Strategies in anti-adhesion therapy: A review article

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Abstract

Bacterial diseases are an important cause of mortality and morbidity worldwide. The Improper and uncontrolled use of antibiotics contribute to the bacterial resistance to antibiotics.
It is well known that the antibiotics stop bacterial infections by killing or inhibiting their growth. Antibiotics are interfering with critical functions that are important for bacterial growth. To overcome this, bacteria developed different mechanisms to resist the antibiotics and survive.
Targeting bacterial function without killing them is a promising way to inhibit bacterial infection. Bacterial adherence is a serious step towards infection. Anti –adhesion therapy aims to inhibit bacterial infection via interfering with bacterial attachment without killing them.
This review will cover different strategies in anti-adhesion therapy.

Key words: Antibiotic resistance, Bacterial attachment, Anti-adhesion therapy

ستراتيجيات في العلاج المضاد للالتصاق: مقال

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الخلاصة:

الأمراض البكتيرية هي سبب مهم للوفيات والاعتلال في جميع أنحاء العالم. إن الاستخدام غير السليم وغير المنضبط للمضادات الحيوية يسهم في مقاومة البكتيريا للمضادات الحيوية.
من المعروف جيدا أن المضادات الحيوية توقف العدوى البكتيرية عن طريق قتل البكتيريا أو تثبيط نموها. المضادات الحيوية تتداخل مع الوظائف المهمة الضرورية لنمو البكتيريا. وللتغلب على ذلك، طورت البكتيريا آليات مختلفة لمقاومة المضادات الحيوية والبقاء على قيد الحياة. إستهداف وظيفة بكتيرية دون قتلها هو وسيلة واعدة لمنع العدوى البكتيرية. يعد التصاق البكتيريا بالخلايا المضيفة خطوة حاسمة نحو العدوى. يهدف العلاج المضاد للالتصاق إلى منع العدوى البكتيرية عن طريق منع التصاق البكتيريا دون قتلها.
هذا المقال سوف يغطي إستراتيجيات مختلفة في العلاج المضاد للالتصاق.

الكلمات المفتاحية: مقاومة المضادات الحيوية، التصاق البكتيريا، علاج مضاد لالتصاق.

Introduction

Bacterial diseases are an important cause of mortality and morbidity worldwide. A lack of acknowledgment about antibiotics has led to their appropriate, misuse and overuse. The Improper and uncontrolled use of antibiotics contribute to the bacterial resistance to antibiotics (1). *Antibiotic resistance* is a *critical problem* throughout the world (2).
Infections caused by multidrug resistant bacteria are difficult to treat. Thus, it has become urgent to develop new

antimicrobial agents able to inhibit bacterial infections. Bacterial attachment is an important stage towards infection. Thus, targeting bacterial attahment is a vital way to inhibit bacterial infection (3,13).

2. Bacterial attachment

The attachment to host cells enable bacteria to survive and cause infection (4). Variety of adhesion factors are expressed by bacteria to enable them to interact with host cells receptors. Initial attachment is essential for interruption of actin cytoskeleton, translocation of bacterial effector proteins or stimulation of host c signalling which assists migration of pathogens (5).

Bacterial attachment involves the binding of particular structures on both host and bacterial cells. The attachment comprises two stages. Firstly, none -specific weak reversible interactions occur between hydrophobin on bacterial cell surface with hydrophobic groups on the host cell surface (Hydrophobin- protein interactions). Then, a specific irreversible interaction happens between bacterial adhesins and host cell receptors (6, 7). The specific interactions involve protein-protein and lectin-carbohydrate interactions. Protein–protein interactions occur between proteinous adhesion agents on bacterial cells and proteins on host cells. *S. aureus* interact with host receptors via surface proteins known as microbial surface components recognizing adhesive matrix molecules (MSCRAMMs). For example, the interaction of Fibronectin binding proteins with host fibronectin (8). Another group of MSCRAMMs is Clumping factors (CIfs) ClfA and ClfB. It has been shown that ClfA interact with fibrinogen protein on host cells (9).

Lectin-carbohydrate interactions refer to the binding of bacterial lectins with sugar moieties on the host receptors such as those present in proteoglycans, glycolipids or glycoproteins (10). *Escherichia coli* is able to bind to host gastrointestinal cells due to the interactions between lectins on bacterial fimbriae with oligosaccharides groups on the host cell surface. Lectins expressed by innate immune cells and contribute to initial recognition of bacterial glycan, such as the interaction of mannose receptors on macrophages with bacterial capsular polysaccharides, peptidoglycan and lipopolysaccharides. This interaction may provide early defense against bacterial infection. (11). However, lectins may be exploited by bacteria to avoid immune defense (12).

Anti-adhesion therapy

Anti -adhesion therapy is another approach to inhibit microbial infection rather than using the antibiotics. It comprises the application of agents that competitively inhibit bacterial adherence (13,14,15).

There are many reasons behind using anti adhesion therapy. Primarily, most of the adhesion inhibitors are natural products. Therefore, no immunogenic or toxic effects might be occurred. In addition, their effect is non-bactericidal. Thus, less resistant strains may occur comparing when using the antibiotics. Moreover, though there is a chance of bacterial mutant, but this might affect on bacterial cell function by decreasing their capability of binding to host surface. Different strategies can be used to competitively inhibit bacterial attachment to host cells. These include; Disrupt adhesins biosynthesis, receptor analogs, adhesin analogs, vaccines, probiotics and an engineered probiotic (13, 16,17)

Disrupt adhesins biosynthesis

In literature, it has been reported that the exposure of bacterial cells to sub inhibitory concentrations of antibiotics leads to lose the ability of adherence. Generally, antibiotics at sub inhibitory concentrations impede protein synthesis and block the formation of fimbriae (16). In a study on *Klebsiella oxytoca*, *Escherichia coli*, *Acinetobacter calcoaceticus* biotype anitratus and *Enterobacter cloacae*, it has been found that the treatment with sub

inhibitory concentrations of ciprofloxacin result in formation of filaments (17). Furthermore, *P. aeruginosa* binding to host cells was inhibited using different sub inhibitory concentrations of piperacillin and tazobactam (18). Disrupting of fimbria/pili by interfering with its assembly through the chaperone–usher pathway (19). pilicides, bicyclic 2-pyridones inhibit *E. coli* adherence to host via their interaction with the surface fragment of the chaperone. Thus, inhibit the binding with the usher protein. Moreover, distraction of curli 16 via curlicides, a group of bicyclic2-pyridone derivatives result in inhibition of bacterial binding to host cells (20).

Receptor analogs

Studies on natural products have shown these products being potential sources for anti-adhesive agents (21).

Receptor analogs are either natural or synthetic agents. Milk and plant extracts are natural receptor analogs. Oligosaccharides, glycoproteins and glycolipids in human milk comprise sugar moieties similar to those on host receptors. Milk glycans bind to host receptors and prevent bacterial attachment and thus inhibit their infection (22). It has been reported that milk glycans have protective role against infant diarrhoea (23). Salcedo *et. al* reported that using milk glycans leads to inhibit bacterial attachment to Caco2 cells (24). Plants are good agents used as bacterial adhesion inhibitors. The attachment of *E. coli* to uroepithelial cells was prevented using Cranberry extract (25). *Camellia sinensis* hinders the binding of different pathogenic bacteria to host cells due to their contents of acidic polysaccharides (26). Lee *et. al.,* shown that polysaccharides from *Panax ginseng* have anti adhesive effects against oral and skin pathogens (27). Salvianolic acid B extracted from *Salvia miltiorrhiza* have been previously used as adhesion inhibitor against *Neisseria meningitidis* (28)

Synthetic receptor anologs are designed to competitively inhibit bacterial attachment (29). It has been reported that using multimeric heptyl-mannosides inhibitors leads to prevent the binding of *E. coli* mediated by type 1 pili to the mannosylated uroplakin Ia (UPIa) receptors on the urothelial cells (30). Trisaccharide globotriose (Galα1, 4Galα1, 4Glc) were competitively inhibiting *E. coli* binding to Galα1, 4Gal groups on the host glycolipids (31). Moreover, the binding of Streptococcus *suis* strains to host glycolipids was inhibited using multivalent adhesive agents containing Galα1-4Gal (32).

Vaccines

The production of adhesin -specific antibodies is promising approach to protect host from bacterial diseases (33). This could be accomplished by active or passive immunization. In literature, it has been reported that K88 fimbria is mediated the binding of enterotoxigenic *Escherichia coli* (ETEC) to piglets' glycosphingolipids. This binding leads to release enterotoxins that cause diarrhea (34). Thus, immunization with antibodies based on K88 fimbriae inhibits diarrhea (35). *P. aeruginosa* infections was inhibited using this approach (36). Streptococcal antigen I/II (SA I/II) mediated the attachment of *Streptococcus mutants* to host. It has been reported that the application of streptococcal antigen I/II (SA I/II) on teeth result in delay bacterial colonization (37).

Probiotics and an engineered probiotic

This strategy is based on using live microorganisms to compete pathogens and inhibit their infection. The competition results from the release of antibacterial copmounds, competition for nutrients and host receptors (38). It has been reported that incubation of Hela cells with the commensal *E. coli* HS leads to prevent the attachment and the cytotoxic effects of *V.parahaemolyticus* (39).

Asahara *et. al.,* reported that Shiga toxin-producing *Escherichia coli* (STEC)

infection was inhibited using *Bifidobacterium breve* strain Yakult and Bifidobacterium pseudocatenulatum DSM 20439 (40). Incubation of Caco-2 cells with *Lactobacillus delbrueckii* subsp bulgaricus reduced *E. coli* attachment (41). Using a murine model, it has been showed that *Lactobacillus casei* Shirota strain prevents the infection of *Salmonella enterica* serovar Typhimurium DT104 (42).

An engineered probiotic has been used to inhibit bacterial infection. It has been shown that using an engineered *Escherichia coli* express lipopolysaccharide similar to host ganglioside prevent diarrheal infections caused by Enterotoxogenic *E. coli* or cholera toxin (43). Pre incubation of Caco2 cells with *L. paracasei* expressing Listeria adhesion protein (LAP) leads to preventing *Listeria monocytogenes* infection (44). Al-Saedi *et. al*., reported that pre incubation of Hela cells with recombinant *E. coli* expressing MAM7 (BL21-HSMAM7) result in decrease the attachment and cytotoxicity of *S. aureus*, *E. faecalis* and *P. aeruginosa* (45). MAM7 from the commensal *E. coli* competes with pathogens and attaches to host cells via the binding to host receptor, sulfatid (45). An engineered bacterium expressing *V. parahaemolyticus* MAM7 was used to impede bacterial infections caused by different pathoges. MAM7 from *V. parahaemolyticus* interact with phosphatidic acids on host cells and able to dislocate pathogenic bacteria from the host surface (46,47).

Adhesin analogs

This strategy involves using adhesion factors that competitively bid to host receptors and inhibit bacterial attachment (48). It is known that the bacterium *Porphyromonas gingivalis* colonize oral cavity and forming biofilms via its binding to the streptococcal SspB polypeptide (BAR) on the *Streptococcus gordonii* cell. It has been stated that using a synthetic peptide comprising the BAR sequence inhibits *P. gingivalis* attachment to *Streptococcus. gordonii* and thus impedes forming biofilms (49).

Using a tissue culture model, it has been shown that beads coupled to the recombinant Multivalent Adhesion Molecule (MAM)7 from the commensal *E. coli* HS inhibit the attachment of different pathogenic bacteria to host cells (45). Moreover, using beads coupled to MAM7 from *V. parahaemolyticus* inhibits *S. aureus* (MRSA) infection without harm host cells (50). In adition to inhibit *P. aeruginosa* infection (51).

Conclusion

The Inappropriate and uncontrolled use of antibiotics lead to bacterial resistance. Infections caused by multidrug resistant bacteria are difficult to treat. Anti-adhesion therapy involves the application of agents that competitively inhibit bacterial attachment to host receptors, and thus inhibit bacterial infection. Characterization of bacterial adhesins and host receptors aids in development and designing adhesion inhibitors**.** Anti-adhesive agents would be a promising choice to treat bacterial infection.

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