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Enterobacterial Fimbriae

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ENTEROBACTERIAL FIMBRIAE

Many different species of the family *Enterobacteriaceae* have been shown to possess fimbrial appendages which emerge from the bacterial cell as straight, rigid organelles distinct from flagella (14). The role of fimbriae (synonym: pili) as adhesins in both enterotoxigenic and uropathogenic isolates of *Escherichia coli* has been demonstrated, and thus the identification of such appendages as virulence determinants was established. Enterotoxigenic *E. coli* strains possess a number of distinct antigenic types of fimbriae facilitating attachment to the epithelial cells of the gastrointestinal tract, and these have been reviewed in detail elsewhere (18). Similarly, the fimbrial adhesins of urinary isolates of *E. coli* and the role of these fimbriae in facilitating colonization of uroepithelial cells have been the subject of extensive investigation (25, 32). Consequently, this review concentrates on recent developments as they pertain to fimbriae of members of the *Enterobacteriaceae* other than *E. coli*, and *E. coli* antigens will be considered only in comparison with heterologous fimbriae.

TYPE 1 FIMBRIAE

Bacteria possessing type 1 fimbriae are characterized by their ability to mediate agglutination of fowl or guinea pig erythrocytes in the absence of α-D-mannose but not in its presence (33). These fimbriae have been observed on many different species of enterobacteria, and the diversity of fimbrial antigenic types within this family was initially determined by using standard bacterial agglutination techniques (12, 31). From these early studies, close serologic relationships were found to exist among the type 1 fimbriae of *Escherichia*, *Klebsiella*, and *Shigella* spp., whereas the fimbriae of *Salmonella* and *Citrobacter* spp. constituted a second serologic group. In addition, the type 1 fimbriae of *Enterobacter*, *Edwardsiella*, *Hafnia*, *Serratia*, and *Providencia* spp. each comprised a distinct serologic group. The presence of fimbriae exhibiting mannose-sensitive reactivity has also been demonstrated in species of *Erwinia* (7), although it is unknown whether this genus shares fimbrial antigens with other members of the *Enterobacteriaceae*.

Type 1 fimbriae have been purified from *E. coli* (43), *Salmonella typhimurium* (23), *Klebsiella pneumoniae* (17), and *Serratia marcescens* (22). In all cases the fimbriae are believed to be polymers of single polypeptide subunits, the molecular weights of which are 17,000, 21,000, 19,500, and 19,000 for the fimbrial subunits of *E. coli*, *S. typhimurium*, *K. pneumoniae*, and *S. marcescens*, respectively. It is interesting, however, that a difference has been reported in the molecular weights of the type 1 fimbrial subunits of "*Klebsiella aerogenes*" (18,000) and *K. pneumoniae*, and it has been suggested that this may reflect a difference in the composition of the subunits among saprophytic and pathogenic klebsiellae (24). In addition, purified preparations of *S. marcescens* fimbriae possess a minor protein component distinct from the major subunit (22). In all examples described above, the isolated fimbriae retained the adhesive function and demonstrated mannose-sensitive hemagglutinating activity. Although these biochemical studies have indicated that the adhesive fimbriae appear to consist in most cases of polymerized forms of a single polypeptide subunit, recent studies of the *E. coli* type 1 fimbriae appear to demonstrate otherwise. Thus, using the cloned gene cluster of *E. coli*, both Maurer and Orndorff (28) and Minion et al. (30) have demonstrated that the adhesive component of the type 1 fimbriae is distinct from the major structural fimbrial subunit. Using a recombinant plasmid encoding type 1 fimbriae of *K. pneumoniae*, we have been able to construct mutants which possess morphologically intact fimbrial organelles when viewed by electron microscopy, but do not agglutinate guinea pig erythrocytes. Therefore, it is possible that throughout the enterobacteria the adhesin responsible for recognition of receptors on the erythrocyte membrane is a moiety separate from that necessary for the structural integrity of the fimbrial filament. In light of these results it is interesting to speculate on the nature of the adherence factor associated with type 1 fimbriae of the enteric bacteria. A common property of these fimbrial organelles is there inability to attach to eucaryotic cells in the presence of α-D-mannose. Therefore, it is possible that the adhesin component of the type 1 fimbriae is similar in all bacterial species. Further insights into the important binding domains which specifically recognize receptors on eucaryotic cells will be facilitated by the analysis of the appropriate genes at the molecular level.

The excellent studies of Falkow and his group on the molecular cloning and characterization of the genes involved in *E. coli* fimbrial expression initially demonstrated the complexity of this genetic system (19, 41, 42). However, there is relatively little information on the equivalent genes in other enterobacteria. Buchanan and co-workers (6) used a DNA probe carrying the gene encoding the 17,000-dalton fimbrial subunit to detect homologous sequences of DNA derived from different genera of enteric bacteria. These results clearly indicated that sequences encoding type 1 fimbriae within this family were not conserved. Only fimbriate bacteria identified as *E. coli* or belonging to the genus *Shigella* possessed DNA which hybridized to the probe, a finding consistent with the close antigenic relationship between these two groups. However, DNA isolated from *Klebsiella* species, a genus also reported to possess fimbriae serologically related to those of *E. coli* (12, 31), did not hybridize to the *E. coli* DNA probe.

The construction and comparison of recombinant plasmids encoding the expression of type 1 fimbriae of *S. typhimurium*, *Enterobacter cloacae*, *S. marcescens*, and *K. pneumoniae* have confirmed the considerable heterogeneity existing in the gene clusters from these genera (8, 9). Fimbrial gene sequences of a single genus of *Enterobacteriaceae* encoded diffusible gene products which are required for the phenotypic expression of type 1 fimbriae. However,

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genes derived from one genus were unable to complement those of a different genus to restore the fimbrial hemagglutinating phenotype. Further analysis of these plasmids by us has shown that the phenotypic expression of fimbrial organelles is dependent upon the interaction of several gene products (9a) and, in this respect, is analogous to the more fully characterized *E. coli* system. All cloned gene clusters encoded a high-molecular-weight polypeptide similar to that identified for *E. coli* (41). Nevertheless, the organization of the genes within each group appeared to be different with respect to location and size of the gene products. As many as six polypeptides were implicated in the expression of *Salmonella* fimbriae, whereas three detectable polypeptides were associated with fimbrial production in *Serratia marcescens*. The regulation of expression of these genes and the interaction of their gene products must await further investigation.

The basic function of type 1 fimbriae of enteric bacteria remains unknown, although the adhesive properties of these organelles most likely impart an important property to the bacterial cell as evidenced by their widespread occurrence among this group. Many investigators believe that type 1 fimbriae of *E. coli* may indeed be important virulence factors for strains isolated from lower urinary tract infections (1, 20, 21). A similar role has been ascribed to the type 1 fimbriae of *K. pneumoniae*, in that these organelles facilitate attachment to mucosal surfaces and this is a determining factor in the ability of the bacteria to cause infection. Fader and coworkers (15, 16) demonstrated that fimbriate *K. pneumoniae* cells adhere to rat bladder epithelial cells and contribute to the infective process. Experimental infection of the urinary tract in mice yielded similar results, again indicating that type 1 fimbriae play an important role in the initial stages of infection (27). In addition, these latter studies suggested that fimbrial phase variation, the ability to alternate between a fimbriate and nonfimbriate phase, is an important mechanism in the survival of the pathogen during the infectious process.

Type 1, mannose-sensitive hemagglutinating fimbriae from other bacterial strains have also been implicated as virulence factors in urinary isolates. Yamamoto et al. (48) recently demonstrated that fimbriae of *S. marcescens* were responsible for attachment to human bladder epithelial tissue but did not bind to mouse cells. These in vitro adherence studies led the investigators to speculate that type 1 fimbriae may bind to bladder tissue and thus act as colonization factors.

The physiological role of *Salmonella* fimbriae remains to be determined, but there is some evidence to indicate that these appendages (i) potentiate bacterial virulence in orally infected mice (13), (ii) may be involved in the adherence of *S. typhimurium* to surface teguments of schistosomes (29, 47), and (iii) are associated with nonspecific adhesion to mineral particles (46). These latter observations are believed to reflect the relative increase in hydrophobicity of the bacterial surface imparted by the presence of fimbriae. Indeed, it has been demonstrated that clinical isolates of enteric bacteria commonly demonstrate high relative surface hydrophobicity associated with the presence of fimbrial appendages (26).

TYPE 2 FIMBRIAE

Nonhemagglutinating type 2 fimbriae have been described for *Salmonella* strains, where it has been shown that these organelles morphologically resemble type 1 fimbriae (39). Indeed, the close antigenic relationship between these two fimbrial types may indicate that the type 2 fimbriae are nonadhesive variants of type 1 fimbriae. The construction of recombinant plasmids encoding nonhemagglutinating fimbriae in *E. coli* demonstrates that the adhesive function can be separated from the fimbrial filament in this species (28, 30). Similarly, as described above, initial data from our studies with the fimbrial gene system from *K. pneumoniae* have determined that fimbriate, nonhemagglutinating transformants can be produced by using chimeric DNA molecules. Consequently, it appears that receptor-binding activity of the fimbrial organelles among some, if not all, bacteria can be separated from the gene products required for fimbrial assembly. In light of these results it may be necessary to reconsider the designation of type 2 fimbriae as structures which could be identical to fimbrial filaments of type 1.

TYPE 3 FIMBRIAE

The early work of Duguid (10) established that some strains of *Klebsiella* and *S. marcescens* are able to agglutinate animal erythrocytes only after the latter have been treated with tannic acid. The fimbriae associated with this activity were classified as type 3 (11). They appear as thin (4- to 5-nm diameter) organelles lacking an axial hole when examined by electron microscopy (35). The recent work of Old and colleagues (4, 34, 36, 38) has demonstrated the ubiquity of type 3 fimbriae (and type 3 fimbrialike structures) among many members of the *Enterobacteriaceae*. Type 3 fimbriae are antigenically distinct from type 1 fimbriae (24, 31). The serological relationships among type 3 fimbriae of various members of the *Enterobacteriaceae* have been examined by immune electron microscopy (37), and the results from such studies have demonstrated complex relationships among these antigens even within a single genus. Thus, type 3 fimbrial antiserum prepared against strains of *Klebsiella* reacted with fimbriate strains of *Klebsiella*, *Yersinia*, and *Salmonella*, whereas serum raised against *Morganella* and *Proteus* species appeared to be genus specific. Type 3 fimbriate strains of two different *Providencia* species each possessed unique antigenic determinants. A more detailed analysis of type 3 fimbriae within the genus *Klebsiella*, using an enzyme-linked immunosorbent assay and partially purified antigens, confirmed that these structures are closely related in this bacterial group (40).

Type 3 fimbriae have been purified from various *Klebsiella* species, and the molecular weights of the fimbrial subunit range from 19,500 to 23,000 (24, 40). In these purified preparations hydrophobic amino acids were approximately 33 to 39% of the total amino acid residues. The relative distribution of amino acids among fimbriae purified from *K. oxytoca*, *K. pneumoniae*, *S. enteritidis*, and *Y. enterocolitica*, was found to be very similar.

No detailed studies on the gene cluster responsible for the expression of type 3 fimbriae have been reported, and therefore the number of genes involved and their organization is, as yet, unknown. Interestingly, preliminary data from our laboratory suggest that *E. coli* strains possessing derivatives of recombinant plasmids encoding type 1 fimbriae of *K. pneumoniae* cross-react with serum prepared against type 3 fimbriae. When examined by electron microscopy, these strains exhibit fimbrial types which resemble both type 1 and type 3 organelles. It is interesting to speculate that the genes encoding these structures may be closely linked on the *Klebsiella* chromosome and that the molecular cloning of these determinants on multicopy plasmids results in altered regulation of the fimbrial genes.

Unfortunately, we have not been able to construct a plasmid which imparts a typical type 3 fimbrial hemagglutination reaction (i.e., agglutination of tanned erythrocytes) upon transformants. Further analyses, including a search for type 3 fimbrial subunits in cell extracts, are being performed with these strains.

Due to the paucity of information available concerning the distribution of type 3 fimbriae among the enteric bacteria, the role of these organelles remains to a large extent speculative. Korhonen et al. (24) demonstrated that type 3 fimbriate bacteria adhere to plant root cells and thus may play an important role in establishing the plant-bacterium relationship of nitrogen-fixing *Klebsiella* strains. However, the early studies of Duguid (10) demonstrated that those *Klebsiella* species producing type 3 fimbriae could adhere not only to plant root hairs but also to yeasts, fungi, cellulose fibers, and glass surfaces. Therefore, the precise function of such appendages is unknown.

OTHER FIMBRIAL TYPES

Within the last few years diverse groups of enteric bacteria have been shown to possess other types of fimbriae in addition to those described above. Due to the lack of uniformity in nomenclature and to the unreliability of distinguishing different fimbrial types by morphology alone, it is difficult to assign the presence of novel fimbrial types to particular species. However, it is possible to exclude the presence of type 1, 2, or 3 fimbriae on these bacterial cells by serology, adhesive activity, and size. Consequently, the fimbrial appendages described below are believed to be distinct from those mentioned above.

Many *Enterobacter aerogenes* strains exhibit a mannose-sensitive type of hemagglutination associated with a fimbrial type distinct from type 1 fimbriae (3). By using immunoelectron microscopy tests, it was shown that this hemagglutinating activity was associated with thin (ca. 4-nm-diameter), nonchannelled fimbriae which, unlike type 1 fimbriae, were species specific. Further information on these fimbrial structures is not available.

The complexity of fimbrial structures in different *Serratia* strains has been well documented (2, 38). In these studies several types of fimbrial appendages were observed by electron microscopy, by adherence to untreated and tanned erythrocytes from various animals, and by reaction with fimbria-specific antibodies. Besides the characteristic type 1 and 3 fimbriae, some strains were also shown to possess fimbriae which agglutinated a variety of erythrocytes but were distinguishable from types 1 and 3. Obviously, *Serratia* strains possess the ability to produce a complex array of fimbrial structures; the regulation of their expression and the relationship of these organelles to others within the *Enterobacteriaceae* have yet to be elucidated.

More recently, considerable attention has been given to the adhesive properties of strains of *Proteus mirabilis*, a species frequently implicated in the pathogenesis of urinary tract infections. Although there is contradictory evidence concerning the role of fimbriae as virulence determinants in these strains (5, 44, 45), there is no doubt that, like *Serratia* strains, they produce a variety of distinct fimbrial types (5, 34). Whether the vast array of hemagglutinating phenotypes found in this species, as well as among *Morganella* and *Providencia* strains, reflects subtle differences in fimbrial components or correlates with distinct fimbrial structures remains to be determined.

CONCLUSIONS

The presence of fimbriae on most strains of enteric bacteria suggests that these organelles play an important role in the life cycle of the bacteria. Although it has been demonstrated that fimbrial appendages facilitate colonization of both human and animal hosts by *E. coli*, the precise role of fimbriae in other genera remains, to a large extent, unknown. Interest has centered on the ability of these organelles to adhere to specific receptors on eucaryotic cells and, thus, to promote efficient colonization of the appropriate animal hosts, a situation analogous to that of the fimbrial adhesins of *E. coli*. In many cases this may be so, but a number of enteric bacteria commonly establish a saprophytic life cycle in which the bacterial cells are required to attach to both animate and inanimate surfaces in order to colonize an ecological niche. In these cases the fimbriae may also play a vital role in maintaining cell viability.

The ability of enteric bacteria to produce a morphologically and antigenically diverse range of fimbriae with varying receptor specificity indicates that individual strains may have evolved to express distinct adhesins under different environmental conditions. For many bacterial species in vitro conditions of culture for the optimal expression of particular fimbrial types have been defined. In many cases the exact parameters affecting fimbrial production in vivo have yet to be determined.

The cloning of the gene clusters encoding specific fimbrial types has facilitated an analysis of the relatedness of this family of genes within members of the *Enterobacteriaceae*. Initial evidence suggests that these gene sequences show little homology and, therefore, may have diverged significantly from one another. However, recent studies by at least two groups of investigators (28, 30) establishing the genetic distinction between the adhesin and the type 1 fimbrial filament of *E. coli* raise the possibility that the mannose-sensitive phenotype of most type 1 fimbriate strains of enterobacteria may be due to a highly conserved gene. Certainly the elucidation of the molecular genetics of this system may answer this question. However, the preliminary evidence suggesting a large degree of heterogeneity among the type 1 fimbrial gene clusters indicates that genes expressing functionally different fimbriae are significantly different at the molecular level.

Within the last decade the techniques of molecular biology have permitted a detailed analysis of the structure-function relationship of specific adhesins, particularly in *E. coli*. Such strategies will eventually prove useful in increasing our understanding of the mechanism of bacterial adhesins as well as in the development of vaccines for protection of humans and animals from infection. Although the fimbrial gene systems of *E. coli* have provided such invaluable information, the application of recombinant DNA techniques to other genera of enteric bacteria is beginning to provide even more information on the biosynthesis and assembly of fimbrial macromolecules. In the near future questions concerning functional aspects, genetic relatedness, and bacterial ligand-receptor interactions among fimbriate strains of other members of the *Enterobacteriaceae* will begin to be answered.

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