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Social networking at the microbiome-host interface

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ABSTRACT Microbial species colonizing host ecosystems in health or disease rarely do so alone. Organisms conglomerate into dynamic heterotypic communities or biofilms in which interspecies and interkingdom interactions drive functional specialization of constituent species and shape community properties, including nososymbiocity or pathogenic potential. Cell-to-cell binding, exchange of signaling molecules, and nutritional codependencies can all contribute to the emergent properties of these communities. Spatial constraints defined by community architecture also determine overall community function. Multilayered interactions thus occur between individual pairs of organisms, and the relative impact can be determined by contextual cues. Host responses to heterotypic communities and impact on host surfaces are also driven by the collective action of the community. Additionally, the range of interspecies interactions can be extended by bacteria utilizing host cells or host diet to indirectly or directly influence the properties of other organisms and the community microenvironment. In contexts where communities transition to a dysbiotic state, their quasi-organismal nature imparts adaptability to nutritional availability and facilitates resistance to immune effectors and, moreover, exploits inflammatory and acidic microenvironments for their persistence.

KEYWORDS polymicrobial community, dental caries, periodontal disease

The strength of the pack is the wolf

And the strength of the wolf is the pack

—Rudyard Kipling from *The Jungle Book*

The polymicrobial communities that inhabit host surfaces and mucosal barriers are complex and dynamic, as well as compositionally and spatially heterotypic. Integration of spatially contextualized information from partner species and from the host microenvironment drives the emergence of community-specific properties, and the community can operate as a functionally cohesive, or quasi-organismal, unit (1). Underlying the development of a polymicrobial community is a regulatory system of interconnected switches and rheostats, which operate both transcriptionally and posttranscriptionally, and which calibrate the pathogenic potential, or nososymbiocity, of the community. Indeed, it is the community *in toto* that constitutes the etiological agent in many cases of disease at mucosal membranes and on host surfaces. Consequently, host responses should be considered with regard to the community in its entirety rather than to individual organisms.

While the principles of interbacterial communication are applicable in communities at any anatomical site, we shall focus here on the oral ecosystem in which many of the core concepts were originally established (2–5). The oral cavity comprises a diverse ecosystem containing an abundant microbiota and both hard and soft tissues; nonetheless, unlike other mucosal environments, for example, the gastrointestinal tract, the ecosystem of the oral cavity is readily accessible. Thus, the microbiome associated with tissue- and site-specific diseases, such as dental caries and periodontal disease, can be sampled

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and studied exclusively. An intricate network of microbe-microbe and microbe-host interconnectivity has been uncovered, which can receive input in the form of physical or chemical signals, and which allows organisms to sense and respond to neighboring cells to coordinate group behavior and adapt to the microenvironment (6). While the extent of interspecies communication is potentially limitless, with hundreds of species capable of colonizing the mouth, the *in situ* configuration suggests that individual organisms have a more restricted sphere of influence. Fluorescent image analysis of subgingival communities shows that any one organism has a limited range of binding partners within distinct spatial structures, while specific microbes in supragingival biofilms can cluster themselves to create a localized pathogenic niche (7–9) (Fig. 1A). This parsimony of association facilitates the development of tractable and scalable models for the study of community development. Interestingly, as we shall explore, responses of an organism to partners show a significant degree of specificity for each pairing (10, 11), which may facilitate rapid adaptation to emerging conditions and allow organisms to have differential influence of community properties.

Interbacterial dialogue

The overall community developmental process of coadhesion and physiological integration belies an often multidimensional array of interbacterial interactions which can have differing outcomes depending on contextual cues. An overview of documented oral bacterial interactions is presented in Table 1, and these are extensively discussed in several excellent recent reviews (4, 13–16). In general, specialized adhesins mediate interbacterial binding which facilitates exchange of metabolites and other small molecules. Bacteria may utilize the information conveyed by attachment to a partner species to optimize fitness, resulting in new physiological functions that cannot be achieved by individual constituents alone. Although not yet resolved in oral bacteria, the outer membrane of other organisms, such as in *Escherichia coli*, can sense stressors including mechanical changes resulting from adhesion (17). In one such pathway, the lipoprotein NlpE senses surface adhesion and activates both the Cpx and BaeSR two-component systems, thus initiating an adhesion-dependent pattern of gene expression (18–20). Physiological integration can then involve cross-feeding or progressive metabolism of complex substrates (21). Increased fitness of community organisms has implications for pathogenicity, as in some instances virulence factors, for example, proteases, have dual functionality involving nutrient uptake in addition to tissue destruction. Indeed, current models of periodontal disease pathogenicity incorporate the role of interbacterial communication. In the polymicrobial synergy and dysbiosis (PSD) model, integration into subgingival communities of pathogens such as *Porphyromonas gingivalis*, even at low number, precipitates disruption of host homeostasis (22, 23). *P. gingivalis* thus fulfills the criteria for a keystone species; one whose supportive influence on its community is inordinately large relative to its abundance, thereby constituting the "keystone" of the community's structure. A keystone pathogen, therefore, is a quantitatively minor but functionally critical component of a disease-provoking microbiota. For instance, at least in the mouse host, *P. gingivalis* fulfills both criteria (low relative abundance and disproportionately large impact) by manipulating host immunity and inflammation in ways that promote the nososymbiocity and persistence of its community, while present at <0.01% of the total bacterial load (22). The concept of keystone pathogen should be distinguished from the action of other important pathogenic species, such as dominant pathogens, which can have a large impact on their communities and the host simply by virtue of their outsize biomass. Interestingly, as we shall explore later, the role played by individual species can vary, and organisms that contribute to dysbiosis in one context can help maintain homeostasis in another.

In other instances, as exemplified by the cariogenic *Streptococcus mutans,* the bacterial cells conglomerate preferentially into homotypic structures. Analysis of intact supragingival communities formed on mineralized host tissue (i.e., the teeth) reveals microbial clusters comprised almost exclusively of *S. mutans* that are surrounded by

TABLE 1 Interspecies interactions among oral bacteria

Organisms	Interactions	References
	Interactions within communities	
Streptococcus gordonii-Porphyromonas gingivalis	Context-dependent regulation of consortia pathogenic potential. *P. gingivalis* exhibits modulation of tyrosine phosphorylation-dependent signaling; regulation of genes encoding fimbrial adhesins; upregulation of genes associated with oxidative stress resistance; increased gingipain activity and hemin acquisition; differential flux through one-carbon metabolism (OCM) pathways. Streptococcal AI-2 regulates expression of genes involved in carbohydrate metabolism in *P. gingivalis*. Short-chain fatty acids from *P. gingivalis* inhibit the competence-stimulating peptide (CSP) quorum-sensing system of *S. gordonii*.	(24–30)
S. gordonii-Veillonella parvula	Consortia-dependent increased expression of streptococcal genes associated with carbohydrate metabolism and increased expression of oxidative stress-related processes in *V. parvula*.	(31)
S. gordonii-Fusobacterium nucleatum	*S. gordonii* genes involved in the biosynthesis and export of cell wall proteins and carbohydrate metabolism, and *F. nucleatum* genes associated with translation, protein export, and sialic acid metabolism are differentially regulated in consortia which have increased survival within macrophages.	(32, 33)
S. sanguinis-F. nucleatum	In a consortium, *F. nucleatum* masks the surface components recognized by H_2O_2 producing mouse oral microbiome constituents.	(34)
S. gordonii-Actinomyces oris	*S. gordonii* scavenges arginine from *A. oris* through the extracellular protease challisin which results in downregulation of streptococcal genes involved in arginine biosynthesis; actinomyces catalase can protect streptococci from oxidative damage.	(35, 36)
S. gordonii-Aggregatibacter actinomycetemcomitans (Aa)	Consortia are synergistically virulent, and Aa displays: a shift from fermentative to respiratory metabolism (cross-respiration); preferential utilization of lactate through carbon resource partitioning; increased production of catalase and complement resistance protein ApiA; regulation of iron uptake mechanisms which lead to modulation of dispersin B production and remodeling of the extracellular matrix to ensure optimal distance from *S. gordonii*.	(37–40)
S. parasanguinis-Aa	Aa promotes accumulation of *S. parasanguinis* through modulating the production of H_2O_2 by fine-tuning the expression of pyruvate oxidase.	(41)
S. gordonii-P. gingivalis, Prevotella intermedia, Tannerella forsythia	*S. gordonii* GAPDH binds heme and forms a reservoir that can be sequestered by HmuY of *P. gingivalis*, PinO of *Pr. intermedia* or Tfo of *Ta. forsythia*.	(42)
S. sanguinis, Aa-*P. gingivalis*	Increased catalase production by Aa in consortia protects *P. gingivalis* from H_2O_2 produced by *S. sanguinis*.	(43)
S. intermedius, S. cristatus-P. gingivalis	Streptococcal arginine deiminase (ArcA) represses expression of genes encoding fimbriae and gingipains in *P. gingivalis*.	(44, 45)
Mitis Group Streptococci (MGS)-*Haemophilus parainfluenzae*	MGS provide NAD and evoke distinct patterns of carbon utilization in *H. parainfluenzae* which is resistant to streptococcal H_2O_2.	(46)
V. parvula-P. gingivalis	*V. parvula* produces a cell-density-dependent soluble molecule which stimulates *P. gingivalis* growth at low cell density and enhances *in vivo* virulence.	(47)
V. parvula-F. nucleatum, S. gordonii	*V. parvula* catalase protects *F. nucleatum* in microaerophilic conditions and from streptococcal H_2O_2.	(48)
V. parvula-F. nucleatum *S. gordonii-F. nucleatum*	*V. parvula* and *S. gordonii* increase amino acid availability for *F. nucleatum*, resulting in enhanced production of fermented and decarboxylated metabolites.	(49)

(*Continued on next page*)

TABLE 1 Interspecies interactions among oral bacteria (*Continued*)

Organisms	Interactions	References
V. parvula, S. gordonii, F. nucleatum-P. gingivalis	Cross-feeding of *F. nucleatum* with *V. parvula* and *S. gordonii* increases polyamine production which accelerated accumulation with *P. gingivalis* and subsequent dispersal of planktonic cells.	(49)
Corynebacterium durum-S. sanguinis	Fatty acids produced by *C. durum* increase streptococcal chain length and promote resistance to phagocytosis.	(50)
P. gingivalis-S. mitis	*P. gingivalis* induces expression of transposases and cell death of *S. mitis.*	(51)
MGS-*S. mutans*	H_2O_2 from MGS inhibit *S. mutans* growth; however, this can be mitigated by pyruvate secretion which depletes H_2O_2; *S. mutans* lantibiotic and non-lantibiotic bacteriocins, tryglysin peptides, and tetramic acids are toxic to MGS; MGS block competence stimulating peptide and *comX*-inducing peptide (XIP) signaling and induce a common contact-dependent pattern of differential gene expression in *S. mutans;* a streptococcal protease (challisin) can degrade CSP and suppress mutacin gene expression; AI-2 from *S. gordonii* stimulates biofilm formation and regulates virulence gene expression in *S. mutans;* SsnA DNase of *S. gordonii* inhibits accumulation of *S. mutans*.	(52–58)
MGS, *S. mutans-Veillonella*	*S. mutans* produces lactate for *Veillonella* metabolism*; Veillonella* enhances expression of *S. gordonii* α-amylase to increase release of lactate.	(59, 60)
V. parvula-S. gordonii, S. mutans	*V. parvula* can protect *S. mutans* from H_2O_2 produced by *S. gordonii* and increases the expression of genes required for the uptake and metabolism of sugars in *S. mutans*.	(61)
S. parasanguinis-S. mutans, *Candida albicans*	*S. parasanguinis* accumulation in consortia is promoted by nitrite through upregulation of reactive nitrogen species (RNS) scavengers. Nitrite drives the metabolic signature of the consortia and restricts virulence factor production.	(62)
F. nucleatum-P. gingivalis	*F. nucleatum* can remove oxygen and promote the growth of *P. gingivalis.*	(63, 64)
F. nucleatum-P. gingivalis, T. denticola, Ta. forsythia	AI-2 from *F. nucleatum* induces expression of adhesins in *P. gingivalis, T. denticola, and Ta. forsythia,* and enhances consortia formation.	(65)
P. gingivalis-Pr. intermedia	*Pr. intermedia* interpain protease extracts heme from hemoglobin and converts to methemoglobin which is a substrate for the extraction of iron(III) protoporphyrin IX by HmuY of *P. gingivalis*.	(66, 67)
T. denticola-P. gingivalis	Glycine, isobutyrate, and thiamine produced by *P. gingivalis* stimulate the growth of *T. denticola*. Succinate and OCM metabolites produced by *T. denticola* stimulate glycine production and growth of *P. gingivalis*; *T. denticola* increases the expression of hemagglutinin adhesin domain proteins in *P. gingivalis* which enhances *P. gingivalis* adhesive capabilities.	(68–71)
Aa-*P. gingivalis*	AI-2 from Aa can regulate expression of genes involved in stress resistance and iron uptake in *P. gingivalis.*	(72)
T. denticola-P. gingivalis, F. nucleatum	Genes encoding *T. denticola* major antigens are suppressed by *P. gingivalis* and *F. nucleatum*.	(73)
	Interactions involving host cells	
S. gordonii-P. gingivalis	Streptococcal H_2O_2 incapacitates *P. gingivalis* gingipain and prevents Notch activation of epithelial cells; *S. gordonii* activates the TAK-NLK pathway and blocks *P. gingivalis* mobilization of FOXO1; *S. gordonii* induces a transcriptional profile which mitigates the impact of *P. gingivalis*.	(74–76)
S. gordonii-P. gingivalis	Spent culture supernatant of *S. gordonii* suppresses inflammatory responses of epithelial cells, fibroblasts, and macrophages to *P. gingivalis* lipopolysaccharide.	(77)
P. gingivalis-F. nucleatum	*P. gingivalis* suppresses endocytic pathway-mediated inflammasome activation in macrophages and prevents activation by *F. nucleatum;* in neutrophils *P. gingivalis* induces Toll-like receptor 2 (TLR2)-C5aR which	(78–80)

(*Continued on next page*)

TABLE 1 Interspecies interactions among oral bacteria (*Continued*)

Organisms	Interactions	References
	activates PI3K and protects *F. nucleatum* from phagocytosis; *P. gingivalis* capsule-mediated association augments epithelial cell invasion by *P. gingivalis*.	
S. gordonii-F. nucleatum	Coaggregation inhibits epithelial cell apoptosis and promotes secretion of tumor necrosis factor and interleukin (IL)-6.	(81)
S. gordonii, *F. nucleatum-P. gingivalis*	Consortium growth causes an increase in Mfa1 expression in *P. gingivalis* and elevated invasion of dendritic cells by *P. gingivalis* and *F. nucleatum*.	(82)
S. cristatus-F. nucleatum	*S. cristatus* stabilizes IκB-α in epithelial cells, blocking nuclear factor kappa B (NF-κB) activation and cytokine secretion induced by *F. nucleatum*.	(83)
P. gingivalis-F. nucleatum	The *P. gingivalis* serine phosphatase SerB dephosphorylates the p65 NF-κB subunit, blocking nuclear translocation and cytokine secretion induced by *F. nucleatum*.	(84)
T. denticola-F. nucleatum	*T. denticola* incapacitates the *F. nucleatum*-induced expression of human beta defensins and IL-8 in epithelial cells by interrupting endo-lysosomal maturation and reactive oxygen species-dependent TLR activation.	(85)

outer layers of other microbial species forming a corona-like spatial arrangement (7, 86) (Fig. 1B). The inner core of *S. mutans* appears to be physically separated from the outer layer of other microbial species by extracellular polymeric substances, including glucans, adhesins, glycoproteins, and eDNA (87). Despite this isolation, the inner *S. mutans* cells interact with the outer members of this spatially ordered community. For example, the presence of *S. oralis* in the outer community induces the expression of *S. mutans atpB,* a key gene associated with acid tolerance and increased fitness at acidic pH, while helping to create a localized acidogenic state via metabolic interactions that contributes to dissolution of the tooth enamel (86). Furthermore, such spatial configuration of the cloistered *S. mutans* cells creates a protective microenvironment against antimicrobials such as chlorhexidine, thus establishing a retentive pathogenic niche (86). These findings highlight the importance of the spatial structure of the microbiome (termed biogeography) in mediating the function and outcome of host-microbe interactions (13)

The *Porphyromonas gingivalis* interactome

The full pathogenic potential of *P. gingivalis* in periodontal disease is only realized in the context of a microbial community (24, 88, 89), and thus networking with other organisms is of considerable importance in shaping the pathoecology of the gingival compartments. While the major component of the oral microbiota is acquired initially as an infant from caregivers and other family members (90), there is an order to the process based on fitness in the dynamic ecosystem (91). Facultative species such as the oral streptococci avidly adhere to the salivary pellicle on enamel surfaces and constitute an abundance of early colonizers (92–94). The reduction in oxygen tension as facultative accrete into densely packed communities facilitates successful colonization by anaerobes such as *P. gingivalis*. Further expansion of *P. gingivalis* is enhanced by inflammation-derived proteinaceous nutritional substrates such as will become available during gingivitis induced by an abundant early community (95). It has also been established that a propensity for slow growth at low cell density contributes to late colonization by *P. gingivalis* (47). This dependency on an autoinducer (AI) can be overcome by the early colonizing *Veillonella parvula,* which provides a soluble growth initiating cue (47) (Fig. 2A). Surfaces encountered by *P. gingivalis* during successful colonization and expansion are populated by a variety of organisms, and *P. gingivalis* is well equipped with adhesins mediating attachment to many of these, including fusobacteria, actinomyces, veillonellae, and streptococci (96–100). Once established in deeper subgingival areas, *P. gingivalis* also coadheres with spirochetes such as *Treponema denticola* (68). For binding to *S. gordonii*, *P. gingivalis* employs the FimA structural subunit fimbriae which engage GAPDH

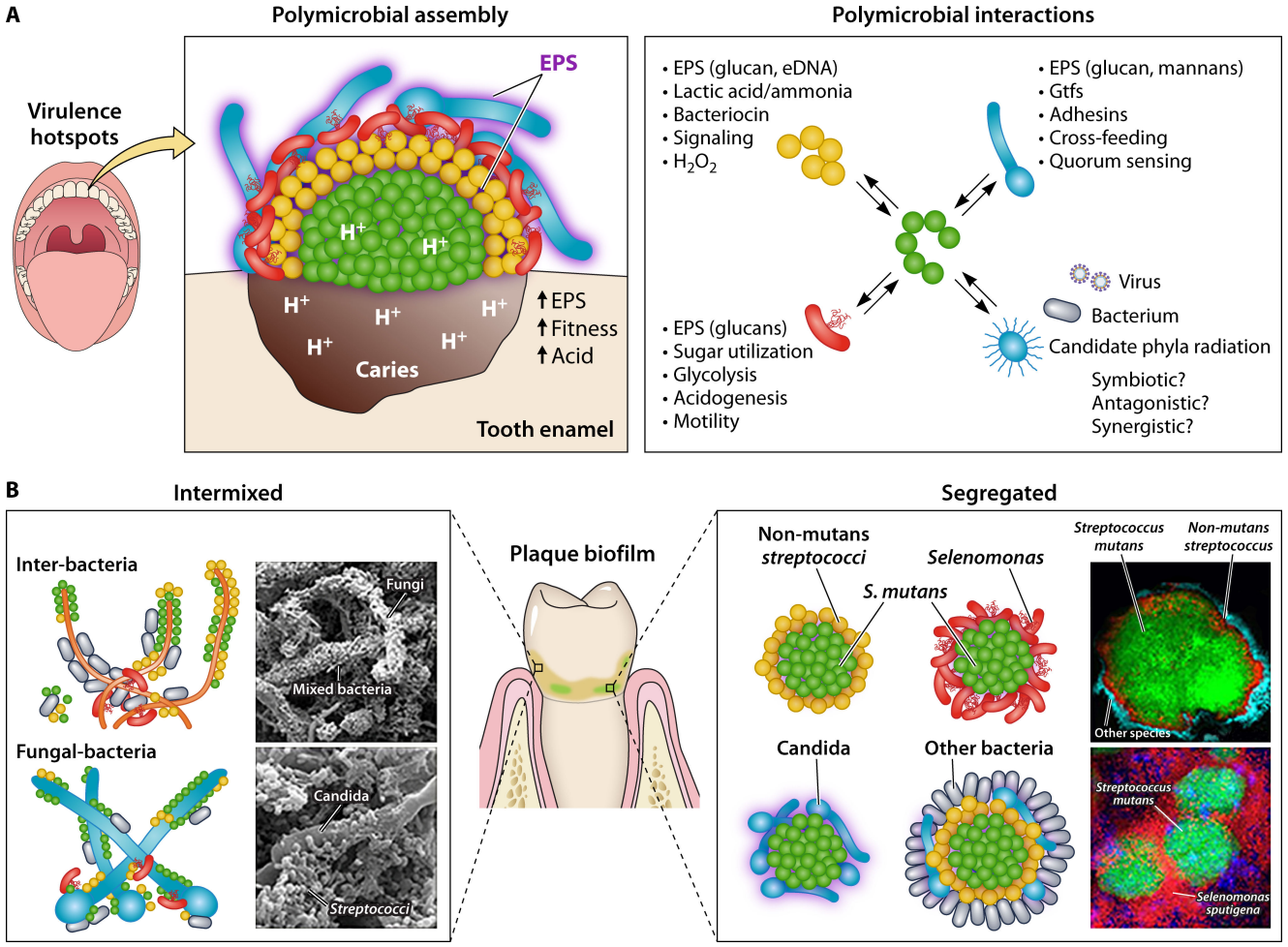

FIG 1 Interbacterial and interkingdom interactions in oral polymicrobial communities. (A) The oral microbiota harbors a multitude of different microbes, including bacteria, fungi, viruses, and ultra-small organisms. These diverse microbial populations engage in complex interspecies or cross-kingdom interactions which drive cooperative, competitive, or both outcomes among community members. Certain species, such as *Streptococcus mutans*, form highly clustered communities with precise spatial structure at the infection site (supragingival) which promotes a disease-causing state (dental caries). (B) Complex physical and chemical interactions with different species promote a multilayered, corona-like spatial arrangement formed by an inner core composed almost exclusively of *S. mutans* and outer layers of other oral microbes, physically separated by extracellular polymeric substances. This spatial structure enhances bacterial fitness and protection, and creates a highly acidic microenvironment, leading to the localized onset of disease. Precise positioning and spatial arrangement combined with polymicrobial interactions can coordinate pathogenesis *in situ* to create virulence hotspots impacting the host tissues. [Adapted from reference (12) with permission from Elsevier.]

on the streptococcal surface, as well as the Mfa1 structural subunit fimbriae which engage SapA/SspB, members of the Ag I/II family of streptococcal surface proteins (24, 101). The functional domain on the SspB protein has been localized to a C-terminal region, designated BAR, spanning aa residues 1,167–1,193 (24, 102). Ag I/II members in other oral streptococcal species that possess a homologous BAR domain (such as *S. mitis* and *S. oralis*) support *P. gingivalis* adherence, whereas those lacking BAR homologs (such as *S. cristatus* and *S. mutans*) do not (25, 98). Of note, both *S. cristatus* and *S. mutans* lack physiological compatibility with *P. gingivalis* (Fig. 2A). Arginine deiminase produced by *S. cristatus* inhibits the expression of fimbrial- and protease-associated genes in *P. gingivalis*, consequently diminishing community formation and pathogenicity *in vivo* (103). Low pH values as are induced by *S. mutans* are antagonistic to *P. gingivalis* (104). Hence, *P. gingivalis* can be seen to have tailored its adhesive repertoire to favor attachment to non-antagonistic organisms. The situation is more nuanced, however, as the relationship

between *P. gingivalis* and *S. mitis* can turn toxic through the induction of multiple transposases and cell death in the streptococci (105).

In contrast, the relationship between *P. gingivalis* and *S. gordonii* remains harmonious and indeed begins prior to attachment (Fig. 2A). Oral streptococci such as *S. gordonii* produce para-amino benzoic acid (pABA) which diffuses freely in and out of bacterial cells and is an essential component of one-carbon metabolism (OCM) (26, 106, 107). Exogenous pABA acquired by *P. gingivalis* can interfere with tyrosine phosphorylation/dephosphorylation-based signaling in *P. gingivalis,* which funnels through the bacterial tyrosine (BY) kinase Ptk1. Ptk1 is a node in a regulatory network which controls the production of virulence factors, including the gingipain proteases, fimbriae, and extracellular polysaccharide (EPS) (27, 108) (Fig. 2B). In addition, Ptk1 is one of only two common fitness determinants of *P. gingivalis* identified in an abscess model with either *S. gordonii* or *Fusobacterium nucleatum* (10). Hence, in conditions of pABA excess, *P. gingivalis* virulence is dampened, both in abscess and alveolar bone loss models of disease (26). Through mechanisms that have yet to be unraveled, physical association between *P. gingivalis* and *S. gordonii* also impacts the phosphorylation/activation state of Ptk1 in a manner which reverses information flow through the circuitry. Consistently, physically integrated *P. gingivalis-S. gordonii* communities are more pathogenic in animal models of periodontal disease compared to either organism alone (89, 109) (Fig. 2B). In this context, we have proposed that *S. gordonii* does not function as a true commensal but rather as an accessory pathogen, an organism that, while not pathogenic in itself, can act synergistically to elevate the pathogenicity of another species or of a community (97).

The OCM pathway, of which pABA is an essential precursor, is an integral part of cellular intermediary metabolism, producing a number of one-carbon unit intermediates (formyl, methylene, methenyl, and methyl), which are required for the synthesis of various amino acids and other biomolecules, such as purines, thymidylate, folate, and redox regulators (110, 111). The participation of pABA in both OCM and virulence provides insight into coordination of physiologic and pathogenic properties by *P. gingivalis*. Tyrosine phosphorylation is required for processing and secretion of gingipains (108), and thus interference of Ptk1 activation by pABA will reduce the availability of amino acids that are also required as substrates to maintain OCM (110). Hence, accumulation of exogenous or endogenous pABA acts as a negative feedback loop to fine-tune OCM. While phosphorylation-mediated coupling of OCM and gingipain activities likely arose as a mechanism to ensure balanced flux through OCM, given the prominent pathological role of gingipains, this axis also drives pathogenicity. This landscape of metabolic pathogenicity may include other organisms, as *T. denticola* can provide OCM metabolites to *P. gingivalis* as a means to increase glycine availability for treponemal growth (69) (Fig. 2A).

The full nature of the trophic web involving *P. gingivalis* remains to be established, but all indications are that it is extensive and multicomponent. For example, in coculture with *F. nucleatum*, *S. gordonii* secretes ornithine via an arginine-ornithine antiporter (ArcD), which supports fusobacterial growth through an increase in amino acid availability. Higher levels of ornithine cause *F. nucleatum* to increase the production of putrescine, a polyamine derived from ornithine by decarboxylation (49). Similarly, coculture with *V. parvula* increases lysine availability, which promotes the production of the polyamine cadaverine by *F. nucleatum*. When *P. gingivalis* is present, both community coalescence and subsequent dispersal of planktonic cells are enhanced by polyamines (49).

The interplay between *P. gingivalis* and *S. gordonii* has relevance for host cell responses to the oral microbiome. *P. gingivalis* has emerged as a potential oncopathogen in oral and esophageal squamous cell carcinoma (112, 113). Certainly, as a monoinfection, *P. gingivalis* has a number of effects on gingival epithelial cells consistent with such a role. These include the suppression of apoptosis, acceleration through the cell cycle, and the induction of epithelial mesenchymal transition (EMT) as well as a dysbiotic inflammatory microenvironment (113, 114). However, *S. gordonii* can mitigate these effects through a

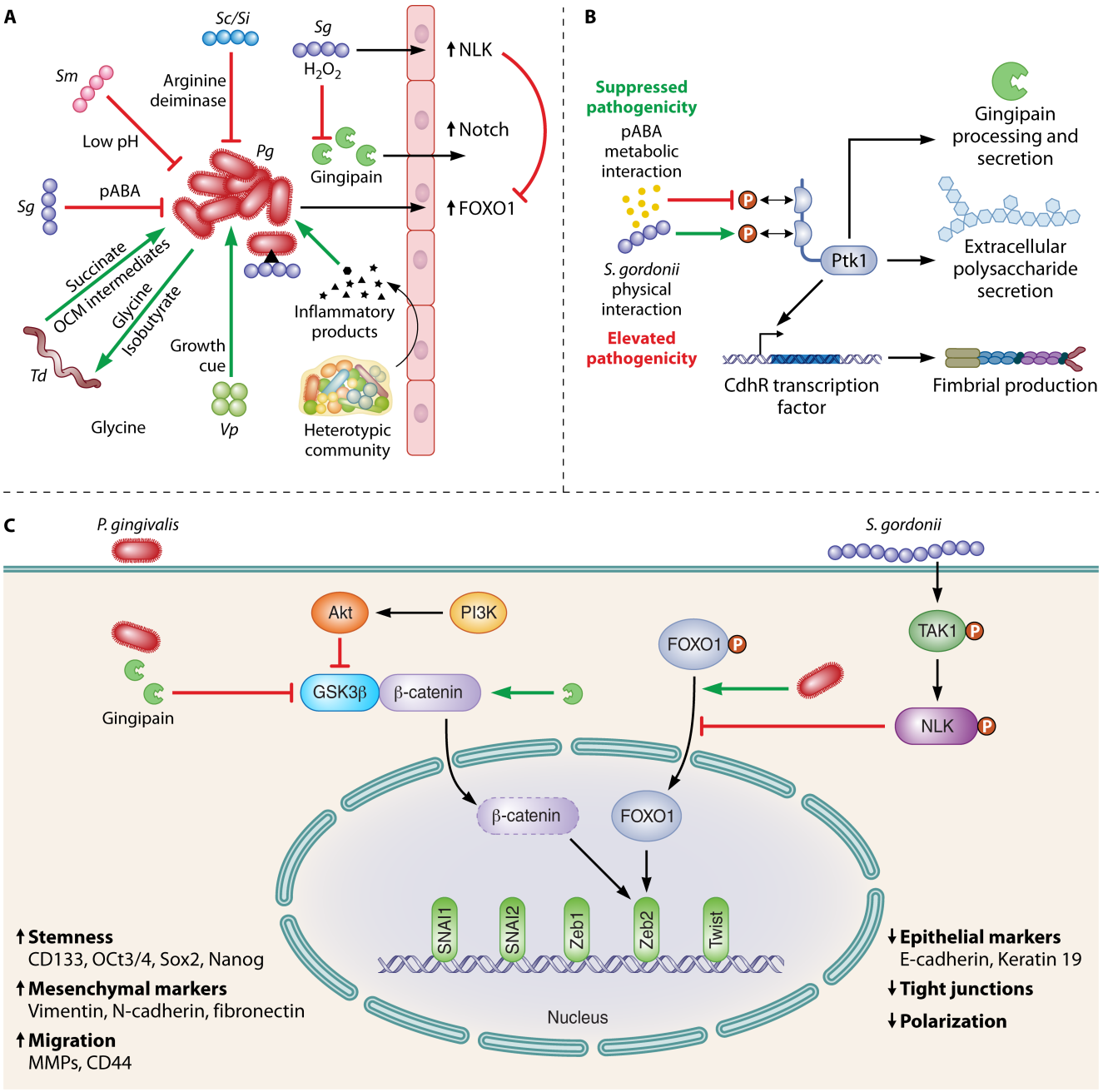

FIG 2 The *P. gingivalis* interactome. (A) Overview (not to scale) of interactions of *P. gingivalis* with other bacteria, bacterial communities, and with gingival epithelial cells. Green arrows represent a synergistic relationship which increases the colonization, growth, or pathogenicity of *P. gingivalis,* or an increase in an epithelial cell signaling pathway. Red flat arrows represent an antagonistic relationship. (B) The streptococcal metabolite para-amino benzoic acid (pABA) and physical attachment between *P. gingivalis* and *S. gordonii* have opposing effects on pathogenicity, although both funnel through activation/inactivation of the Ptk1 tyrosine kinase signaling pathway. (C) Indirect communication between *S. gordonii* and *P. gingivalis* involving the epithelial cell as an intermediary. *S. gordonii* can activate the TAK1-NLK pathway, which mitigates *P. gingivalis* stimulation of FOXO1-Zeb2 signaling. *P. gingivalis*, however, can enhance Zeb2 activity through pathways that are insulated from *S. gordonii*.

variety of processes. For example, *P. gingivalis* upregulates genes encoding components of the Notch signaling pathway, including the downstream effector olfactomedin 4 (OLFM4), which is required for epithelial cell migratory, proliferative, and inflammatory responses to *P. gingivalis* (74). This regulation can be overridden by *S. gordonii* through the production of hydrogen peroxide, which inactivates the *P. gingivalis* gingipain proteases and prevents proteolytic cleavage and activation of the Notch1 extracellular

domain (74) (Fig. 2A). In this context, we have proposed that *S. gordonii* functions as a homeostatic commensal, suppressing the impact of potential pathogens to help maintain eubiotic host responses. Production of hydrogen peroxide will be higher on oral mucosal membranes, compared to periodontal pockets, due to differences in oxygen availability, and this may be one reason that *S. gordonii* exhibits distinct "personalities" at these sites. Remarkably, *S. gordonii* can also influence the behavior of *P. gingivalis* indirectly by using the epithelial cell as an intermediary. *S. gordonii* can program gingival epithelial cells to resist FOXO1-Zeb2-dependent regulation of EMT markers initiated by *P. gingivalis* (75). Mechanistically, *S. gordonii* prevents serine-phosphorylation-mediated activation of FOXO1 by inducing the phosphorylation and activation of the TAK1-NLK-negative regulatory pathway, even in the presence of *P. gingivalis* (75) (Fig. 2C). Moreover, RNA-Seq of epithelial cells infected with *P. gingivalis*, *S. gordonii,* or both organisms in combination, shows that the dual organism challenge induces a pattern of gene expression which resembles that of *S. gordonii* more closely than that of *P. gingivalis* (74). It is likely, therefore, that *S. gordonii* possess additional mechanisms to diminish the influence of *P. gingivalis* on epithelial cell function. Related oral streptococcal species may perform similar roles, and *S. sanguinis,* for example, can override the effect of *P. gingivalis* on epithelial cells with regard to the production of inflammatory cytokines (115). Interestingly, however, *P. gingivalis* can impact epithelial cell circuitry in ways that are insulated from streptococci (Fig. 2C). This includes pathways that can promote Zeb2 activity and may allow *P. gingivalis* to manipulate host cell physiology to a sufficient degree even in the presence of organisms with opposing activity (116). In addition, *P. gingivalis* can suppress epithelial cell production of the neutrophil chemokine IL-8 and the T-cell chemokine IP-10 in a heterotypic infection with otherwise stimulatory organisms (117, 118). The immunosuppressive features of *P. gingivalis* can thus counteract the effects of community partners and may contribute to the keystone pathogen features of the organism.

Corynebacterium-streptococcal interactions

Studies of bacterial interplay in the oral microbiome have focused traditionally on organisms deemed important in terms of bulk presence or absence. More recent image analysis by fluorescent *in situ* hybridization of communities recovered *in vivo* has identified organisms playing functional roles in establishing biogeography (9). One such organism is *Corynebacterium durum* which assembles into structures known as "corncobs" with oral streptococci (119). *C. durum* has a dramatic effect on the morphology of *S. sanguinis* provoking an increase in chain length, a phenomenon effectuated by fatty acids likely delivered in corynebacterial membrane vesicles (50). Mixtures of palmitic, stearic, and/or oleic acids induce streptococcal chain length elongation; however, the process also involves metabolic coordination of fatty acid production in *S. sanguinis*. The streptococcal *fab* operon, which encodes fatty acid biosynthetic reactions, is downregulated in the presence of *C. durum* supernatants, and deletion of genes within the operon, such as *fabH* or *acpP,* phenocopies the chain length effect in the absence of exogenous fatty acids. *C. durum* also induces an increase in the expression of *gldA*, encoding an enzyme which converts glycerol into dihydroxyacetone (glycerone), and ablation of *gldA* expression in *S. sanguinis* prevents chain length regulation (50). Thus, there would appear to be regulatory connections between lipid metabolism and chain length in *S. sanguinis*, which can be intercepted by exogenous fatty acids provided by *C. durum*. The influence of *C. durum* on *S. sanguinis* extends beyond chain length, and interbacterial association increases streptococcal growth rate as well as resistance to phagocytosis and killing by macrophages (50). The association of *S. sanguinis* with *C. durum* in corncob structures will benefit the streptococci, therefore, by providing protection from innate immunity.

Streptococcal interaction with *Candida*

Oral streptococcal interactions with *Candida albicans* are associated with enhanced virulence of early childhood caries and oropharyngeal diseases (120–122). *C. albicans* interacts with mitis group streptococci (MGS) to enhance bacterial colonization and biofilm formation, while *C. albicans* becomes more invasive, thus promoting mucosal tissue infection and destruction (120). *C. albicans* physically interacts with MGS, including *S. gordonii*, *S. sanguinis*, and *S. oralis,* through cell surface proteins and receptors. Streptococcal cell surface adhesins, SspA and SspB, interact with the *C. albicans* surface, while Als and HWP adhesins on the fungal cell wall appear to mediate binding to MGS. Specifically, SspB and Als3 mediate intercellular binding through the N-terminal domain of Als3 (123). These interactions may also involve O-mannosyl residues in Als adhesins and other cell wall proteins, such as Sap9. *In vivo* studies show that coinfection of *C. albicans* and *S. oralis* results in increased mucosal tissue invasion and augmented inflammatory responses due to induction of neutrophil-activating cytokines (IL-17, CXCL1, MIP-2/CXCL2, TNF, IL1α, and IL-1β) and upregulation of Toll-like receptor 2-dependent proinflammatory signaling as well as increased epithelial μ-calpain activity (124). How the host orchestrates immune responses against *C. albicans*-streptococcal-mediated mucosal infection and the role of this cross-kingdom interaction in host immune evasion need further elucidation (120).

In contrast to MGS, the cariogenic *S. mutans* employs distinctive mechanisms to associate with *C. albicans*. In addition to antigen I/II adhesins (125), *S. mutans* secretes glucosyltransferase (Gtf) exoenzymes that bind avidly to the *C. albicans* cell surface and convert sucrose to large amounts of EPS α-glucans on the fungal surface. The EPS provides bacterial binding sites and promotes coassembly with *C. albicans* in saliva while promoting colonization of the tooth surface and interkingdom biofilm formation that exacerbates the severity of dental caries (126, 127). Mechanistically, *S. mutans*-derived GtfB binds with high affinity to N- or O-linked mannans located on the outermost layer of the *C. albicans* cell wall and maintains its catalytic activity to produce α-glucans *in situ* (128). The formation of glucan-rich matrix provides a scaffold for both surface adhesion and cell-to-cell cohesion while establishing chemical and nutrient gradients by modulating diffusion. It also provides an additional benefit to the fungi by creating a "drug-trapping matrix" that prevents uptake of the antifungal fluconazole, reducing *C. albicans* killing efficacy (129).

Complex signaling, cross-feeding, and metabolic interactions occur within the interkingdom MGS- or *S. mutans-Candida* biofilms. Signaling/quorum sensing (QS) and other biomolecules appear to facilitate these interactions, including AI-2, peptidoglycan fragments, exoenzymes, and hydrogen peroxide (H_2O_2) (130) (Fig. 1A). For example, nutrient byproducts as well as AI-2 signaling and H_2O_2 from *S. gordonii* stimulate *C. albicans* hyphal development within biofilm communities, while *S. oralis* activates expression of fungal aspartyl proteases. *C. albicans* can promote streptococcal proliferation by providing growth-stimulating factors and reducing oxygen tension. The impact of *C. albicans* and MGS synergism on the host-pathogen interaction has been demonstrated *in vivo,* whereby heterotypic *C. albicans-S. oralis* community growth enhances neutrophil infiltration, leading to increased severity of soft tissue lesions (120–122). *C. albicans* and *S. mutans* display interesting synergistic mechanisms, whereby *S. mutans* converts sucrose to glucose that can be more readily metabolized by *C. albicans. C. albicans* activates *S. mutans* competence, virulence gene expression, and GtfB production via QS molecules such as farnesol, while enhancing acidogenicity and aciduricity of the community (122, 131).

Notably, cross-kingdom interactions can also repress functions of the member species to modulate population growth, biofilm structure, and spatial organization. *S. mutans*-derived mutanobactin A and fatty acid signaling through trans-2-decenoic acid can inhibit *C. albicans* hyphal formation (132, 133). Furthermore, competence-stimulating peptides secreted by *S. mutans* (134) or *S. gordonii* (135) can inhibit *C. albicans* hyphal formation. Paradoxically, farnesol produced by *C. albicans*, which stimulates *S. mutans*

growth and *gtfB* expression at low concentrations, disrupts bacterial growth at higher concentrations. Hence, similar to the situation described above for *S. gordonii-P. gingivalis* interactions, a tightly regulated cooperative and antagonistic balance through stimulus-inhibition mechanisms appears to mediate bacterial-fungal interactions, which can become synergistic when conditions are conducive for disease.

Host responses dependent on community properties

Since the early 20th century, different theories have been proposed for the microbial etiology of the inflammatory periodontal lesions, ranging from the "non-specific plaque hypothesis" (disease caused by mere increase in the quantity of subgingival plaque bacteria beyond a certain threshold, regardless of the species involved) to the implication of specific organisms (including an oral amoeba later named *Entamoeba gingivalis*) or a select few bacteria (such as the red complex of *P. gingivalis, T. denticola, and T. forsythia*) [reviewed in reference (23)]. As outlined above, it is now well established that periodontal disease is driven by mutually reinforcing interactions between a polymicrobial dysbiotic community and the host inflammatory response. The PSD model of periodontal disease pathogenesis was founded upon knowledge from modern metagenomic and metatranscriptomic studies with insights into the dynamic changes in the composition and structure of the periodontal microbiome, as well as from mechanistic studies in clinically relevant animal models on how bacteria synergize to maximize nososymbiocity [reviewed in reference (24)]. According to the PSD model, the emergence of dysbiosis (hence the potential for destructive inflammation) is determined not by specific individual organisms acting independently but by the combined output of community action; the latter is molded by interspecies interactions as well as host genetic and environmental variables that impact on both the microbial community and the immune response (24). In other words, what matters is not so much the identities of individual species but rather the presence of the appropriate complement of genes and their interaction with the host environment. This concept is consistent with published mechanistic studies, such as the ones briefly discussed below.

Independent studies in model organisms show that combinations of different oral pathogens cause increased periodontal inflammation and bone loss as compared to each pathogen alone (136–139). *P. gingivalis* is incapable of causing periodontitis by itself in germ-free mice, although it can colonize this host after repeated oral inoculations; however, the pathogenic potential, or keystone pathogen function, of *P. gingivalis* is readily expressed in the context of an oral microbial community, as occurs when the pathogen is introduced into the oral commensal microbiota of conventional mice (88). Mechanistically, *P. gingivalis* interacts with phagocytes in ways that disrupt immune surveillance (e.g., extracellular killing, phagocytosis) and stimulate inflammatory pathways, factors that favor the outgrowth of pathobionts, thus enhancing the community's nososymbiocity (78, 88, 140). Reciprocally, *P. gingivalis* receives metabolic and colonization support from accessory pathogens (47, 89, 97, 141) (Fig. 3). Thus, in this give-and-take relationship, the capacity of *P. gingivalis* to provide keystone function to the community is dependent upon help from companion species.

The aptitude by which *P. gingivalis* manipulates the host immune response to promote dysbiosis depends heavily on its ability to exploit complement signaling pathways (78, 142, 143). The recent success of a complement-targeted clinical trial for the treatment of periodontal disease might thus not be attributable only to inhibition of inflammation but also to counteraction of complement-dependent immune subversion by *P. gingivalis* (144). In addition to subverting the host response, *P. gingivalis* may mediate keystone function via direct interactions with community members. For instance, introduction of this keystone pathogen into an otherwise health-compatible microbial community leads to major transcriptomic and proteomic alterations with potential for increased virulence expression (145, 146). *P. gingivalis* may also contribute to dysbiosis via elimination of health-associated species, such as by inducing cell death in *S. mitis* as mentioned above (105).

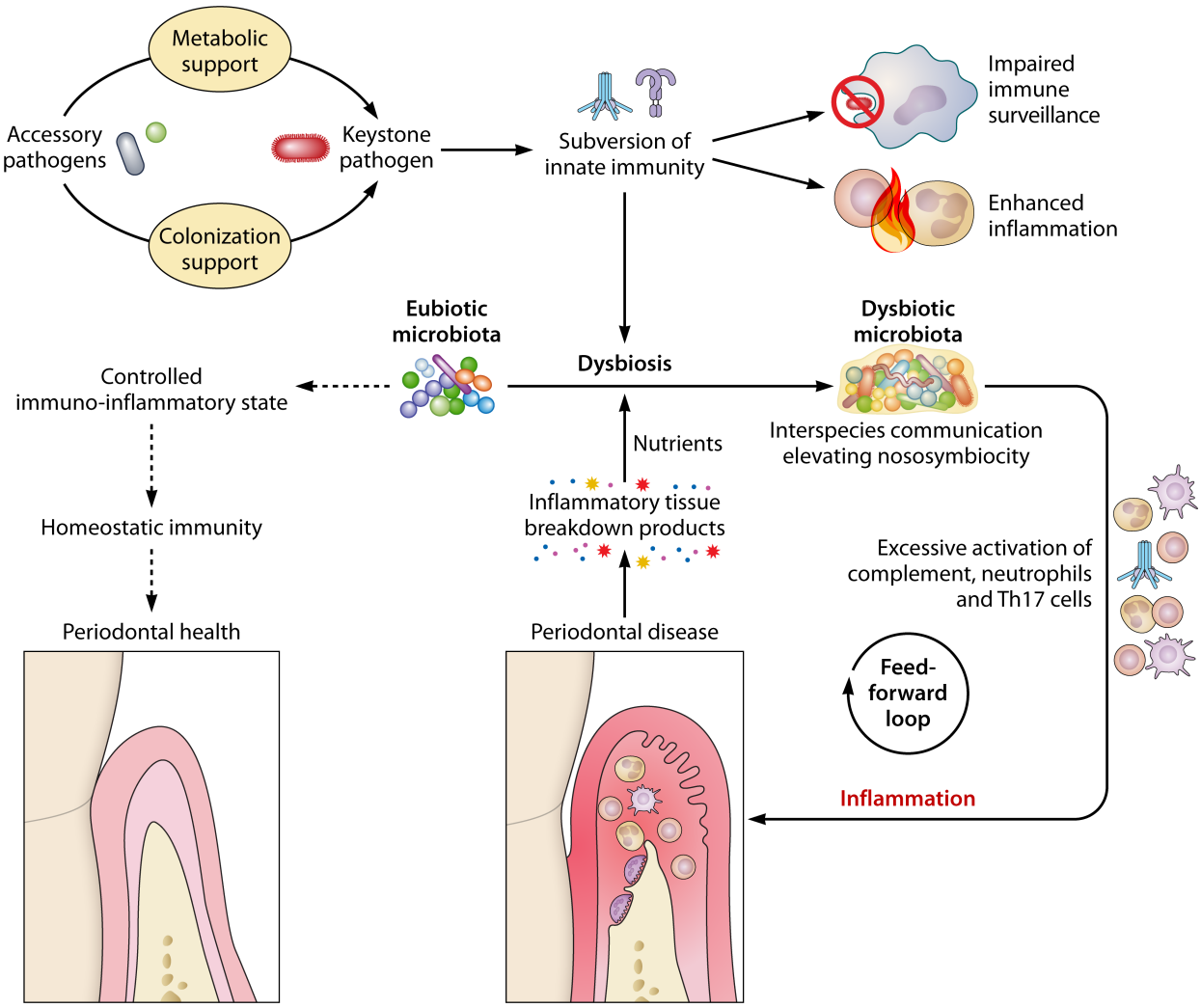

FIG 3 Interspecies and microbe-host interactions that promote dysbiosis and inflammatory disease. Whereas communities of predominantly eubiotic commensals induce balanced immune responses that contribute to homeostatic immunity and a healthy periodontal tissue, dysbiotic communities induce dysregulated inflammatory responses that are detrimental for the host and ineffective in controlling the bacteria. In polymicrobial communities associated with periodontitis, keystone pathogens are aided by accessory pathogens in terms of metabolic and/or colonization support and, once established, can subvert host immunity in a manner that contributes to the outgrowth of inflammophilic pathobionts. Community members engage in complex interspecies communication that elevates the expression of virulence factors and the pathogenicity of the entire community. A key environmental factor that aggravates dysbiosis and pathobiont expansion is destructive inflammation, which not only drives bone loss but also generates tissue breakdown products that can be used as nutrients by the dysbiotic community. These mutually reinforcing interactions between dysbiosis and inflammation represent a self-sustained feed-forward loop that constitutes the actual driver of periodontitis and can explain, in great part, its chronic nature.

That inflammatory periodontal lesions are driven predominantly by dysbiotic, rather than multitudinous (as the non-specific plaque hypothesis would predict), communities is also supported by a study using the ligature-induced periodontitis model in mice. Ligature placement in posterior teeth of conventional mice results in rapidly increased bacterial biomass and structural changes in the microbial community of affected sites, as compared to unligated, hence, healthy, contralateral sites. These changes are associated with gingival inflammation and loss of alveolar bone (147). Administration—via the drinking water—of different antibiotics, either alone or in combinations, revealed that inflammatory bone loss was not necessarily associated with an increase in the total microbial load. Specifically, those antibiotic treatments which inhibited inflammation (as assessed by expansion of $CD4^+$ T helper 17 cells) and bone loss also invariably caused compositional changes within the community, without—however—always decreasing

the total microbial load (147). Therefore, although a dysbiotic community may be highly abundant relative to health-associated communities, it is mainly the qualitative differences (the collective gene pool as altered in dysbiosis) that dictate its increased pathogenic potential. Such dysbiotic communities are quite stable and can transmit disease both horizontally and vertically.

Specifically, a dysbiotic microbial community, which was established in the mouse oral cavity following inoculation with *P. gingivalis*, could be stably transferred to germ-free mice, which subsequently developed periodontal bone loss (148). The same study showed that the *P. gingivalis*-induced microbial community could also be transferred from parents to offspring, which developed significant bone loss relative to offspring of periodontally healthy control parents. Moreover, antibiotic treatment of mice with oral microbial dysbiosis could only transiently reverse dysbiosis, as dysbiosis was readily restored upon antibiotic termination (148). This implies a degree of resilience inherent in the interspecies communication within the dysbiotic community and perhaps also in the community's interactions with a favorable host environment upon cessation of treatment. Inflammation is a major ecological factor that contributes to the dysbiotic shift in the microbial population structure associated with periodontitis. Through the availability of nutrients derived from inflammatory tissue breakdown, inflammation exerts selective pressure on the community organization, favoring the expansion of inflammophilic pathobionts at the expense of species that cannot endure or capitalize on an inflammatory environment (6, 149) (Fig. 3). This concept is further supported by observations in a controlled multispecies community environment. The addition of serum, hemoglobin, or hemin (which are by-products of destructive inflammation) to an *in vitro* generated oral multispecies community selectively favors the expansion of pathobiont species. These, moreover, upregulate the expression of genes that can facilitate increased exploitation of a nutritionally favorable inflammatory environment; indeed, the upregulated genes encode for proteases, hemolysins, and molecules required for the acquisition of hemin (150). Other host-related factors that contribute to the emergence of dysbiosis include inherited and acquired traits, such as immune deficiencies, smoking, unhealthy diet, obesity, diabetes, and systemic inflammatory disorders, as well as aging (1, 151, 152).

The effects of periodontal dysbiosis are not restricted locally since oral pathobionts and their proinflammatory products can spill into the circulation through the ulcerated and richly vascularized gingival epithelial barrier (153, 154). The resulting systemic inflammation can cause functional alterations in a variety of organs, including the bone marrow, where induction of maladaptive myelopoiesis exacerbates not only periodontitis but also systemic comorbidities, such as rheumatoid arthritis (155). Moreover, oral pathobionts may translocate to extraoral sites including, for example, the intestine, where they can aggravate colitis (156). It can readily be envisioned that ectopically colonizing oral microbes can cooperate or synergize with the resident dysbiotic microbiota (e.g., in the lungs or intestine), thereby further promoting disease at extraoral sites. This concept of an interconnected microbiome with enhanced virulence is supported, in principle, by certain observations. Orally aspirated *P. gingivalis* is detected together with *Pseudomonas aeruginosa* in tracheal aspirates of individuals with acute exacerbation of chronic obstructive pulmonary disease (157). Importantly, the ability of *P. aeruginosa* to invade respiratory epithelial cells, modulate host cell apoptosis, and ultimately cause host cell death is enhanced in the presence of *P. gingivalis* (158, 159).

Whereas periodontal dysbiotic communities induce immune and inflammatory responses that are ineffective, dysregulated, and detrimental for the host, both locally and systemically, communities of predominantly eubiotic commensals induce balanced immune responses that contribute to homeostatic immunity and maintain host-microbe equilibrium that characterizes a healthy periodontium (160). The mechanisms underlying homeostatic interactions between eubiotic communities and the host immune system have been extensively studied in the gut and might have parallels in the oral cavity. Different members of such communities contribute to diverse mechanisms that

collectively contribute to homeostasis (e.g., by inducing antimicrobial proteins to resist pathogenic species, stimulating regenerative responses to promote tissue repair, and activating regulatory T-cell responses to restrain potentially destructive inflammation) (161–166).

Conclusions

With the exception of invasive exogenous pathogens, microbes in and on humans assemble into spatially constrained heterotypic communities. Nutritional, signaling, and physical interactions among community participants drive the emergent properties of the community. Pairs of organisms can interact through multiple mechanisms, and the collective outcome, for example, increased or diminished nososymbiocity, varies according to context. In many cases, such as dental caries and periodontal diseases, it is the community that represents the fundamental etiological unit. Dysbiotic microbial communities fundamentally represent a quasi-organismal entity, where constituent organisms with functional specialization engage in intimate interactions within the community and with the host to maximize its pathogenic potential and outcompete health-compatible communities. The mutually reinforcing interactions between dysbiotic communities and inflammation not only drive periodontitis but, being self-sustained, may also contribute to the chronicity of this oral disease. In dental caries, host dietary sugars can modulate the dysbiosis and polymicrobial interactions in supragingival communities leading to highly structured and localized acidic microenvironments that shape the persistence and metabolic activity of the community to promote disease development and severity.

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