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Review: Bacterial adhesion and pathogenicity

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Summary

Bacteria adhere to almost any surface via specific surface molecules of recognition through which a firm union is established for successful colonization of the host. Studies have shown that adhesion plays an important and critical early role in the pathogenesis of infectious diseases, and a series of adhesins have been well documented in a certain number of strains and species of bacteria of medical importance. Attempts have been made to interfere with, or prevent adhesion of, harmful bacteria to the host tissue, using receptor analogues or bacterial adhesin-vaccines as prophylactic measures to protect recipients from specific bacterial diseases. Although much success has been reported from such procedures in laboratory animals and livestock, extensive clinical trials are required to assess the efficacy of such procedures in humans. However, reports from limited studies have shown some encouraging results. Future studies must also be directed to the isolation and characterization of more adhesins and receptors and their specific interactions, which would provide fuller understanding of mechanisms of bacterial adhesion, especially at molecular level.

Résumé

Les bactéries adhèrent à presque n'importe quel surface par les molécules spécifiques de reconnaissance. A ce façon une union ferme pour la colonisation de l'hôte est bien établie. Les études ont montré que l'adhésion constitue la role importante et critique dans la pathogenèse des maladies infectieuses et un séries d'adhesins ont étaient bien documenté dans certains numéros des strains et spécies bactéries avec l'importance medicale. Les rechercheurs ont tenté à tripoter ou empêcher l'adhésion des bactéries nuisibles sur les tissues d'hôte, employant les analogues des recepteurs ou les vaccins adhésins des bactéries comme les mesures prophylactiques pour protéger les bénéficiaires contre les maladies causés par certains bactéries spécifiques. Bien qu'on a eut beaucoup de succès à ce façon chez les animaux laboratoires et chez les bétaux, il y a beaucoup à faire à ce qui concerne les essais à clinique pour établir l'efficace propre de cette méthode chez les humains. A quelques bulletins, cependant, les études en cette direction montrent les bons résultats. A l'avenir, les rechercheurs peuvent concentrer leurs énergies à l'isolement et caractérisation de plus d'adhésins et recepteurs, et leurs interactions spécifiques qui pourrait nous fournir d'une compréhension complète des mécanismes d'adhesions bacterielles, particulièrement au niveau moléculaire.

Introduction

The ability of bacteria to adhere to, and grow on, almost any surface has long been recognized [1]. Attempts have also been made to define several adhesive agents on bacterial surfaces. However, it is only in recent years that intensive studies have begun to reveal that adhesion of bacteria to mucosal surfaces is an important initial event in the pathogenesis of most infectious diseases caused by bacteria in animals and humans [1, 2]. This has also been found to be the case for the successful existence of saprophytic bacteria [3–5]. This 'new' realization has resulted into a sudden upsurge of interest in bacterial adhesion studies, as evidenced by the large number of publications on the subject in the last two decades. Indeed, bacterial adhesion studies have proved to be very attractive not only among microbiologists and epidemiologists engaged in investigations

of infectious diseases but also among those involved with the broader aspects of microbial ecology [6].

Current reports have pointed to the fact that a better understanding of the mechanisms of bacterial adhesion may lead to new approaches with regard to the prevention of bacterial infections. This, of course, is to be expected, since a device to disrupt the initial contact between the harmful bacteria and the host may tilt the balance in favour of the latter. Although much progress has been reported in this respect, a lot still needs to be done especially in the areas of isolation and characterization of adhesins and receptors at molecular level.

It is disturbing to note, however, that despite increased interest in this exciting and very promising area of study elsewhere, there is little or nothing to show for it in the local literature. This should not be so. It is my intention in this short and rather selective review (more detailed reviews have been presented elsewhere [3–8]) to draw attention to this anomaly with a view to generating some interest in the subject.

Mechanism of bacterial adhesion

It has been shown that bacteria adhere to host tissues through certain specific surface molecules of recognition [9, 10]. These structures were first called adhesin [11]. They are also called fimbriae when possessed by Gram-negative bacteria, especially enterobacteria where they have been most exhaustively studied. They should never be confused with pili, which are best reserved for those appendages that are directly involved in the conjugative transfer of deoxyribonucleic acid [1, 3, 4]. Fimbriae are often composed of large polymeric structures that are essentially protein (fimbriin) in nature. Other adhesins, such as hairy projections on streptococci that lack regular size and shape, are called fibrillae. It is important to note, however, that some adhesins are non-fimbrial and non-fibrillar in nature.

In order to attach to a host tissue, a bacterium cell uses its adhesin to recognize a specific receptor on the host cell with which it forms a firm union. The kinetics of this interaction are not fully understood, although a number of possible explanations has been suggested in the past [1, 9, 10]. However, it seems clear that the kinetics would be greatly influenced by several non-specific factors that would impair the normal local defence mechanisms of the host cell. Most of the specific receptors on the host cells are yet to be isolated, identified and characterized. They are most commonly recognized by indirect methods. Receptors recognized as such to date are essentially carbohydrates, which are presumably constituents of surface glycoconjugates [5]. Further studies are obviously required in this direction.

Methodology

Several models have been proposed for studying adhesive activities of bacteria. The general principles behind all the methods are the demonstration of adhesive ability and recognition of adhesive agents. These are achieved in two ways. Firstly, indirect methods, which include bacterial agglutination of red blood cells [4, 12], haemagglutination inhibition by receptor analogues or specific adhesin antiserum [13], attachment to epithelial cells such as buccal or intestinal epithelium [14] and, more recently, hydrophobic aggregation of bacterial cells ('salting out') as a measure of the degree of their adhesiveness [15]. Secondly, direct visual demonstration of adhesive agents on bacteria by the technique of electron microscopy. This indeed is invaluable in the identification and characterization of fimbriae and their correlation with different types of haemagglutinins that are often encountered (Fig. 1).

Difficulties are of common occurrence when investigating a bacterial strain that produces more than one type of adhesin [4, 16, 17]. In such cases a combination of methods of investigation is imperative. We have also shown in recent reports [17–19] that the technique of immuno-electronmicroscopy, whereby a specific coating of particular fimbrial type is rendered visible with the aid of electron microscope, is indispensable in distinguishing between different types of fimbriae (adhesins) that may be formed by a single bacterial strain of the family *Enterobacteriaceae*. Whichever method(s) is chosen, it is important to note that certain fac-

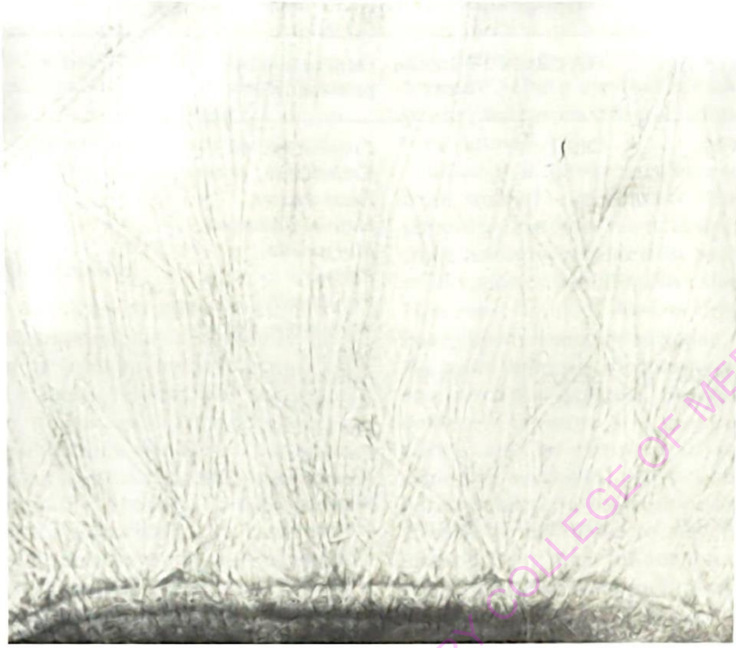

Fig. 1. Electronmicrograph of bacterium from MS-HA⁺ broth culture of *Klebsiella* species showing thick, channelled (type-1) fimbriae, 8-nm diameter (uranyl acetate, × 100,000).

tors, including growth conditions such as temperature and time of incubation, media for isolation, performance of tests, and even phenomenon of phase variation [4], could influence results obtainable from these procedures.

Despite the deficiencies that are often associated with each test model, the haemagglutination (HA) system, when used in conjunction with electron microscopical, serological and chemical techniques, has aided the classification of both fimbrial and non-fimbrial adhesins. Such an analysis has resulted in the recognition and description of five main classes of haemagglutinins in enterobacteria (Table 1), some of which have been further characterized as essential colonization factors [8, 20].

Bacterial adhesion as a pathogenic factor

Infection-forming processes involve a series of stages of complex procedures *in vivo*. In order to cause an infection, a pathogenic organism must enter the host, multiply in host tissues, resist or not stimulate host defences, and damage the host [21]. Moreover, it is clear that successful pathogens not only must be capable of penetrating the local defence system to adhere to mucosal cells but also must be able to replenish the new surfaces as colonized cells become desquamated and penetrate the epithelial cell barrier by invasion, either by the organism itself or by an excreted product such as toxin [9, 10]. It is obvious, therefore, that results from bacterial adhesion studies must be interpreted with caution with regards to extrapolation of their in-vivo significance in bacterial infection.

Because fimbriae confer on bacteria the ability to adhere to epithelium, it was thought that they might play an essential role in the pathogenesis of certain bacteria possessing them. Reports supporting this hypothesis are now emerging in the literature. Although earlier reports have suggested that there is no apparent correlation between type-1 fimbriae and infectivity of certain members of *Enterobacteriaceae* [4, 22], such a correlation has been firmly established for the host-specific fimbrial adhesins of non-invasive enterotoxigenic *Escherichia coli*

Table 1. Haemagglutinins (HAs) and fimbriae of enterobacteria

HA type*	HA classes	Fimbrial type†	Genera in which principally found	References
MS	One	1	*Citrobacter*, *Escherichia*, *Enterobacter*, *Hafnia*, *Klebsiella*, *Morganella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*	[4, 6, 17, 18]
MR/E	Several	MR/E	*Escherichia*	[33]
MR/K	One	3	*Klebsiella*, *Morganella*, *Proteus*, *Providencia*, *Serratia*	[11, 16, 18]
MR/P	Several	MR/P	*Morganella*, *Proteus*, *Providencia*, *Serratia*	[4, 16, 18]
MR/Y	One	MR/Y	*Yersinia*	[34]

*MS = *D*-mannose sensitive, MR/E = *D*-mannose resistant and eluting, MR/K = *D*-mannose resistant (Klebsiella-like), MR/P = *D*-mannose resistant (Proteus-like), MR/Y = *D*-mannose resistant (Yersinia-like).

†Some MR/E-HAS are non-fimbrial; MR/P constitutes more than one fimbrial type.

(ETEC) strains [21] and indeed for some fimbrial adhesins of other bacteria of medical importance [1, 8]. The relationship between the ability of certain species of pathogenic bacteria possessing fimbriae or fibrillae to adhere to epithelial cells *in vitro*, and their ability to produce infectious diseases, has been reported by several authors [1, 5, 6, 8, 12]. Originally it was the presence of K88 fimbrial antigen on certain strains of *Escherichia coli* that was shown to be responsible for their strong adhesive ability for epithelial cells *in vitro* and high infectivity for pigs [23]. Mutant strains that lacked K88 antigen were non-adhesive and of very low infectivity. Moreover, immunization of pregnant sows with K88 antigen protected newborn piglets against *E. coli* diarrhoea [24]. Similar observations were later reported for ETEC strains possessing K99 fimbriae leading to infection in calves [25] and 987P causing diarrhoea in pigs [26, 27]. Even more convincing was the report from another study [28] that showed a strong correlation between the possession of colonization factor antigen (CFA) by ETEC strains with strong adhesion to epithelial cells *in vitro*, and high infectivity leading to acute diarrhoea in man. Again, mutant strains lacking CFA were unable to produce diarrhoea in human volunteers even though the non-adhesive mutant retained the ability to produce toxin. Moreover, the CFA^- mutant was shed in the stools of infected volunteers for much shorter periods than was the parent strain [29]. This observation suggests that CFA was essential for the effective functioning of the produced toxin since its presence would serve to promote close association between the bacilli and host cells.

Since then, a series of host-specific surface adhesive agents has been described and recognized as being of critical importance in the pathogenesis of ETEC strains of *E. coli*, causing diarrhoea in different host animals, as well as of strains of *E. coli* involved in urinary tract

infection, as indicated in Table 2. Important adhesins of other bacteria of medical importance have also been described [6]. In each case it was firmly established that adhesins were important virulence factors enabling the organisms to adhere *in vivo*, therefore playing a critical early event in the pathogenesis of their associated infections.

Conclusions and speculation

One of the goals of bacterial adhesion studies is the eventual development of measures to prevent adhesion of harmful bacterial to host cells. Evidence from current reports has suggested the critical role of bacterial adhesion in the pathogenesis of infectious diseases. Therefore, the question is, can bacterial infections be prevented by blocking the adhesion of bacteria to mucosal surfaces? Theoretically this should be possible. But, of course, not without its attendant difficulties. Bacterial adhesion is not always harmful to the host. Indeed, adhesion of pathogens to phagocytes is probably beneficial to the host. Procedures to prevent bacterial adhesion must, therefore, be sufficiently selective so as not to interfere with such interactions. However, this question can be addressed in two ways: firstly, isolated purified bacterial adhesin, membrane receptors or analogues of these substrates may be applied to prevent adhesion by competitive inhibition; secondly, adhesins as vaccines may be applied to induce formation of local antibodies, which would coat the organism and thereby prevent adhesion as a prophylactic measure. These approaches have been demonstrated with some degree of success in laboratory animals [1].

Since it is dangerous to extrapolate results from animal experiments directly to human patients, it would seem that extensive clinical trials are now required to assess whether fimbrial vaccines would be as effective in humans. However, limited reports from pilot studies have shown some encouraging results [1, 8, 30]. As more adhesins become characterized, and receptors get isolated, the future trends will definitely be more at a molecular level. More efforts will be required in studies aimed at achieving successful prevention of adhesion of harmful bacteria to their hosts. Attempts are already being made to develop reagent kits incorporating receptor analogues for identification of adhesive bacteria that may be harboured by susceptible hosts [31]. This will enhance early recognition of patients at risk and afford better management of such patients.

Emergence of antibiotic-resistant bacteria is now a source of major concern to diagnostic microbiologists. Attention has been drawn to the world-wide problem posed by outbreaks of infection due to drug-resistant enterobacteria [32]. This was attributed to the widespread and indiscriminate use of anti-microbial drugs in

Table 2. Host specific colonization adhesins of animal and human strains of *Escherichia coli*

Adhesin	Host species	Erythrocyte species agglutinated	References
K88	Pig	Guinea-pig, fowl	[23]
K99	Cattle, sheep, pig	Horse, sheep	[25]
987P	Pig	None or fowl	[26, 27]
F41	Cattle, pig	Human, guinea-pig, horse, sheep	[35]
—*	Pig	Pig	[36]
CFA I	Human	Human, cattle, fowl	[12]
CFA II	Human	Cattle, fowl	[37]
E8775	Human	Human, fowl	[38]
P	Human	Human	[39]
RDEC	Rabbits	—	[40]

*Not stated.

man and animals, thus necessitating the need to search for alternative means of treating, and probably preventing, bacterial infection. Because adhesins play an important early event in the establishment of bacterial infection, selective prevention of bacterial adhesion is in the forefront of alternative means of treatment or prevention that must be considered.

Although much work remains to be done, especially in the isolation and identification of specific receptors from host cells and the molecular mechanisms of bacterial adhesion, it seems clear that the prevention of, or interference with, initial interaction between bacteria and host cells might add a new dimension to the control and treatment of many serious infectious diseases before the causative organisms secure any chance to establish themselves to cause any damage to the host. This may bring about a great reduction in the incidence of drug abuse with its attendant social complications, reduce to a great extent cost of treatment, and reduce or possibly eliminate the problem of drug resistance. However, these must remain only speculations at this stage until more studies are performed.

In the last 10 years, bacterial adhesion studies have become very dynamic and exciting. If the current momentum in adhesion studies is maintained, it should be possible in the very near future to eradicate some of the many devastating infectious diseases that have plagued mankind for so long.

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References

1. Beachey EH. Bacterial adherence: adhesin-receptor interactions mediating the attachment of bacteria to mucosal surfaces. J Infect Dis 1981;143:325–45.
2. Gibbons RJ, van Houte J. Bacterial adherence and the formation of dental plaques. In: Beachey EH, ed. Bacterial Adherence. London: Chapman and Hall, 1980:60–104.
3. Jones GW. The attachment of bacteria to the surfaces of animal cells. In: Reissig JL, ed. Microbial Interactions. London: Chapman and Hall, 1977:141–76.
4. Duguid JP, Old DC. Adhesive properties of *Enterobacteriaceae*. In: Beachey EH, ed. Bacterial Adherence. London: Chapman and Hall, 1980:184–217.
5. Jones GW, Isaacson RE. Proteinaceous bacterial adhesins and their receptors. Crit Rev Microbiol 1983;10:229–60.
6. Old DC. Bacterial adherence. Med Lab Sci 1985;42:78–85.
7. Ottow JCG. Ecology, physiology and genetics of fimbriae and pili. Ann Rev Microbiol 1975;29:79–108.
8. Gaastra W, de Graaf FK. Host-specific fimbrial adhesins of non-invasive enterotoxigenic *Escherichia coli* strains. Microbiol Rev 1982;46:129–61.
9. Ofek I, Beachey EH. General concepts and principles of bacterial adherence in animals and man. In: Beachey EH, ed. Bacterial Adherence. London: Chapman and Hall, 1980:3–29.
10. Ofek I, Beachey EH. Bacterial adherence. In: Stollerman GH, ed. Advances in Internal Medicine, Vol. 25. Chicago: Year Book Medical Publishers, 1980:503–32.
11. Duguid JP. Fimbriae and adhesive properties in Klebsiella strains. J Gen Microbiol 1959;21:271–86.
12. Evans DG, Evans DJ Jr, Tjoa W. Haemagglutination of human group A erythrocytes by enterotoxigenic *Escherichia coli* isolated from adults with diarrhoea: correlation with colonisation factor. Infect Immun 1977;18:330–7.
13. Gibbons RJ, Jones GW, Sellwood R. An attempt to identify the intestinal receptor for the K88 adhesin by means of a haemagglutination inhibition test using glycoproteins and fractions from sow colostrum. J Gen Microbiol 1975;86:228–40.
14. Ofek I, Beachey EH, Eyal F, Morrison JC. Postnatal development of binding of streptococci and lipoteichoic acid by oral mucosal cells of humans. J Infect Dis 1977;135:267–74.
15. Lindahl M, Faris A, Wadstrom T, Hjerten S. A new test based on 'salting out' to measure relative surface hydrophobicity of bacterial cells. Biochim Biophys Acta 1981;677:471–6.
16. Old DC, Adegbola RA. Haemagglutinins and fimbriae of *Morganella, Proteus* and *Providencia*. J Med Microbiol 1982;15:551–64.
17. Adegbola RA. Fimbrial haemagglutinins of the tribe *Klebsielleae*. PhD thesis, University of Dundee, Scotland.
18. Adegbola RA, Old DC. New fimbrial hemagglutinin in *Serratia species*. Infect Immun 1982;38:306–15.
19. Old DC, Adegbola RA. Antigenic relationships

among type-3 fimbriae of *Enterobacteriaceae* revealed by immuno-electronmicroscopy. J Med Microbiol 1985;20:113–21.

20. Kallenius G, Mollby R. Adhesion of *Escherichia coli* to human periurethral cells correlated to mannose-resistant agglutination of human erythrocytes. FEMS Microbiol Lett 1979; 5:295–9.
21. Smith H. Microbial surfaces in relation to pathogenicity. Bacteriol Rev 1977;41:475–500.
22. Adegbola RA, Old DC, Senior BW. The adhesins and fimbriae of *Proteus mirabilis* strains associated with high and low affinity for the urinary tract. J Med Microbiol 1983;16:427–31.
23. Jones GW, Rutter J. The association of K88 antigen with haemagglutination activity in porcine strains of *Escherichia coli*. J Gen Microbiol 1974;84:135–44.
24. Rutter JM, Jones GW. Protection against enteric disease caused by *Escherichia coli* — a model for vaccination with a virulence determinant? Nature 1973;242:531–3.
25. Ørskov I, Ørskov F, Smith HW, Sojka WJ. The establishment of K99, a thermolable, transmissible *Escherichia coli* K antigen, previously called "Koo", possessed by calf and lamb enteropathogenic strains. Acta Pathol Microbiol Scand 1975;83:31–6.
26. Isaacson RE, Nagy B, Moon HW. Colonisation of porcine small intestine by *Escherichia coli*: colonisation and adhesion factors of pig enteropathogens that lack K88. J Infect Dis 1977;135:531–9.
27. Awad-Masalmeh M, Moon HW, Runnels PL, Schneider RA. Pilus production, hemagglutination and adhesion by procine strains of enterotoxigenic *Escherichia coli* lacking K88, K99 and 987P antigens. Infect Immun 1982;35:305–13.
28. Satterwhite TK, DuPont HL, Evans DG, Evans DJ Jr. Role of *Escherichia coli* colonisation factor antigen in acute diarrhoea. Lancet 1978;ii:181–4.
29. Evans DG, Satterwhite TK, Evans DJ Jr, Dupont HL. Differences in serological responses and excretion patterns of volunteers challenged with enterotoxigenic *Escherichia coli* with and without the colonisation. Infect Immun 1978;19:883–8.
30. Beachey EH, Eisenstein BI, Ofek I. Bacterial adherence in infectious diseases. In: Current Concepts Series. Michigan: Upjohn Co. 1982: 1–52.
31. Svenson SB, Kallenius G, Hollby R, Hultberg H, Winberg J. Rapid identification of p-fimbriated *Escherichia coli* by a receptor specific particle agglutination test. Infection 1982;4: 209–14.
32. WHO Technical Report Series No. 624. Introduction. In: Surveillance for the prevention and control of health hazards due to antibiotic-resistant enterobacteria. Geneva: World Health Organization, 1978:7–9.
33. Duguid JP, Clegg S, Wilson MI. The fimbrial and non-fimbrial haemagglutinins of *Escherichia coli*. J Med Microbiol 1979;12:213–27.
34. MacLagan RM, Old DC. Haemagglutinins and fimbriae in different serotypes and biotypes of *Yersinia enterocolitica*. J Appl Bacteriol 1980;49:353–60.
35. Morris JA, Thorns C, Scott AC, Sojka WJ, Wells GA. Adhesion *in vitro* and *in vivo* associated with an adhesive antigen (F41) produced by a K99⁻ mutant of the reference strain *Escherichia coli* B41. Infec Immun 1982;36: 1146–53.
36. Aning KG, Thomlinson JR, Wray C, Sojka WJ, Coulter J. Adhesion factor distinct from K88, K99, F41, 987P, CFA1 and CFA 11 in porcine *Escherichia coli*. Vet Rec 1983;112:251.
37. Evans DG, Evans DJ Jr. New surface-associated heat labile colonisation factor antigen (CFA 11) produced by enterotoxigenic *Escherichia coli* of serogroups 06 and 08. Infect Immun 1978;21:638–47.
38. Thomas LV, Cravioto A, Scotland SM, Rowe B. New fimbrial antigenic type (E8775) that may represent a colonisation factor in enterotoxigenic *Escherichia coli* in humans. Infect Immun 1982;35:1119–24.
39. Kallenius G, Mollby R, Sevenson SB *et al.* Occurrence of P-fimbriated *Escherichia coli* in urinary tract infections. Lancet 1981;ii:1369–72.
40. Edelman R, Levine MM. Summary of a workshop on enteropathogenic *Escherichia coli*. J Infect Dis 1983;147:1108–18.