negative pathogens (*E. coli* and *Salmonella* Typhimurium) but is not effective in inhibiting attachment of gram-positive organisms such as *Staphylococcus aureus* or *Bacillus subtilis*. Muc1 has little effect on the detachment of pre-bound bacteria from host cells, restricting its use to prophylactic rather than therapeutic applications.[55]

Inhibition of bacterial binding can also be based on sialic acid moieties present on mucins, which act as decoys by mimicking host sialylated receptors. Human breast milk also contains an abundancy of sialic acid-containing oligosaccharides, which are thought to protect the infant from colonization by bacterial pathogens, particularly of the intestinal tract.[27,56,57] However, the anti-adhesive properties of human milk oligosaccharides are intrinsically difficult to evaluate in vivo, due to the fact that they impact the host in many ways, for example by affecting the composition of the microbiota and modulating immunological development.[58] Soluble sialic acid-containing oligosaccharides isolated from milk or synthetic oligosaccharides mimicking the structure and multivalency of endogenous sialic acid-containing decoys show great promise as anti-adhesive compounds both in tissue culture models and animal studies.[59,60] For example, the human milk derived oligosaccharide disialyllacto-N-tetraose was shown to prevent necrotizing enterocolitis, one of the most common and fatal infections in preterm infants, in a rat model of infection.[60] Sugar-based inhibitors are also being extensively investigated for use against respiratory pathogens, many of which are biothreat agents, and this has been recently reviewed.[61]

Peptide-based inhibitors. Even though peptide-based inhibition of bacterial adhesion has been demonstrated extensively in vitro,[62-64] its therapeutic potential has not been fully realized yet (**Fig. 2D–F**). Thus, peptide-based anti-adhesives remain rather understudied compared with sugar-based inhibitors. Examples of peptide-based inhibitors demonstrating the potential of this approach are anti-caries (anti-cavity) peptides. *Streptococcus mutans,* one of the main causative agents of dental caries, expresses a surface protein streptococcal antigen (SA) I/II that binds to salivary receptors adsorbed on the hydroxyapatite matrix of the tooth surface. SA I/II is the key attachment factor of *S. mutans* and monoclonal antibodies raised against SA I//II can prevent tooth colonization and caries in nonhuman primates as well as colonization of the oral cavity in humans.[65,66] Both full-length SA I/II as well as a recombinant 38 kDa peptide matching the proline-rich or P-region of SA I/II were tested for inhibition of *S. mutans* adhesion to salivary receptors and saliva-coated hydroxyapatite beads. The full-length protein and the peptide inhibited binding by 80% and 65%, respectively, when used at a concentration of 1 mg/ml. Since the peptide motif is well conserved across a range of oral streptococcal species, this approach promised to be useful in the prevention of caries as well as other streptococcal infections.[67] The same authors subsequently developed a shorter (22 residue) synthetic peptide, p1025, matching a smaller epitope of the same region that was able to inhibit binding to salivary receptors in vitro. In human volunteers, topical application of the peptide to teeth twice a week over three weeks prevented recolonization with *S. mutans* after its prior depletion from the oral flora using chlorhexidine. Even though the peptide was persistent in saliva and plaque for only a few hours, its protective effect extended over several days and repeated application prevented *S. mutans* recolonization over the entire period of the study (120 d) in most subjects. The initial exclusion of *S. mutans* probably allows sufficient time for other species to colonize the niche and to establish a competitive advantage.[68,69] The minimal dosage required to prevent recolonization was not established, but is likely to be far lower than the 10 mg/ml dosage used in the study.

Another promising candidate for the development of a peptide-based anti-adhesive is the bacterial surface protein multivalent adhesion molecule (MAM) 7. MAM7 is involved in the initial host attachment in a range of species, including enteropathogenic *E. coli* (EPEC), *Yersinia pseudotuberculosis*, *Vibrio cholerae*, and *Vibrio parahaemolyticus* and uses two host surface receptors, fibronectin and the membrane lipid phosphatidic acid.[6,70] MAM7-coupled polymer beads were successfully used to decrease surface attachment and infection by a range of multidrug-resistant bacteria isolated from patient wounds in tissue culture models.[71,72] The broad-spectrum efficacy of MAM7-based inhibitors holds promise for the prevention of a range of gram-negative infections but their development is still at an early stage. It has yet to be investigated if smaller peptide epitopes could be used for inhibition instead of full-length protein and whether variants with improved affinity could be engineered.

A few factors have to be considered in the design and use of peptide-based anti-adhesives, such as their stability and persistence in the host environment and their binding avidity. Peptide stability can be improved by using tailored delivery systems, allowing sustained and targeted release of the inhibitor at the treatment site.[73,74] Moving from full-length proteins toward identifying minimal binding epitopes and using synthetic peptides will allow us to improve inhibitors with respect to their stability and affinity by introducing chemical modifications unnatural or D-amino acids. Peptides may also be used as design templates for peptide mimetics.[75,76] Lastly, it is important to note that some adhesins, by binding to host receptors, may trigger signaling pathways which favor infection. In a therapeutic setting, this may cause unwanted side-effects and therefore should be the main consideration and focus of pre-clinical studies on peptide-based inhibitors.[77] Although peptide inhibitors may seem like challenging targets for the pharmaceutical industry, their large-scale synthesis is feasible and such drugs can be successful. This has been exemplified by the drug Fuzeon, a peptide-based HIV fusion inhibitor. This drug consists of a 36-residue peptide corresponding to part of the envelope glycoprotein gp140 and competitively blocks the binding and fusion of viral particles to host cells. Fuzeon has shown efficacy in phase III clinical trials and has been approved by the FDA for treatment of drug-resistant HIV infections.[78]

Anti-Adhesion Antibodies and Vaccines

Several studies have reported the development and use of antibodies or antisera directed against bacterial adhesins as an anti-adhesive strategy (**Fig. 2G**). In principle, several approaches are possible. The host can be directly or passively immunized using a bacterial adhesin, an adhesin subunit (as in the case of multi-subunit adhesive organelles, such as fimbriae), or an immunogenic peptide fragment based either on an individual adhesin or on the consensus derived from a group of adhesins. Lastly, the host can be immunized using a DNA vaccine encoding the adhesin or part thereof, and we will describe examples of these strategies below.

The treatment for *Salmonella enterica* serovar Typhi, the causative agent of typhoid fever, is increasingly complicated due to the emergence of multidrug resistant strains. The *S.* Typhi adhesin T2544 is a major contributor to bacterial host interaction and disease pathogenesis and a potential target for development of an anti-adhesion vaccine. Deletion of T2544 results in reduced systemic invasion and a 10-fold increase in LD50 in a murine model. T2544 is highly immunogenic and elicits elevated titers of serum IgG and intestinal secretory IgA in immunized mice. T2544 antiserum enhances both the uptake and clearance of bacteria by macrophages as well as complement-mediated lysis. Mice either immunized with T2544 or passively immunized with anti-T2544 antiserum were protected against subsequent bacterial challenge and showed increased bacterial shedding. As T2455 is widely distributed in clinical isolates of *S.* Typhi and *S.* Paratyphi and shows very limited variation, it is potentially a good candidate for vaccine development.[79] However, T2455-based immunization did not completely inhibit disease and this is likely due to other structures promoting cellular invasion, such as type IV pili.[79-81] With *S.* Typhimurium, the effect of multifactorial adhesion on the outcome of immunization attempts is equally problematic. SadA, a trimeric autotransporter involved in biofilm formation, autoaggregation and host binding by *S.* Typhimurium, was tested as a vaccine candidate. Although purified SadA itself triggered an immune response, which was even more pronounced when administered together with an adjuvant, it provided only limited protection against subsequent bacterial challenge.[82]

Subunit-based vaccines are often used in the context of fimbrial adhesins and several of them have been described for therapeutic use against pathogenic *E. coli*. Enterotoxigenic *E. coli* (ETEC) are a major cause of diarrheal disease in humans and other animals and pathogenicity is to a large extent caused by enterotoxins. A fusion protein consisting of FaeG, the major subunit of *E. coli* K88ac fimbriae, an epitope from the B subunit of heat-labile (LT) toxin and the A subunit of shiga toxin (STa) was used to immunize rabbits. Animals generated anti-K88ac, anti-LT and anti-STa antibodies, which inhibited adhesion of fimbrial *E. coli* to small intestinal enterocytes and neutralized both shiga toxin and cholera toxin.[83] A similar strategy was pursued to generate antibodies against enterohemorrhagic *E. coli* (EHEC). EHEC attachment to the host is primarily due to intimin and the subsequent pathology is caused by shiga toxin. A fusion protein containing two different toxin antigens as well as an intimin antigen fragment, was used to immunize mice. The SSI fusion protein induced a strong humoral immune response, with both toxin neutralizing and anti-adhesion antibodies being generated. Subsequent bacterial challenge of twice-immunized mice with an otherwise lethal dose of EHEC strain O157:H7 did not cause any pathology.[84] The use of preventive vaccines against recurring UTIs based on fimbrial subunits FimCH has been investigated quite extensively both in animal models and clinical trials. Immunization with candidate FimH vaccines reduced in vivo colonization of the bladder mucosa by more than 99% in a murine model.[85] Immunization of monkeys with FimCH adhesin–chaperone complex in combination with an adjuvant elicited a strong IgG antibody response and protected 3/4 of the animals against subsequent UPEC infection.[86] A recent clinical study comparing the efficacy of preventive vaccination to prophylactic treatment with antibiotics concluded that vaccination was a more effective strategy to reduce frequency, duration and severity of recurring UTIs.[87]

An example for a consensus-based vaccine developed against *Pseudomonas aeruginosa* was described by Cachia and Hodges.[88] *P. aeruginosa* is an opportunistic pathogen causing a broad spectrum of diseases, such as urinary and respiratory tract infections, skin infections, and systemic infections, particularly in immunocompromised patients. *P. aeruginosa* strains are increasingly resistant to traditional antimicrobials and only a few groups of antibiotics are left to treat *P. aeruginosa* infections especially if they persist over an extended period, for example in cystic fibrosis patients. Cachia and Hodges developed a synthetic peptide consensus sequence anti-adhesin vaccine and a related therapeutic monoclonal antibody to be used

in prevention and treatment of *P. aeruginosa* infections. They identified a small peptide structural element found in *P. aeruginosa* strain K (PAK) bacterial pili that binds host epithelial cells. Since heterologous peptides were found in all sequenced *P. aeruginosa* strains, they used a peptide based on the consensus sequence to raise anti-adhesin antibodies, which were effective against multiple strains. Another study utilizing *P. aeruginosa* strain K pili as an immunogenic target described the generation of monoclonal antibodies which were also cross-protective against *P. aeruginosa* PAO and PAK strains when used for active immunization in a murine model. The authors noted that the generation of an effective antibody relied on the appropriate presentation of the immunogenic peptide, which was achieved through conformational restriction of the peptide by both C- and N-terminal coupling to a carrier.[89]

To improve surface display of bacterial antigens and trigger both humoral and cellular immune responses, several approaches have been taken to ensure the epitope is displayed in a physiological conformation. For example, this can be achieved by associating adhesin antigens with outer membrane vesicles and this strategy was used to create vaccines against *Neisseria meningitides*, a causative agent of meningitis and septicemia.[90-92] Alternatively, antigens can be displayed on the surface of live, attenuated bacterial strains which can be used as oral vaccines.[93] This is a low cost approach and thus particularly suitable for the prevention of zoonotic infectious diseases as it could be used to immunize large herds of animals. For example, a live attenuated *Salmonella* Typhimurium strain expressing a combination of *E. coli* fimbrial antigens (K88ab, K88ac, FedA, and FedF) prevented post-weaning diarrhea in piglets when used to immunize pregnant pigs. No environmental exposure was reported because no live bacteria from the vaccine strain were shed by the animals following immunization.[94,95] However, caution must be paid to evaluate risks associated with environmental exposure to genetically modified organisms and the potential of the attenuated vector to revert to a virulent strain.[96]

DNA vaccines contain DNA encoding pathogen-derived antigens, which upon their expression in the host are able to elicit protective immunity. Theoretically, this strategy is advantageous because it improves antigen processing and presentation and induces both humoral and cellular immune responses.[97] DNA vaccines have been generated and tested as a tool to prevent *S. aureus* infections. *S. aureus* causes a broad spectrum of diseases, ranging from wound infections to life-threatening conditions such as endocarditis, osteomyelitis and septicemia. Treatment of infections becomes increasingly complicated by the high level of multidrug resistance seen with *S. aureus*. *S. aureus* binding to host cells is mediated by a number of surface proteins binding to extracellular matrix components with extremely high affinity. A DNA vaccine based on collagen-binding protein (CNA), a major *S. aureus* adhesin, was used to immunize Balb/c mice. Mice injected with three doses of the eukaryotic expression vector pCNA, expressing the collagen-binding domain of CNA, showed evidence of both antibody- and cell-mediated immune response against CNA. Even though the antibodies recognized intact bacteria and inhibited binding to collagen in vitro, they failed to protect mice against intra-peritoneal infection by *S. aureus*.[98] A polyprotein DNA vaccine against S. *aureus*, consisting of a series of plasmids expressing clumping factor A(ClfA), fibronectin binding protein A (FnBPA), and the enzyme sortase (Srt), triggered both antibody production and T-cell response and provided partial protection against *S. aureus* isolate Sa042 and full protection against reactive arthritis after challenge with *S. aureus* strain Newman.[99]

One of the major drawbacks of anti-adhesion therapy is the high degree of redundancy in bacterial adhesive strategies that in many cases interfere with effective treatment. The use of anti-adhesion antibodies or vaccines may still be effective in such cases as antibody opsonization can increase bacterial uptake and clearance by macrophages and antibodies may trigger complement-mediated bacteriolysis, even if they are unable to fully inhibit bacterial adhesion.[79] Although one could argue that antigenic variability of bacterial adhesins can potentially impair the efficacy of anti-adhesion antibodies, the fact is that many adhesins show a remarkable degree of conservation, making them good vaccine candidates.[100,101]

Advantages of Anti-Adhesion Therapy

One of the major reasons why anti-adhesion strategies are being considered as an alternative approach to conventional antimicrobials is that their mechanism of action does not give rise to bacterial resistance. Because anti-adhesive compounds only inhibit bacterial binding without affecting microbial viability, there is no selective pressure upon the pathogen that would affect the balance between wild-type and treatment-resistant mutants in the population. Although in principle it is possible that mutations affecting the efficacy of anti-adhesion compounds could occur, these would also directly affect the pathogen's ability to bind the host receptor. As a result, resistance against anti-adhesion treatment would negatively impact the pathogen's fitness and likely be naturally selected against. It has been shown that individual point mutations in bacterial adhesins can change tissue tropism and even distinguish commensal from pathogenic strains.[102] Knowledge of such variations opens up the potential to design species-specific and even strain-specific anti-adhesive compounds, thus avoiding side effects caused by changes in the microbiota.[103] An additional advantage of anti-adhesion compounds is their stability under physiological conditions. Both bacterial and host receptor molecules are evolutionary adapted to withstand the physiological conditions encountered upon extracellular exposure. As such, anti-adhesion compounds designed to closely mimic bacterial or host surface structures are likely to be more resistant against degradation than conventional antimicrobial compounds, which are artificially introduced into the host system and have to be specifically designed to be both bio-available and yet able to cross the bacterial outer membrane and be stable under physiological conditions. Because anti-adhesion compounds are not bactericidal, they circumvent problems associated with the therapeutic use of certain bactericidal drugs, such as the release of bacterial toxins and endotoxins, which have detrimental effects on patients' health.[104,105] Instead, they leave the host exposed to

intact but non-functional bacteria, enabling the host to elicit protective immunity that protects against re-infection and speeds up immunological clearance of bacteria that have not been removed mechanically.[79]

Improving Efficacy by Exploiting Multivalency

Despite the many beneficial attributes associated with anti-adhesion therapy, there are downsides to this approach and we will have to overcome these before anti-adhesion approaches can gain broad validity in the treatment of a wide range of infections. One of the main practical problems in the use of competition-based anti-adhesion inhibitors is to achieve high enough avidity to efficiently compete with bacteria, which often carry hundreds of adhesion molecules on their surface. A variety of clever ways have been thought out to deal with this challenge, and most of them rely on tethering monovalent ligands to functionalized scaffolds, such as polymers,[32] dendrimers,[106] nanoparticles,[107] or even fullerenes.[108] By introducing multivalency, inhibitors can be used at lower concentrations than monovalent compounds to achieve the same extent of inhibition. Methods for introducing multivalency into inhibitors have been reviewed extensively,[109-111] as has the possibility of using engineered bacteria to produce soluble oligosaccharides, thus preventing problems attached to the large-scale organo-synthesis of such molecules.[112] In the following, we will describe two approaches to multivalency of perhaps more general relevance.

Use of dynamic scaffolds for ligand clustering. Tethering of functional ligands to scaffolds often restricts their freedom of movement due to the rigidity of the backbone structure, which may render them less able to adapt to the conformation of bacterial surface receptors and thus make them less effective in treatment. An alternative approach is the use of supramolecular dynamic scaffolds, which may give the tethered epitopes more freedom of movement thereby allowing them to maximize their interactions with surface receptors. One such example is pseudopolyrotaxanes, "beads on a string" structures consisting of "wheels" or "beads" of clustered mannoside ligands arranged on a polymer "string", allowing the ligands to freely rotate around and move along the backbone. This way, these scaffolds provide much more scope for adjustments in affinity, ligand density and mobility than rigid scaffolds.[113] Several such assemblies showed inhibition of UPEC adhesion to uroepithelial cells in a tissue culture model of infection.[114] Lipid-based nanostructures, such as functionalized liposomes, supported colloidal bilayers, or protocells, which allow the display of embedded receptors or receptor analogs in an optimal conformation and density, are another approach to the dynamic presentation of inhibitors.[115] Proof-of-principle in vitro studies have demonstrated that such lipid membrane assemblies can function efficiently in inhibiting pathogen-mediated effects.[116,117]

Designer probiotics. A cheap and efficient way to achieve the necessary multivalency of inhibitive epitopes is their heterologous expression on the surface of probiotic bacteria.[118] The protective effects of probiotic bacteria against infections has long been appreciated, and has been systematically demonstrated, at least in some settings, in a range of trials (for reviews of some of these, see refs. 119 and 120). More recently, probiotic strains have also been used to reduce pathogen colonization of animals raised for human consumption. For example, treatment of broiler chicken with a multi-species probiotic consisting of bacteria isolated from the chicken gut prevented their colonization by *Campylobacter jejuni*.[121] The beneficial effects of probiotics are, to some extent, due to competitive exclusion of pathogenic bacteria from host binding sites,[122-124] although this is challenging to demonstrate in vivo because of the complexity of the probiotics' mechanisms of action. Over recent years, probiotics have been specifically engineered to mimic sugars on host receptors, thereby blocking the host cell binding of toxins released by pathogenic bacteria including ETEC, shiga toxin-producing *E. coli* (STEC) and *V. cholerae*.[125-127] As a basis for these probiotics, non-pathogenic *E. coli* strains expressing a truncated lipopolysaccharide (LPS) core terminating in a glucose residue were used. Transformation of these strains with constructs encoding heterologous glycosyltransferases from *Neisseria gonorrhoeae* and *C. jejuni* resulted in the production of chimeric LPS where the terminal glucose is conjugated to oligosaccharides mimicking the functionalities of host cell receptors. For example, a strain expressing LPS terminating in Galα(1→4)Galβ(1→4)Glc was used to mimic globotriaosyl ceramide (Gb3), a glycolipid receptor of the structure Galα(1→4)Galβ(1→4)Glc-ceramide recognized by shiga toxins. The recombinant strain efficiently bound free shiga toxin and protected mice against an otherwise lethal dose of STEC after oral administration.[128] The use of probiotics for host receptor mimicry has been reviewed in more detail elsewhere[118,126,129] but the message should be that such agents could be a viable and cheap way to achieve efficient presentation of multivalent epitopes for anti-adhesion therapies.

Outlook and Future Prospects

Despite the advances made in recent years, which have brought many anti-adhesion therapies within the realms of possibility, there is still much progress to be made to make these approaches applicable on a large scale. Further advancements will be achieved by improving the stability and affinity of currently available compounds and by developing combinatorial approaches to therapy (e.g., improving the efficacy of conventional antimicrobials against biofilms by combining it with an anti-adhesive). Discovery of novel leads will rely on the use of high-throughput screening methods for bacterial adhesion or for evaluation of the impact of bacterial adhesion on tissues.[130,131] Where possible, efforts should be made to test more inhibitors in in vivo settings or at least under physiologically relevant conditions. Parameters not usually present in ex vivo settings, such as fluid dynamics and shear stress, can have a large impact and even reverse the outcome of inhibition studies and their influence on the experimental outcome can be counterintuitive.[132]

Finally, we would like to point out that the repertoire of anti-adhesive strategies is by far not exploited. For example, a recent study tested the concept of interfering with the mechanical compliance of pili to decrease bacterial adhesion. Bacteria can

withstand high amounts of fluid shear and this is in part due to their ability to redistribute external forces among a large number of adhesive surface structures such as pili. When exposed to force, pili can reversibly extend by the uncoiling and recoiling of their quaternary structure. Compounds interfering with the pilis' structural dynamics (coilicides) could potentially enable bacterial surface detachment. In a proof-of-principle experiment, the purified pilin PapD was shown to impair recoiling of P pili fibers, thus leaving them unable to withstand flow.[133] This just goes to show that new and unconventional approaches targeting bacterial adhesion may be conceived, revealing new targets for anti-adhesion therapy.

Note

We would like to remark that this review is far from being comprehensive and can only act in exemplifying selected recent studies underlining emerging concepts of anti-adhesion strategies. We would like to apologize for any omissions we had to make due to space limitations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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