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MINIREVIEW

Adhere Today, Here Tomorrow: Oral Bacterial Adherence

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INTRODUCTION

The oral cavity is home to a large and diverse population of microbes comprising over 350 taxa and in which 37 genera of bacteria are represented (37, 38). Coaggregation, or cell-to-cell recognition of genetically distinct partner cell-types, has been observed with isolates from the 18 genera tested so far (25, 26); these 18 genera constitute the bacteria most frequently isolated from dental plaque. Like other saprophytic and pathogenic bacteria that inhabit or invade various human tissues, members of the oral flora possess specific cell surface-associated adherence proteins responsible for initiating colonization. These bacterial adhesins recognize protein, glycoprotein, or polysaccharide receptors on various oral surfaces, including other cell types. In dental plaque, the ability to attach to bacteria already anchored to hard or soft tissues may provide secondary colonizers with the same advantages enjoyed by primary colonizers. Essentially all oral bacteria possess surface molecules that foster some sort of cell-to-cell interaction (26); some constitutively synthesize a coterie of adhesins that permit a cell to participate simultaneously in multiple interactions with partner cell types (32). Other oral bacteria, such as the cariogenic mutans streptococci, synthesize extracellular glucans and a major surface protein antigen (14) that contribute to their ability to adhere to teeth (29). This kind of adherence has been extensively studied by many laboratories and appears to be distinct from coaggregation.

In other ecosystems, there is surprisingly little or no evidence for coaggregation among resident bacteria. Juxtapositioning of genetically unrelated bacterial microcolonies in metabolic consortia performing anaerobic biodegradations (36, 49) is different from coaggregations which are characterized by direct and viability-independent cell-to-cell recognition. Bacterial predation and conjugation, the action of the pheromone system of *Enterococcus faecalis* (44), invertebrate animal intestinal tract microbes (5), and nutritional symbionts have some similarities to the highly specific mechanisms of oral bacterial recognition.

Coaggregation may be intra-, inter- or multigeneric, and it is different from the interactions among clonal populations, for example rosettes among caulobacters. Generally, secondary colonizers synthesize protein adhesins that recognize receptors on primary colonizers such as the streptococci and actinomyces (30). This review will deal with the characteristics of adhesin and receptor molecules and the potential roles they play in dental plaque accretion. Equally important to adherence in developing oral microbial consortia are the nutritional relationships among plaque bacteria, which have been reviewed elsewhere (26) and will not be discussed further here.

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HABITAT

Most oral bacteria exhibit the property of intergeneric coaggregation (26). The partnerships are specific, and in some instances the interactions are site specific. For example, veillonellae isolated from the tongue coaggregate primarily with streptococci isolated from the tongue, whereas, subgingival-plaque veillonellae coaggregate with streptococci from subgingival plaque (17). Besides this site specificity, the partnerships are specific with respect to the time that different cell types colonize a freshly cleaned tooth surface (Fig. 1) (25, 26).

The earliest colonizers are overwhelmingly streptococci, which constitute 47 to 85% of the cultivable cells found during the first 4 h after professional teeth cleaning (39). Within 12 h the population diversifies to include actinomyces, capnocytophagae, haemophili, prevotellae, propionibacteria, and veillonellae. Many of the early colonizers are known to recognize components of the acquired pellicle, a thin coating that covers the freshly cleaned tooth surface and consists primarily of glycoproteins, mucins, and enzymes found in saliva. Some of the salivary components have been purified and tested for specific binding by oral bacteria. The best studied of these is a group of acidic proline-rich proteins, whose Pro-Gln dipeptide at the carboxy terminus appear to be the minimal receptor for *Streptococcus gordonii* (12). The type 1 fimbriae of *Actinomyces naeslundii* confer on the actinomyces the ability to bind to acidic proline-rich proteins also, but recognition is to other regions of the molecules (11). Both *A. naeslundii* and *Fusobacterium nucleatum* bind to statherin, another phosphoprotein in the acquired pellicle. *F. nucleatum* also binds to salivary proline-rich glycoprotein (not shown in Fig. 1), while *S. gordonii* recognizes α-amylase (41) and acidic proline-rich proteins but not statherin. The possibility that bacterial cell fragments are constituents of the acquired pellicle has been discussed elsewhere (25). Neither coaggregation nor bacterial recognition of host receptors in the acquired pellicle are energy dependent.

Of the more than 300 isolates of *A. naeslundii*, *S. gordonii*, *Streptococcus mitis*, *Streptococcus oralis*, and *Streptococcus sanguis* tested in pairwise intergeneric coaggregations, more than 90% coaggregate (26). These are highly specific actinomyces-streptococcus partnerships and are characterized on the basis of sugar inhibition of coaggregation, protease (or heat) sensitivity of either or both cell types, and simultaneous loss of a cluster of coaggregation partnerships by coaggregation-defective mutants (26). Although pairwise mixing of 300 isolates could result in a very large number of random coaggregations, the resultant coaggregation patterns are arranged into just six coaggregation groups of actinomyces and six coaggregation groups of streptococci, indicating the nonrandomness of coaggregations. Equally high speci-

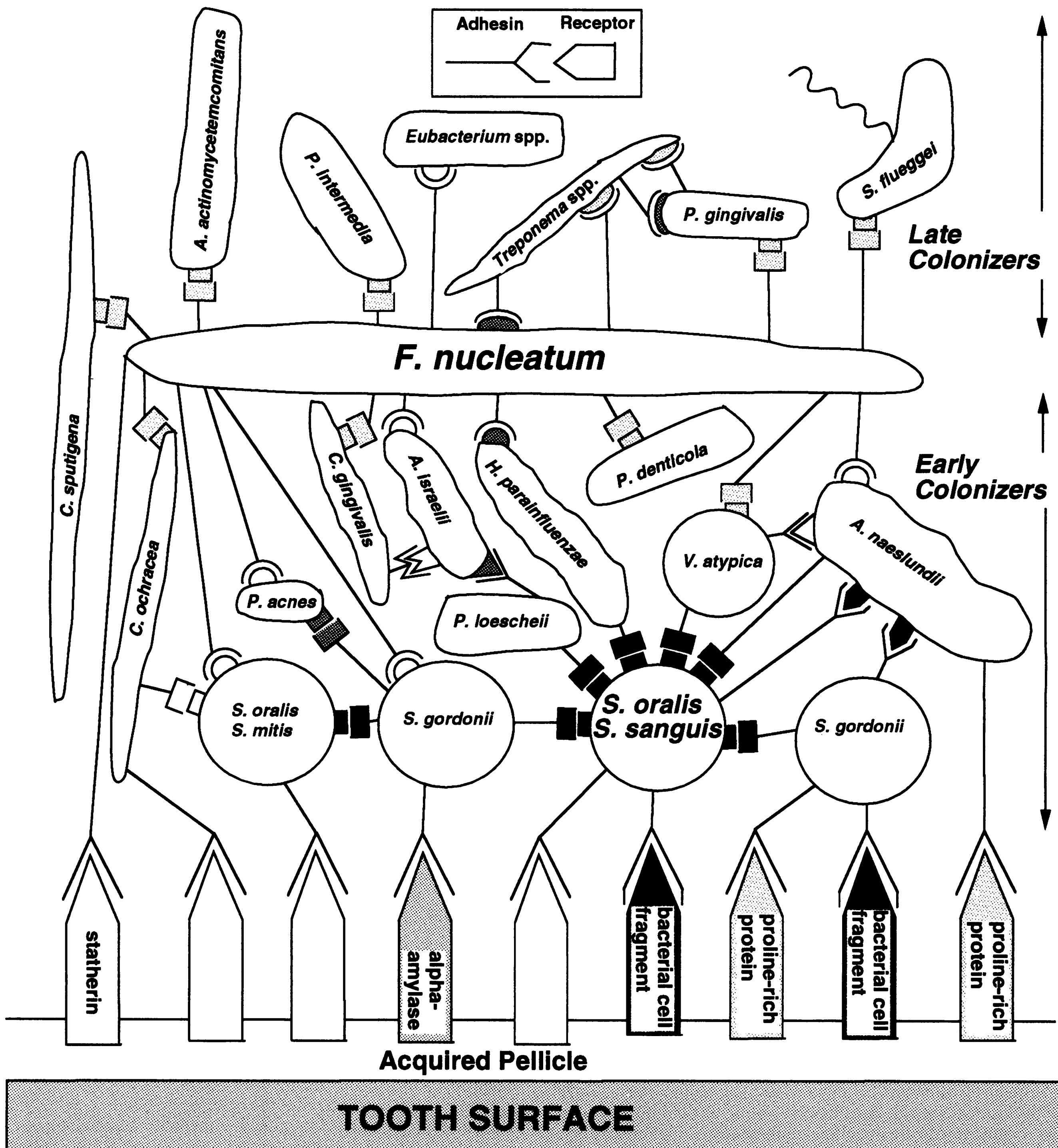

FIG. 1. Diagrammatic representation of proposed bacterial accretion in dental plaque. Early colonizers bind to receptors in the acquired pellicle. Each newly adherent cell type becomes in turn the nascent surface and bridge for additional accreting cell types. The complementary sets of adhesin receptor symbols (an example is shown in the box at the top) represent the various kinds of coaggregations as well as interactions with molecules in the acquired pellicle. The symbol with a stem (adhesin) represents a cellular component that is heat inactivated (cell suspension heated to 85°C for 30 min) and sensitive to protease treatment. The cell type exhibiting the complementary symbol (receptor) is insensitive to either treatment. Identical symbols are not intended to indicate identical molecules, but they are likely to be related functionally. The symbols with rectangular shapes represent lactose-inhibitable coaggregations; symbols with other shapes represent lactose-noninhibitable coaggregations. The bacterial strains shown are *Actinobacillus actinomycetemcomitans*, *Actinomyces israelii*, *Actinomyces naeslundii*, *Capnocytophaga gingivalis*, *Capnocytophaga ochracea*, *Capnocytophaga sputigena*, *Eubacterium* spp., *Fusobacterium nucleatum*, *Haemophilus parainfluenzae*, *Porphyromonas gingivalis*, *Prevotella denticola*, *Prevotella intermedia*, *Prevotella loescheii*, *Propionibacterium acnes*, *Selenomonas flueggei*, *Streptococcus gordonii*, *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus sanguis*, *Treponema* spp., and *Veillonella atypica*.

ficity has been observed for all genera tested (26). Both streptococci and actinomyces coaggregate with only certain strains of capnocytophage, haemophili, prevotellae, propionibacteria, and veillonellae. Not only is the ability to coaggregate a general trait, but most coaggregations are inhibited by lactose and other galactosides (Fig. 1 [lactose-inhibitable interactions are depicted as complementary rectangle symbols]) (26, 34).

The interactions shown in Fig. 1 represent only a portion of the known types of interactions occurring among oral bacteria and are presented here as examples. They also include the interactions that have been investigated more thoroughly. Although seemingly complex, those interactions that have been studied function independently of other collateral coaggregations (21). For example, the lactose-inhibitable interaction of *Prevotella loescheii* with *S. oralis* (or *S. sanguis*) (Fig. 1, lower center) is independent of the lactose-noninhibitable interaction (triangle symbols) with *Actinomyces israelii*. This sort of multigeneric coaggregation has been termed a coaggregation bridge with *P. loescheii* being the bridge organism (22). Close examination of Fig. 1 reveals that coaggregation bridges are an integral part of plaque as depicted here. Sequential coaggregation is a bridging process manifested as bacterial accretion.

Most of the early-colonizing streptococci (*S. oralis*, *S. sanguis*, and *S. mitis*; shown in Fig. 1) offer receptor molecules to the indigenous flora. *S. gordonii* is an exception, having acquired a number of adhesins (see top center of Fig. 1) which take advantage of the available receptors on the other streptococci. Some interactions are galactose-inhibitable (Fig. 1, rectangle symbols), and some are not inhibited by sugars (obelisk symbols). The adhesins (obelisk symbols) from *S. gordonii* and *S. sanguis* (Fig. 1, lower right) that mediate coaggregation with *A. naeslundii* are lipoproteins (discussed below).

Two foci are depicted in Fig. 1. The first is the cell in the lower right, identified as *S. oralis* or *S. sanguis*. It is recognized by five genera of partners, including other streptococci. The significance of the functional relatedness of the adhesins is discussed below. Here, we want to point out that coaggregation-defective mutants of *S. oralis* (or *S. sanguis*) that were selected for failure to coaggregate with *P. loescheii* also simultaneously lost the lactose-inhibitable (rectangle symbols) coaggregations with *S. gordonii*, *Haemophilus parainfluenzae*, *Veillonella atypica*, and *A. naeslundii*, but remained capable of lactose-noninhibitable (obelisk symbols) coaggregation with *A. naeslundii*. Apparently, the same receptor on *S. oralis* (or *S. sanguis*) is recognized by the complementary adhesins borne on the partners.

The second focus of Fig. 1 is the central role played by *F. nucleatum*. As a group, fusobacteria coaggregate with some strains of all 17 genera that have been tested so far, but each strain of *F. nucleatum* coaggregates only with a certain set of partners (23). Although fusobacterial coaggregations span all genera, surprisingly, fusobacteria do not show intrageneric coaggregation, which occurs extensively among the early-colonizing streptococci (24). Fusobacteria are infrequently found in the first 12 h after teeth are cleaned; however, they are among the most frequently isolated bacteria in plaque from healthy sites. Their numbers increase about 10-fold in plaque sampled from periodontally diseased sites, and they are often the most frequently isolated oral bacteria.

The fusobacterium is depicted as a bridge between early colonizers and late colonizers. Early-colonizing bacteria coaggregate extensively among each other and with *F. nucleatum*. Late colonizers, such as *Selenomonas flueggei*, do not coaggregate with early colonizers and instead coaggregate almost exclusively with *F. nucleatum* (23). In another study, five *Eubacterium* species coaggregated only with the six *F. nucleatum* strains in a group of 33 isolates representing 10 species, including *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Prevotella intermedia* (10). Coaggregation of *Treponema denticola* and *P. gingivalis* (15) correlates with the observation that *T. denticola* was never detected in periodontally affected sites unless that site was also inhabited by *P. gingivalis* (43). Because of their ability to participate in a broad range of coaggregations and their status as a very frequently (if not the most frequently) isolated species in established dental plaque in both healthy and diseased sites, it is proposed that fusobacteria act as a bridge between early- and late-colonizing bacteria.

ADHESINS AND RECEPTORS

Many of the cell-to-cell interactions described in the literature can be inhibited or reversed by addition of simple sugars, suggesting that many adhesins are lectinlike proteins (26). Galactosides appear to be the sugar moiety most commonly recognized by oral bacterial lectins (26), although other sugars, such as rhamnose, have also been implicated (3, 46). Among oral bacteria, these adhesins are found intercalated into the outer membrane or cell wall (20, 45, 46), or they may be associated with fimbriae (47). Where adhesin activity is not associated with major outer membrane proteins, these proteins are found in relatively low numbers. Adhesin-specific-antibody-binding studies with *Capnocytophaga gingivalis* or *P. loescheii* suggest that these bacteria, like enteric bacteria (19), have only 300 to 500 (maximum) adhesin molecules present on the surface of each cell (48). Among oral bacteria, a number of adhesins have been identified (26, 30); a smaller number have been isolated or characterized and, in a few instances, the genes encoding these molecules have been cloned and sequenced.

A large galactoside-specific adhesin (75-kDa monomer) on *P. loescheii* PK1295 that mediates attachment to *S. oralis* 34 and neuraminidase-treated erythrocytes was isolated in an active form and characterized (31). The 2.4-kb *plaA* gene encoding this protein has recently been cloned, sequenced, and found to undergo a +1 frameshift after translation of the nucleotides encoding the first 28 amino acids of the mature protein (33). The portion of the gene encoding the mature protein contains 2,477 nucleotides; theoretically, only 2,006 nucleotides are required for expression of the complete gene product. Thus, the frameshift and excess coding information may provide a mechanism for producing more than one protein or a bifunctional polypeptide from that particular DNA sequence. A putative 45-kDa adhesin from *V. atypica* PK1910 facilitates coaggregation with the same strain of *S. oralis* as the one recognized by *P. loescheii* (Fig. 1); its specificity for galactoside-containing receptors suggests that the adhesin functions in a similar manner (16). In contrast, the binding site for the 150-kDa membrane-associated adhesin of the gram-negative bacterium *Capnocytophaga ochracea* is specific for rhamnose-containing polysaccharides on a different strain of *S. oralis* (Fig. 1, left side, open rectangle symbol) (46).

Nonlectin adhesins (proteins whose binding properties are not affected by sugars) also have been reported from the gram-negative *P. gingivalis* (27, 28). Instead of the adhesin mediating a coaggregation function, the adhesin is either part of or associated with a fibrinogenolytic protease. Other

nonlectin adhesins, such as the SsaB and ScaA proteins from *S. sanguis* 12 and *S. gordonii* PK488, respectively, have been characterized, and their genes have been cloned and sequenced (1, 9). Because both streptococcal strains are coaggregation partners of *A. naeslundii* PK606 and because the two gene products, ScaA and SsaB, are 91% identical (1), it is thought that the two adhesins (Fig. 1, lower right, obelisk symbols) probably perform similar, if not identical, functions. Both contain the Leu-X-X-Cys (the Cys is at position 20) signal peptidase II cleavage site motif of prolipoproteins. The Cys residue of ScaA is thought to be acylated, as was shown for SsaB (8). Similar genes and gene products, respectively, have been detected by oligonucleotide probe and immunoblot analyses in the viridans streptococcal reference strains of all six coaggregation groups, suggesting that the protein is conserved and fulfills some essential service, perhaps colonization, for the bacterium (1). A third streptococcal species, *Streptococcus parasanguis* FW213, also expresses a closely related adhesin, FimA, which is important in binding the streptococci to saliva-coated hydroxyapatite (6). There is a growing awareness that these gram-positive lipoproteins (18, 25, 40) may be involved in more general recognition functions, such as the binding protein-dependent transport systems reported for numerous gram-negative bacteria. Other interactions, not shown in Fig. 1, are also thought to be mediated by lipoproteins (18) or by other proteins (35) that contain the LPxTGx motif of many membrane-anchoring cell surface proteins (42).

S. oralis and *S. sanguis* strains possess cell wall-associated polysaccharides that are believed to be receptors for coaggregation. Two of these carbohydrate molecules, found on *S. oralis* ATCC 55229 (*S. sanguis* H1) (3) and *S. oralis* 34 (34), respectively, have been isolated and demonstrated to be receptor molecules. The hexasaccharide unit of the polysaccharide isolated from *S. oralis* ATCC 55229 contains an L-rhamnose disaccharide that appears to be the interactive site for the streptococcus-specific *C. ochracea* adhesin (2, 13). In contrast, the *N*-acetylgalactosamine-galactose (GalNAc-Gal) disaccharide of the *S. oralis* 34 hexasaccharide unit probably facilitates coaggregation with the diverse variety of gram-positive (*Streptococcus* and *Actinomyces* species) and gram-negative (*Haemophilus*, *Prevotella*, and *Veillonella* species) partners shown in Fig. 1 (lower right). In the hexasaccharides isolated from *S. oralis* strains ATCC 55229 and 34, the respective receptors are located at opposite ends of the six-membered unit, whereas other putative streptococcal receptors are found internally; this suggests that virtually any position in these structures can serve as a target for adhesins. It should be noted, however, that the putative adhesin-binding site is on the reducing end of a galactofuranose residue (25). It is also curious that other constituents of the basic units, e.g., glucose or ribitol, are not used as receptor sites.

EVOLUTION

The fundamental importance of the adherence process to the survival of oral bacteria in the oral cavity raises related questions regarding the mechanism of attachment and the nature of progenitor molecules of adhesins. It has been suggested that the lectinlike adhesins are derived from carbohydrate transport proteins that generally reside in the membrane (19). This is probably the least complicated possibility, involving duplication of a gene encoding a protein with a sugar-binding site and the ability to transit a membrane. A variation of this hypothesis is the excision, cassette style, of that portion of a gene coding for a carbohydrate-binding region of a common sugar-catabolizing enzyme and the fusing of this to another gene carrying information for a signal sequence or a transmembrane segment to facilitate export of the entire gene product. There is no published evidence that either process was responsible for the evolution of lectinlike adhesins.

The ancestry of adhesins participating in protein-protein interactions is not much clearer. While proteases are generally thought to be release mechanisms hydrolyzing adhesins or receptor molecules (4, 7), a diametrically opposed hypothesis has been proposed (28). Studies with strains of *P. gingivalis* found that mutants defective in or lacking functional extracellular proteases lost the ability to interact with *A. viscosus* (28). Furthermore, it was reported that protein solutions inhibited cohesion of the two cell types. However, if the protease should ultimately degrade the "receptor" region on the partner cell, it is difficult to envisage anything but a temporary interrelationship. On the other hand, the fibrinogenolytic protease synthesized by *P. gingivalis* possesses a specific binding site distinct from the catalytic site (27). If the fibrinogenolytic activity were lost, a bona fide adhesin would result (27). Again, there are few other clues to the origins of these adhesins, but as more adhesin genes are cloned and sequenced, the derivation of these molecules may become clearer.

In contrast to the absence of an ancestral derivation for adhesins per se, a clearer view of the forces driving adhesin development in the oral cavity is emerging. The diverse constellation of bacteria that exhibit an affinity for *S. oralis* (or *S. sanguis*) (Fig. 1, lower right) or *F. nucleatum* (Fig. 1, upper center) suggests that ability to compete (22) for the respective receptor sites confers some survival advantage and argues for directed evolution of adhesins. Because both of these bacteria are present in relatively large numbers even under conditions of health, they provide, either directly (by attachment to the tooth surface) or indirectly (by attachment to the streptococci already on the tooth), a support system for the colonization and survival of other bacteria. Whether these respective adhesins were acquired independently by convergent evolution or by a horizontal transfer process is not clear. The latter notion is particularly attractive because, in plaque, bacteria lie in close proximity to one another, facilitating exchange of genetic information. This question may soon be resolved; several of these adhesin genes have already been sequenced (1, 6, 9, 33), and, when other sequences become available, a direct comparison may reveal conserved regions that are transcribed into homologous binding domains.

CONCLUSIONS

A rationale now exists for establishing a relationship between coaggregation and the appearance of certain bacteria in plaque. Late colonizers either do not adhere to saliva-coated hydroxyapatite or adhere nonspecifically. A corollary to this generality is that late colonizers primarily coaggregate with fusobacteria, which bridge these coaggregations with early colonizers. Early colonizers exhibit quite different properties; many adhere directly to pellicle and exhibit extensive inter- and intrageneric coaggregations. All early colonizers coaggregate with streptococci and/or actinomyces, the two cell types that constitute more than 90% of the viable cells in early plaque.

While we have considerable information about pairwise coaggregations, we know very little about the adhesins and

receptors of these coaggregations. To ameliorate this deficiency, studies are needed on the topics of (i) the organization and regulation of loci encoding adhesins, (ii) environmental regulation of gene expression, (iii) metabolic interactions between coaggregating pairs, and (iv) the role of genetic transfer within the oral habitat.

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