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Interkingdom networking within the oral microbiome

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Abstract

Different sites within the oropharynx harbour unique microbial communities. Co-evolution of microbes and host has resulted in complex interkingdom circuitries. Metabolic signalling is crucial to these processes, and novel microbial communication factors are progressively being discovered. Resolving interkingdom networks will lead to better understanding of oral health or disease aetiology.

Keywords

Biofilms; Quorum sensing; Microbial communities; *Candida albicans*; *Streptococcus*; *Porphyromonas*

1. Introduction

Omes, beyond the originally coined genome, have become fashionable for depicting wholeness in the data-rich biological sciences: proteome, lipidome, interactome etc. Much has been researched and written about the oral microbiome. At least 2000 different microbial taxa have been detected in the human oral cavity and more than 350 genomes have been fully sequenced. Recent systematic biomolecular analyses of dental calculus from adult human skeletons c. 950–1200 CE shows that the oral cavity has long served as a reservoir for microbes implicated in oral and systemic diseases [1]. Despite changes in lifestyle, diet and oral hygiene over a millennium, DNA and proteins from *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola*, bacteria that are associated with periodontal disease, were abundant in ancient dental calculus samples. The presence of other potential pathogens such as *Streptococcus mutans*, *Filifactor alocis*, *Olsenella uli*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Neisseria meningitidis*, shows that the oral cavity has long harboured bacteria associated with oral infections, bacteraemia and cardiovascular disease. The functional profiles of human proteins present within modern or ancient calculus are also highly similar [1].

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Conflict of interest

The authors have no conflicts of interest.

Despite such commonalities, microbial diversity in communities colonizing tooth enamel, mucosal surfaces etc. is individual specific and site specific [2]. There is a conserved oral community in healthy mouths at the genus level. Abundant groups include *Streptococcus, Granulicatella, Gemella, Rothia, Neisseria, Haemophilus, Lautrophia* and *Prevotella*. On the other hand, there is evidence that a wide range of polymicrobial consortia can be associated with periodontal disease. Deep sequencing has confirmed decades of evidence from traditional laboratory culture studies that Gram-negative bacteria (e.g. *Selenomonas, Prevotella, P. gingivalis, T. denticola, T. forsythia, Catonella*, etc.) are enriched in periodontal disease samples [3].

Oligotyping provides a higher taxonomic resolution of communities in different habitats and across individuals [4]. Instead of simply recognizing the existence of a taxon, it is possible to assign sequence variants within a taxon with differential localization. Perhaps surprisingly, oligotypes characteristic of subgingival plaque tend to be detected also in tonsillar crypts, suggesting that the tonsils provide a habitat for oral anaerobes [4]. Making use of the invaluable Human Oral Microbiome Database (HOMD; www.homd.org), oligotypes were related to named species such that co-occurrence data were obtained at both the oligotype and species levels. Distinct oral site distributions of *Streptococcus gordonii* and *Streptococcus salivarius* were revealed, confirming that the latter organism is only found at mucosal sites, and not present in supra- or sub-gingival plaque. Conversely, *Streptococcus infantis* and *Streptococcus mitis* oligotypes were found in all oral samples taken from 9 different sites, including plaque [4]. Veillonellae were found at all sites, but could be divided into two oligotypes, differing by a single nucleotide, one oligotype being found in plaque and the other on mucosal surfaces.

Complementing these molecular-based detection methods, visualization of species within oral microbial communities can be performed by CLASI-FISH (combinatorial labelling and spectral imaging - fluorescence *in situ* hybridization) [5]. This can distinguish multiple differentially-labelled microbes in oral microbial communities with proximity analyses revealing co-occurrence. In dispersed dental plaque, *Streptococcus, Veillonella, Prevotella* and *Actinomyces* predominated, the two latter genera showing the most inter-species associations [5].

These various metagenomic and co-occurrence maps provide essential information about who goes where, but not much about what they get up to. From a functional viewpoint we would like to determine: how different species recognize each other and what mediates their physical interactions; the metabolic networks that are crucial to community stability; the ecological benefits for interspecies connections; molecular to cellular effects on the host; and how the host responds. The communities in the oral cavity are more biologically complex than current views might indicate. For example, fungi interact with bacteria, viruses that are exogenous or indigenous interact with bacteria and host, and microbes are preyed upon by protozoa. Different taxonomic kingdoms have co-evolved in generating the human oral ecosystem, and components of all kingdoms interact with the host, in sickness or in health. Studies of interkingdom communication are in their infancy, but it is quickly becoming evident that signals and responses between members of different kingdoms are intricately involved in shaping the oral microbiome.

2. Deconstructing the oral microbiome

Communication between bacteria is fundamental to social evolution theories for microbial communities, so-named sociomicrobiology [6]. Cooperation between cells will be favoured when the individuals have a shared selfish interest in doing so. Evolution of cooperation can occur when the waste product of one individual provides a nutrient for another. A well cited example of this in oral microbial communities is the physical interaction of *Veillonella* with *Streptococcus*, wherein lactic acid produced by the latter is a carbon source for the veillonellae [7]. Benefits can flow in both directions too, known as cross-feeding, and this can occur between different variants of the same species, or between different species. For example, cooperation between two early colonizers of dental plaque *Streptococcus oralis* and *Actinomyces oris* can be mutually beneficial [8].

These kinds of metabolic interactions are only just beginning to be dissected and they probably account, in large part, for the inability to cultivate in pure culture a significant proportion of the oral microbiota identified as a result of metagenomic analyses. Metabolic dependency is likely rife within the microbial communities, and new approaches to isolating oral microbiota components that depend on others for growth, or that are mutually dependent, involve utilizing specific enrichments (mini-trap), single cell cultivation and nutritionally deprived growth media [9]. Recently, these sorts of approaches have led to the cultivation of a TM7 phylum bacterium, which up until now has been recalcitrant to cultivation [10]. The bacteria are reported as small cocci (about 300 nm diam.) and are obligate ectosymbionts living in tight surface and metabolic associations with a strain of *Actinomyces odontolyticus* [10]. The TM7 genome is small (705 kb) and reveals complete deficiency in amino acid synthetic capacity. Transcriptional analyses suggest that signalling occurs between these two phyla, and that inflammatory cytokine tumour necrosis factor-alpha (TNF-α) production in macrophages, induced by *A. odontolyticus*, is repressed in the presence of TM7. It seems likely that other obligate epibiotic interactions, episymbiotic, and endosymbiotic associations between microorganisms will be discovered in the future.

3. Bacterial wires and mobiles

3.1. Cell-cell contact

Studies of microbial coaggregation between subgingival organisms have begun to identify the mechanistic basis of these interactions. For example, fusobacteria are thought to bridge the early and later colonizers within dental plaque [11]. *Fusobacterium nucleatum* expresses at least one adhesin that recognizes streptococci, and a galactose-specific lectin that interacts with *P. gingivalis*. These consortia are locked in metabolic communication that can be considered as signalling, because the organisms sense and respond to specific molecules. Contact-dependent signalling has been demonstrated in *P. gingivalis* following interaction of the short fimbrial adhesin (Mfa) with *S. gordonii* SspA/B adhesins. This initiates a signalling cascade in *P. gingivalis* that prepares the organisms for community biofilm living [12].

One of the best characterized examples of contact-dependent communication is bacterial conjugation mediated by sex pili assembled by type IV secretion systems. It has recently been demonstrated that type IV-like pili [13] are induced by *S. pneumoniae* undergoing

transformation in response to the competence-stimulating peptide signal. The pili appear to be involved directly in extracellular DNA (eDNA) binding [14] and can be also critical for biofilm formation by oropharyngeal microorganisms [15]. The discovery that some kinds of pili, denoted nanowires, can propagate charge [16] suggests that there may be much more to learn about pilus function in oral cavity intermicrobial communication and host cell signalling. Of course bacteria-host cell contact is fundamental to adhesion, internalization and intracellular signalling processes that are dealt with in other papers as part of this special collection.

3.2. Cell-cell signalling

Through the exchange of small chemical signals, such as acyl homoserine lactones (AHLs) or oligopeptides, bacteria are able to monitor population density and regulate gene expression by the process of quorum sensing (QS). There has been little evidence for AHL-mediated signalling in oral microbial communities, although a *Pseudomonas* species producing AHL has recently been isolated from the tongue surface [17]. AHLs have been shown to be chemoattractants for neutrophils, alter barrier integrity of epithelial cells, and increase macrophage phagocytic activity [18]. However, another QS molecule named autoinducer-2 (AI-2) appears to be well utilized in oral microbial communities, and the *luxS* gene encoding the synthase enzyme for AI-2 has been widely detected [8]. Although QS evolved as a means for bacteria to coordinate behaviour, evidence is emerging that QS may provide a means for bacteria to directly interact with eukaryotes. AHL-based signalling molecules are able to modulate inflammatory responses and induce apoptosis, possibly through G-protein coupled receptors [19]. *P. aeruginosa* produces AHL that kills hyphal filaments produced by the fungus *Candida albicans*, but not the yeast forms [20], and secretes phenazines that inhibit fungal respiratory metabolism [21].

Bacterial cell wall peptidoglycan fragments, or muropeptides, have long been known to serve as signals between bacteria and eukaryotic organisms. Muropepetides, and *N*-acetyl-D-glucosamine derived from peptidoglycan, stimulate *C. albicans* to undergo yeast to hyphal filament transition [22]. Peptidoglycan is also a key stimulant of immune responses. Pneumococcal (*S. pneumoniae*) peptidoglycan triggers the production of interferon-γ (IFN-γ) and interleukin-17 (IL-17) from T helper cells, contributing to acquired immunity to pneumococcal infections [23]. Recruitment of macrophages required for pneumococcal clearance is enhanced by peptidoglycan sensing [24], while the resident microbiota generates peptidoglycan fragments that systemically prime the innate immune system [25]. NOD1 and NOD2 (Nucleotide-binding Oligomerization Domain proteins) are cytosolic pattern-recognition receptor proteins that respond to intracellular peptidoglycan fragments. NOD1 is expressed in a range of cell types, while NOD2 production is more restricted [26]. NOD1 detects D-glutamyl-*meso*-diaminopimelic acid (iE-DAP), a dipeptide found in Gram-negative bacteria and some Gram-positive bacteria. NOD2 detects muramyl dipeptide (MDP) that is always present in peptidoglycan [26]. Activation of NODs drives innate inflammatory responses through the nuclear-factor (NF)-κB and mitogen-activated protein kinase (MAPK) signalling pathways. This leads to expression of pro-inflammatory immune factors such as TNF-α, interleukin-6 (IL-6), CC-chemokine ligand 2 (CCL2), interleukin-8

(IL-8), and defensins. These help drive recruitment and priming of innate immune cells, including neutrophils and monocytes, in response to both bacterial and viral infections.

Oxidized fatty acids, or oxylipins, are signalling molecules that are transmitted and received by organisms from different kingdoms. Fungi found in the oral microbiome, such as *C. albicans*, *Candida dubliniensis* and *Candida glabrata*, can produce prostaglandin E_2 (PGE_2) from arachidonic acid supplied by the host. PGE_2 modulates inflammation, pulmonary function, fertility and gastric mucosal integrity. *C. albicans* also produces eicosanoids, one of these being resolvin E_1, which is anti-inflammatory and attenuates neutrophil migration [27]. Low levels of resolvin E_1 produced by *C. albicans* could dampen the adaptive immune response and protect the fungus from immune recognition. Some of the signals covered in this section and their identities are summarized in Table 1.

4. Host emissions

Microbial endocrinology is a relatively new research area that focuses on the ability of microorganisms to sense host-associated chemicals such as hormones. Prokaryotic responsiveness to catecholamine hormones (e.g. noradrenaline, adrenaline, dopamine) is widespread, and there is evidence for enhancement of growth (and virulence) of bacteria colonizing the gastrointestinal tract, skin and oral cavity [28]. The fact that some oral bacteria implicated in periodontitis e.g. *Eikenella*, *Campylobacter*, are especially stimulated by catecholamines (stress hormones) [29] has been linked to the knowledge that stress is a known risk-factor for periodontal disease. The QseC sensor kinase is a bacterial receptor for adrenaline/noradrenaline in *Escherichia coli* and activates virulence genes in response to the adrenergic signals [30]. It is not clear at present if QseC orthologs found in other Gram-negative bacteria, e.g. *Aggregatibacter actinomycetemcomitans*, are generally responsive to catecholamine hormones or have different cognate signals.

Noncatecholamine mammalian hormones, such as estradiol, are found in saliva [31], and this hormone enhances *C. albicans* infectivity by promoting the yeast to hypha transition and growth [32]. Estradiol also impairs dendritic cell function, such that the cells are less efficient at up-regulating antigen-presenting pathways, interleukin-23 (IL-23), and Th17 immune response, thus rendering the host more susceptible to *C. albicans* infection [33].

5. Cool reception

Quorum sensing molecules produced by bacteria and fungi can directly modulate the behaviour of human cells, as mentioned briefly above [18]. AHLs have been shown to be taken up into epithelial cells where they affect the distribution of a GTPase-activating protein and phosphorylation of Rac1 and Cdc42, which are upstream effectors of actin remodelling [34]. However, there is a vast array of molecules produced by microorganisms that affect host cells and only a few pertinent to the oral microbiome will be considered here. Moreover the complexity of the signals produced will depend upon the complexity of the microbial community.

An interesting area of investigation is into the effects of neuroactive compounds, produced by the microbiota, which can influence components of the host nervous system and

ultimately the brain. Production of γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter of the mammalian brain, by microorganisms has been known for decades, but this is only one of numerous neuroactive signals produced including dopamine, acetylcholine and agmatine [35]. The pathways used by the microbes to produce these substances are exactly the same as the host's pathways. Neuroendocrine hormones secreted by the microbiota exert anti-inflammatory activities. *Lactobacillus* spp. can produce milligram quantities of GABA and this could be a mechanism for prophylaxis of inflammatory conditions by administration of probiotics. Moreover there is now evidence that bacteria secreting neuroendocrine hormones can influence host behaviour. Since common synthesis pathways exist, it is possible that the microorganisms utilize neurochemicals for intercellular communication, and that the brain can therefore influence the prevalence of certain microbial species [35].

Other microbial signals that are immunomodulatory include 2-amino acetophenone produced by *P. aeruginosa* [36], and indole, which is produced by many oral bacterial species including *Fusobacterium* and *T. denticola*. Indole elicits an epithelial cell response that strengthens host cell-barrier properties [37], down-regulates IL-8 and increases anti-inflammatory cytokine interleukin-10 (IL-10) production. Commensal oral bacteria *F. nucleatum* and *S. gordonii* perturb the gingival transcriptiome much less than does *P. gingivalis* [38], and it is suggested that indole acts as a beneficial signal and is not recognized as a pathogenic signal.

Farnesol is a QS molecule that regulates virulence and morphogenesis in *C. albicans*. Farnesol controls hyphal filament formation by blocking the degradation of Nrg1, the major repressor of hyphal development [39]. In addition, farnesol promotes epithelial cell defence against *C. albicans* by up-regulating Toll-like receptor 2 (TLR2) expression and increasing production of IL-6 and human β-defensin 2 [40]. These various examples of microbial production of signals that cool host immune responses relate to the development of an oral microbiome that in health lives in relative harmony with the host.

The transition of a relatively benign commensal oral cavity microbiota to a dysbiotic periodontal microbiota can result in deregulated inflammation of gingival soft tissues. This occurs through elevated neutrophil transmigration into the tissues, and activation of bone-resorbing osteoclasts through RANK ligand expression by $CD4^+$ T cells. Recent studies in mice have suggested that *P. gingivalis*, even in low abundance, can trigger dysbiosis of the community structure leading to development of periodontal disease [41]. A current hypothesis is that local tissue damage, for example initiated by *P. gingivalis*, leads to accumulation of commensal bacteria that secrete NOD1-stimulating ligands e.g. iE-DAP (see above). This results in chronic inflammatory stimulation with NOD1-mediated neutrophil recruitment to induce bone loss [42]. To add further microbial complexity to the periodontal disease process, the presence of both fungi (e.g. *C. albicans*) and of protozoa (e.g. *Entamoeba gingivalis*) has been correlated with periodontitis [43, 44].

6. Going viral

It has been suggested that viruses play a role in various types of destructive periodontal disease. Human cytomegalovirus (HCMV), Epstein-Barr virus (EBV) and other herpesviruses have been closely associated with active periodontitis [45]. Synergism between specific periodontal pathogens (*P. gingivalis, Prevotella, T. denticola, A. actinomycetemcomitans*) and herpesviruses might therefore contribute to increased aggressiveness in disease pathogenesis. It is speculated that the HCMV latent genome is carried into the inflamed periodontium by infected macrophages and T cells. Subsequent CMV activation infects other cell types, triggers release of IL-1β and TNF-I, and results in increased susceptibility to tissue breakdown and loss of alveolar bone [46].

It is well known of course that immunocompromised subjects with human immunodeficiency virus type 1 (HIV-1) infection are more susceptible to a number of opportunistic microbial pathogens. However, it has not been so well appreciated that *P. gingivalis* can induce HIV-1 reactivation through production of butyric acid and thus aid progression of HIV-1 [47]. In addition, HIV-1 particles trapped on the *P. gingivalis* cell surface can become internalized when bacteria invade $CD4^-$ epithelial cells [48]. These various synergies between virus, bacterium and host are only just becoming understood, and show clearly that interkingdom interactions play major roles in shaping health or disease. Even the beneficial effects of vaccination may be subject to interkingdom influences, and unintentional consequences, for the live attenuated influenza virus vaccine can enhance oropharyngeal carriage of *S. pneumoniae* [49].

7. A mushrooming field

7.1. Fungi in the oral cavity

Fungi represent a small but significant component of the oral microbiome, and it is worth noting that many, if not most, microbiome studies have not included probes for fungi. Even some of the more recent metagenomics approaches do not incorporate fungal genome assemblies into data for periodontal disease microbiomes, despite evidence for *Candida* spp. being present in subgingival plaque. Fungi, especially *Candida* spp., are carried orally by everybody at one time or other in life, and approximately 40% of humans are continuously colonized. *C. albicans* now represents one of the most common microorganisms in hospital-acquired infections, with candidemia having a mortality rate of approximately 50%. Opportunisitc *Candida* infections occur when the host's immune defences are compromised, from restricted salivary flow associated with ill-fitting dentures (denture stomatitis) to HIV-1 infection or immune suppression following surgery. Since most infections appear to arise from indigenous colonizing fungi, reduction in carriage levels might reduce incidence of disease.

7.2. Signalling in fungi

Similar to bacteria, fungi produce a range of QS molecules that provide a check on population density and control virulence factor expression. Farnesol (see above) is produced by growing populations of *C. albicans* and inhibits the formation of hyphae and biofilms [39]. The receptor for farnesol has not been identified, but the histidine kinase Chk1 and

Ras-Cyr1 (adenylyl cyclase) pathway is activated and Tup1, transcriptional cofactor repressor of filament formation, is upregulated [50]. Farnesol also acts as an interspecies QS molecule with, for example, *C. tropicalis*, acts intergenerically with *Aspergillus*, and impacts the host (see above). Tyrosol, an aromatic alcohol produced by *C. albicans*, acts in opposition to farnesol by inducing hyphal filament formation. As described above, *C. albicans* produces oxylipins that act as QS molecules, increasing filamentation under some conditions. Fungi are also responsive to carbon dioxide (CO_2) and the yeast to hyphae morphological transition associated with pathogenesis in *C. albicans* is triggered by elevated CO_2 [51]. This is sensed by Cyr1, activating the catalytic domain, increasing cAMP synthesis, and activating protein kinase A (PKA) [52]. Cyr1 also senses pH and temperature, and is directly activated by bacterial peptidoglycan (MDP, see above) binding to the LRR (leucine-rich repeat) domain [52].

7.3. Signalling between fungi and bacteria

Fungal-bacterial interactions are implicated in promoting colonization, biofilm formation, and virulence. Cross-kingdom signalling seems to have become an intense area of research over recent years. A range of small molecules with signalling or QS functions, produced by fungi or bacteria, modulate the collective behaviour of mixed species communities. When species of oral streptococci form biofilms with *C. albicans*, both bacteria and fungi seem to benefit in that dual species biofilms are more luxurious in growth than the single species biofilm counterparts [53–56]. *C. albicans* is able to lower O_2 tension, and may also provide growth stimulatory factors for *S. gordonii*. In turn, growth with *S. gordonii* enables *C. albicans* to persist under conditions <pH 4.5, and *S. gordonii* produces nutrient by-products that are stimulatory to *C. albicans*, enhancing the length of hyphal filaments [53]. A number of interactive signals are proposed for these phenomena. *S. gordonii* appears to block, at least in part, the inhibitory effects of farnesol [53]. There is also evidence that AI-2 [53], peptidoglycan fragments [22, 52] or hydrogen peroxide [57] produced by these catalase-negative bacteria could enhance filamentation. There may be additional growth factors or catabolites that are produced by the interkingdom partnership that promote synergy, such as enabling increased efficiency of energy production (new carbon sources or provision of amino acids).

In *S. mutans* dual species biofilms with *C. albicans*, the streptococcal QS system for development of competence for DNA uptake is turned on by *C. albicans* [55], as are at least two genes associated with virulence [56]. Co-infection resulted in enhanced development of carious lesions over and above those caused by *S. mutans* alone [56]. Paradoxically, the competence-stimulating peptides released by *S. mutans* [58] and by *S. gordonii* [59] both modulate biofilm formation by *C. albicans*, suggesting that *C. albicans* can sense these signals produced by streptococci just as the bacteria can sense farnesol, and perhaps other QS molecules produced by fungi. Trans-2-decenoic acid formed by *S. mutans* [60] is also inhibitory to hypha formation.

7.4. Mediators of fungi-bacteria communication

It has long been known that a variety of oral streptococci are able to coaggregate with *C. albicans* and that the interactions occur principally with hyphal filaments [53], although *C.*

albicans cells primed for hypha formation are also bound by oral streptococci. Several cell-wall anchored proteins e.g. SspA, SspB and CshA, on the surface of *S. gordonii*, all appear to be involved in the binding of *C. albicans* by the bacteria. More specifically, the SspB polypeptide has been shown to interact with a hyphal cell wall protein designated Als3 [61]. This is a member of the Als protein family in *C. albicans* that comprises glycosylphosphatidylinositol (GPI)-modified proteins linked to the fungal cell wall. Als3 is the only member of the family to be expressed uniquely on hyphae, while Als1 is expressed at the site of initial hyphal filament extension [62]. The interaction of SspB protein on *S. gordonii* with the N-terminal region of Als3 [63] is thought to drive, at least in part, the formation of dual species biofilms of these organisms. Als3 and other cell wall proteins are glycosylated, and early stage *O*-mannosylation of these proteins is critical for activation of hyphal adhesin functions [64]. Als3 is also a receptor for *Staphylococcus aureus* binding to *C. albicans* [65], which facilitates staphylococcal invasion into host tissues leading to systemic infection.

7.5. Consequences of communication between fungi and bacteria

In the oral cavity, *C. albicans* has the potential to associate with hundreds of different species of bacteria, and so it is likely that there are novel physical and chemical interactions to be discovered. However, one consequence of the interactions of *C. albicans* with streptococci, in addition to providing metabolic synergy, might be that persistence of the fungus in the oral cavity is enhanced. The virulence of coaggregating bacteria or fungi may also be promoted. Colonization of the oral cavity by *S. oralis* in experimental animals was augmented in the presence of *C. albicans* [66]. Co-infection also resulted in enlarged oral thrush lesions, upregulated the mucosal inflammatory responses, and promoted deep organ dissemination of *C. albicans*. This is a form of pathogenic synergy, also exemplified in *S. aureus* co-infections with *C. albicans* [65], which can turn a non-lethal monomicrobial infection into an infection with high mortality rate. Clearly these kinds of co-infections have serious implications for clinical management of patients, so better understanding of the mechanisms of these interkingdom networks should impact on improving patient treatment outcomes.

The relations between oral bacteria and *C. albicans* have been largely focused on extracellular associations (Fig. 1) in which streptococci adhere to hyphal filaments, sometimes in specific regions [65], and then form clusters or microsocieties surrounding or enveloping the hyphal filaments. This we believe represents an upregulation of streptococcal surface proteins as a result of adherence to the hyphae, or receiving a chemical signal from the fungi, and the intercellular aggregation of streptococci to form clumps (Fig. 1). In *S. pneumoniae*, development of competence is accompanied by clumping of cells, effected by the release of eDNA. A similar process may occur in the eDNA-mediated interactions of *S. gordonii* with *C. albicans* in biofilms [59].

Associations of *Helicobacter pylori* with *C. albicans* may be even more intimate. *Candida* spp. isolated from the oral cavity of dyspeptic patients were found to contain bacteria-like bodies inside their vacuoles. These contained *H. pylori*-specific 16S rRNA and *H. pylori* proteins such as urease, vacuolating toxin (VacA), periredoxin and thiolperoxidase [67].

Fluorescence microscopy revealed *H. pylori* cells inside the mildly-acidic vacuoles of mother and daughter cells, suggesting that the endobacteria could multiply and transmit. The accommodation of *H. pylori* in endosymbiosis with *Candida* that grow on the oral cavity mucosa could contribute to persistence of *H. pylori* in the gastrointestinal tract. It would be interesting to determine in future if members of the resident oral microbiota (e.g. streptococci) are also able to interact with *C. albicans* in this way. This would have implications for persistence of oral bacteria outside of the oral cavity environment, and could provide mechanisms for resisting effects of antibacterial agents or hiding from immune system components.

8. Messages for home

Interkingdom networking of free living microorganisms and the host in the oral ecosystem provides a fascinating view of how cell population regulatory molecules have been shared or adapted. Interactions between viruses, bacteria, fungi and the host that have been discussed in this article are summarized in Fig. 2. We are just at the tip of the iceberg in understanding the multitude of potential cross-kingdom interactions that go to determine health or disease for the host, and life or death for the microbes. The immense biological data set for the oral cavity ecosystem will provide new understanding of the ways in which human microbial communities develop, and will be mined for new molecules that might be utilized for influencing community development or host response. Many of these microorganisms may also have evolved unique biological factors significant for our wellbeing. Thus compounds biosynthesized by microbiota components may have potential therapeutic applications. An inhibitor of *C. albicans* biofilm formation, designated mutanobactin, has been isolated from *S. mutans*, and is roughly 300 times more potent than farnesol [68]. The human microbiome could also be a promising source of new antibiotics. The biosynthetic gene clusters for a class of antibiotics, thiopeptides, are widely distributed in metagenomes of the human microbiota. One of these, lactocillin, is produced by the vaginal microbiota and has potent activity against a range of Gram-positive vaginal pathogens [69]. It is evident then that interkingdom signalling molecules that are utilized by microbes to manipulate populations could also be used by us, the host, to manipulate our microbiota. New molecules will likely also be found that will impact directly on host cells, hopefully as a means of controlling unwanted inflammatory responses, apoptotic processes, or haemostasis.

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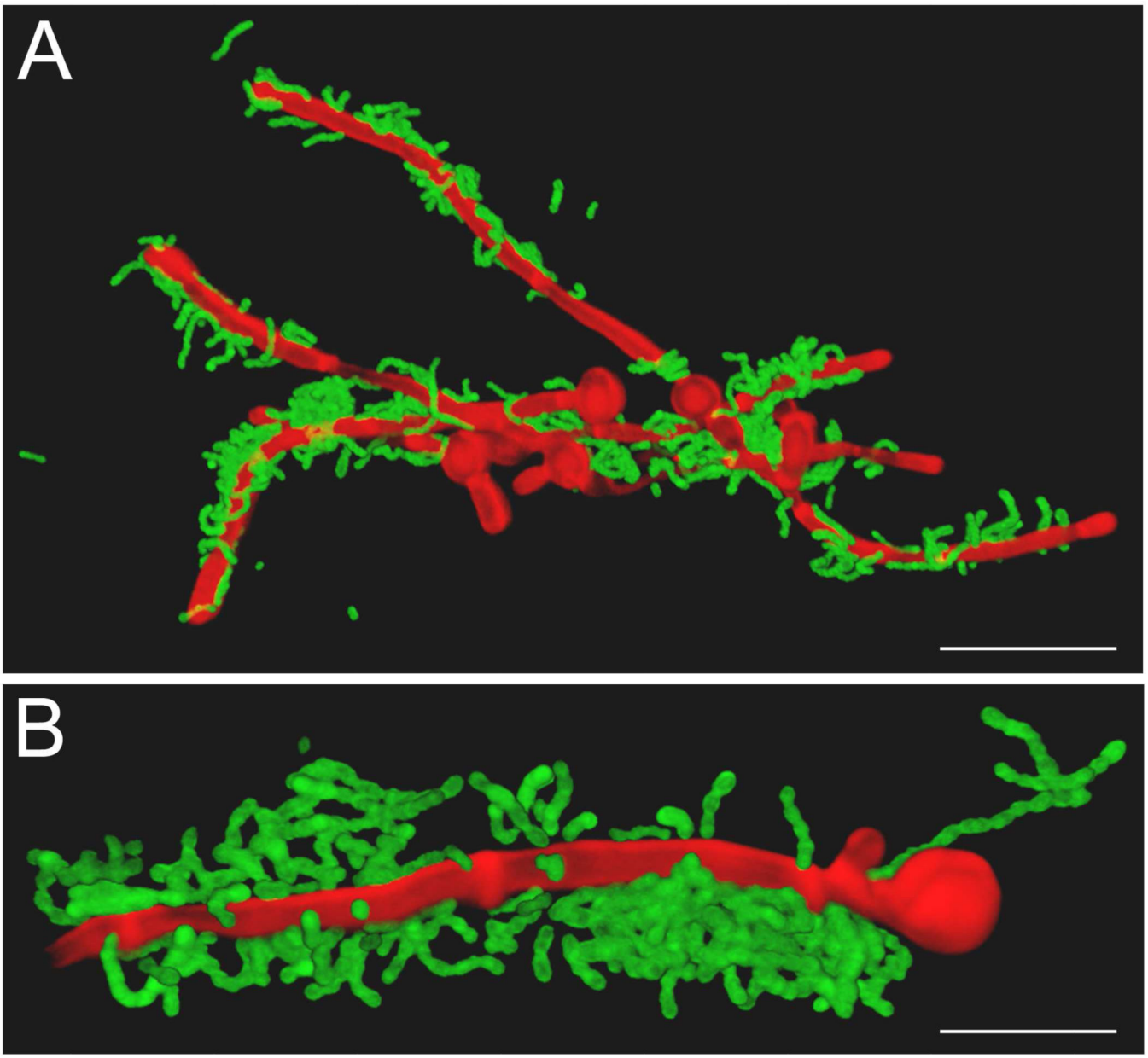

Fig. 1.

Fluorescence confocal scanning laser micrographs of interactions of oral streptococci with *Candida albicans*. Panel A: *Streptococcus gordonii* DL1 cells interacting with *C. albicans* hyphae. Bacterial cells were labelled with fluorescein isothiocyanate (FITC) [64] and incubated with hypha-forming cells of *C. albicans* for 2 h at 37°C. *C. albicans* cells were stained with calcofluor white [64]. Note that streptococci are attached only to hyphae, they form micro-societies in some areas, and are able to cross-link the *C. albicans* hyphae. Panel B: *Streptococcus oralis 34* cells interacting with *C. albicans* hyphae under similar conditions to panel A. Large aggregates of streptococci have formed around sites of contact with hyphae, suggesting a process of adherence followed by aggregation and accumulation. Note a chain of streptococci in intimate contact with the hyphal filament close to the mother cell.

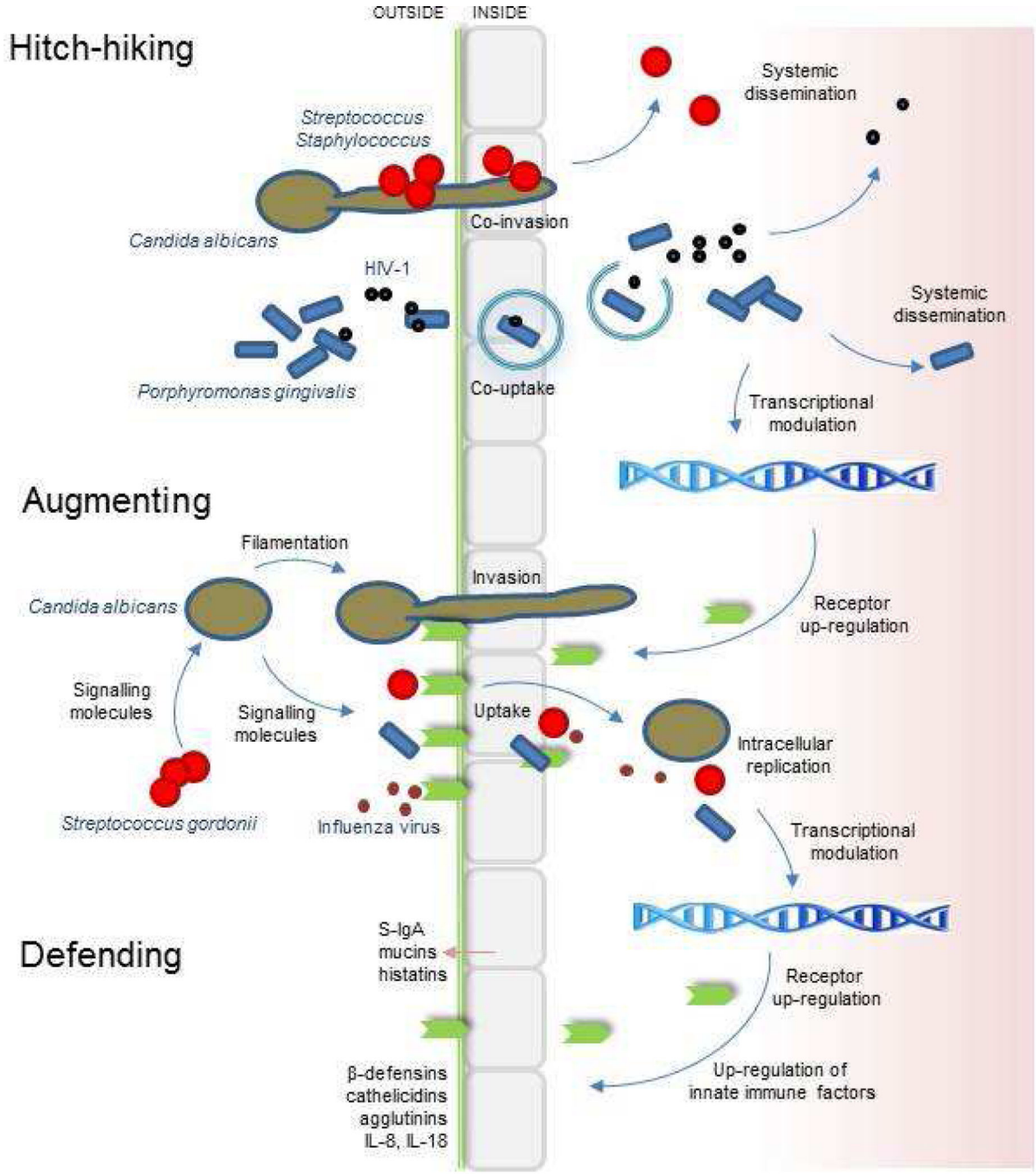

Fig. 2.

Summary of interkingdom interactions associated with the oral microbiome and epithelial barrier. Hitch-hiking involves the carriage of one organism by another across the epithelial cell barrier, as exemplified in the diagram by interactions of fungi-bacteria and bacteria-virus. Bacteria-bacteria hitch-hiking is also documented [70] but is not shown. Hitch-hiking extends the repertoire of microbe-host cell interactions. Internalization may lead to degradation through autophagy pathways, intracellular replication, uptake by macrophages and systemic spread. Upregulation of surface receptors (e.g. E-cadherin, proteoglycans,

integrins) as a result of microbial adhesion or invasion promotes secondary interactions e.g. influenza-*Streptococcus pneumoniae*. Signalling molecules produced by bacteria (e.g. AHLs) are able to modulate *C. albicans* hyphal morphogenesis and epithelial cells, while signalling molecules produced by fungi (e.g. farnesol) may affect bacteria and host cells. All of these various interactions may augment the virulence and pathogenesis of the oral microbiome. Host epithelial cell small-molecule responses to microbes include upregulation of antimicrobial peptides (e.g. β-defensins) and cytokines (not specifically addressed in this review paper). Agglutinins (mucin-like proteins) such as gp340 are macromolecular defences secreted by epithelial cells. Other macromolecular defence factors (e.g. mucins) are secreted by specialized cells. The reader is directed to the many recent specialist reviews on antimicrobial peptides, mucins, and other elements of innate immunity for further information.

Table 1

Some of the small-molecule signals produced by oral microorganisms and received by human cells or vice versa.

Microbial products influencing microbiome and host			Host products influencing microbiome	
Compound	**Example of producer**	**Effects**	**Compound**	**Effects**
Acyl-homoserine lactones (AHLs)	*Pseudomonas*	QS in bacteria, kill *C. albicans* hyphal filaments, neutrophil chemoattractants, stimulate phagocytes, actin remodelling in epithelial cells	Estradiol	Stimulates growth of *C. albicans*, impairs dendritic cell function and Th17 response
Muropeptides	*S. pneumoniae*	Promote *C. albicans* yeast to hypha transition, trigger production of IFN-γ, IL-17	Catecholamines	Stimulate *Actinomyces*, *Eikenella*, *Campylobacter*, inhibit *P. gingivalis*
iE-DAP	*P. gingivalis*	Activates NOD, stimulates production of TNF-α, IL-6, CCL2, IL-8, and defensins (e.g. HBD)	Hydrogen peroxide	Induces oxidative stress in bacteria, triggers *C. albcians* filamentation, kills susceptible microorganisms
Farnesol	*C. albicans*	Inhibits *C. albicans* filamentation, upregulates epithelial TLR2, increases IL-6 and HBD production	Antimicrobial peptides	Various species-or strain-specific inhibitory effects on bacteria and fungi
Indole	*Fusobacterium*, *T. denticola*	Inhibits AHL-mediated QS, promotes apoptosis, down-regulates IL-8, upregulates Il-10		
Hydrogen peroxide	*Streptococcus*, *Lactobacillus*	Induces oxidative stress in bacteria and fungi, triggers *C. albicans* filamentation, kills susceptible microorganisms		
Oxylipins	*C. albicans*	Attenuate neutrophil migration, affect mucosal integrity		
Neuroactive compounds	*Lactobacillus*	Anti-inflammatory		
Butyrate	*P. gingivalis*	Reactivation of HIV-1, apoptosis, increases HBD production, causes cell cycle arrest in fibroblasts		