

The Oral Microbiome

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Introduction

Research into the microorganisms that live within our mouths has a long history. In 1683, Antoni van Leeuwenhoek scraped plaque from his teeth, mixed it with rainwater, and examined it under a microscope. Despite what he thought of as a rigorous daily tooth-cleaning regime, he was astonished to describe *dierken* ('little animals' or 'animalcules') 'very prettily a-moving', representing the first recorded observations of oral bacteria (1).

The oral microbiome is the collection of microorganisms that live in the oral cavity, encompassing bacteria, viruses, archaea, and fungi. The content of this review focuses mainly on bacteria, its most characterized inhabitants. This characterization is largely thanks to recent developments in sequencing techniques, particularly using relatively cheap amplicon sequencing to target 16S ribosomal RNA genes shared among prokaryotes (2–4). Such culture-free investigation has improved our understanding of the diversity of the oral microbiome but there is still much to understand, particularly regarding the oral microbiome's relationship with its host: us.

Defining and characterising the oral microbiome

Development and resilience

The oral microbiome exhibits body-site specificity six weeks after birth (5) and undergoes substantial increase in diversity between 0-3 years especially after the eruption of teeth (6), followed by a maturation process that continues into adulthood (7). Even once established, the oral microbiome is subject to continual perturbation. Unlike more internal environments within the body, the mouth experiences daily physicochemical fluctuations in temperature, oxygen content, acidity, and carbohydrate availability, and yet the oral microbiome exhibits marked stability over time. It has been suggested that this need to be robust to multivariate fluctuations may explain the salivary microbiome's greater resilience to antibiotic perturbation when compared to the more homogenous gut microbiome (8).

The resilience of the oral microbiome once established causes the phenomenon of 'colonization resistance', where established microorganisms confer protection from external pathogens by occupying available surfaces and environmental niches (9). Many authors have observed that the normal 'commensal' microorganisms that confer protection from external pathogens are also responsible for a wide range of oral diseases (10,11). This apparent paradox can be resolved by relaxing the distinction between the symbiotic and the pathogenic, which can be artificial and misleading in the context of human-associated microbiomes. Indeed, the etiology of oral microbial diseases such as caries and periodontitis has undergone several paradigm shifts over the twentieth century, as molecular techniques have expanded in scope from individual pathogens to the entire oral microbiome (12).

The complex structure of the oral environment

Referring to 'the' oral microbiome might suggest a degree of homogeneity within the mouth, but it should be stressed that the biogeography of the oral cavity leads to highly structured and differentiated microenvironments with correspondingly different microbial populations. Examples of microenvironments within the oral cavity include the periodontal sulcus, tongue, hard palate, buccal mucosa, and saliva

(13), although there is clearly overlap and some degree of mixing between these sites. More generally, a broad distinction can be made between hard tissue surfaces (dental plaque) and soft tissue surfaces (14), which clearly separate in terms of microbial community composition.

The complex nature of oral biofilms is beginning to be explored with new techniques that promise to reveal a great deal about their development and progression. A recent pioneering study by Welch et al. (15) combined metagenomic sequencing with fluorescence in situ hybridization to reveal complex radial structures in supragingival plaque, with anaerobic taxa at the centre and aerobes at the edges. Co-localization of consumers and producers of metabolites within such structures supports the real functional importance of such spatial organization within the oral microbiome. Such biofilm structure can also be investigated with in vitro models that allow the culturing of previously unculturable oral microbes (16).

Difficulties in characterizing the oral microbiome

Marker gene sequencing allows easy characterisation of the oral microbiome, but this ease can be misleading. Importantly, it is well-established that many oral microbes with highly similar 16S rRNA gene sequences can have different genomic content and correspondingly different ecological niches. For example, Eren *et al.* (17) reanalyzed Human Microbiome Project (HMP) data sampled from multiple oral locations within the same individual, and found that *Neisseria* oligotypes varied greatly in spatial distribution. An oligotype of *N. flavescens/subflava* that was detected in high abundance in keratinized gingiva, but rare at all other sites sampled, had over 99% sequence similarity in the V3-V5 region of the 16S rRNA gene. Furthermore, different choices of primers can result in differential PCR amplification from different bacterial families because of primer mismatch (18) that can lead to biased diversity metrics (19,20), and differences between variable regions can lead to reduced specificity depending on the bacterial genus.

While partitioning oral microbes into ecological units based on marker genes is a powerful technique, it is important to bear in mind that while high-resolution techniques such as oligotyping (21) and minimum entropy decomposition (MED) (22) may offer higher resolution and specificity than operational taxonomic unit (OTU) clustering, they still may not separate out true ecological differences (23). Indeed, oral microbes with identical 16S rRNA can still possess dramatically different gene complements due to mobile DNA e.g. highly dynamic integron gene cassette arrays (24,25).

The oral ‘mobilome’ and antimicrobial resistance

The majority of the oral microbiome resides in multi-species biofilms where the opportunities for horizontal gene transfer (HGT) are greater than in mixed planktonic cultures. Furthermore, increased stress conditions can contribute to increased rates of HGT (26), including via bacterial sensing of mediators of acute host stress (27). This has important implications for the oral microbiome in terms of its adaptive ability to the many stresses of the oral environment.

The functional role of horizontal gene transfer

Oral microbiota are repeatedly exposed to a range of natural antimicrobials in our diet. These include plant-based essential oils and flavonoids (28,29), as well as anthropogenically added antimicrobials used as preservatives (e.g. sodium benzoate) and those used for personal hygiene such as chlorhexidine and triclosan (30). In addition, exposure of the oral microbiome to antibiotics (whether clinical or environmental) is likely to select for HGT events which lead to the acquisition of genes that confer an increased tolerance to these compounds.

There is a wealth of information on the presence of antibiotic and antiseptic resistance genes within cultivable bacteria and metagenomic DNA isolated from the oral cavity (31,32). Such genes are often described in association with mobile genetic elements such as plasmids and transposons (33). This has led to the oral microbiome being described as a reservoir for antibiotic resistance genes (34). The term “reservoir” might be taken to imply these genes are simply inert and waiting to be acquired by a transient pathogen i.e. that they are not functional prior to this transfer event. This seems highly unlikely, as maintenance over time within their commensal host suggests a continued benefit.

Adaptive potential of the oral microbiome

Functional metagenomic studies investigating antimicrobial resistance from the oral cavity have provided information on novel antibiotic resistance genes; e.g. the tetracycline resistance genes *tet*(37) and *tetAB*(60) which could not have been predicted based on sequence data alone (35,36). Furthermore there is experimental evidence that “house-keeping” genes for certain species can confer antimicrobial resistance to a range of compounds when expressed in a heterologous host. Resistance to the common antiseptics cetyltrimethylammonium bromide and triclosan can be conferred when *E. coli* expresses either an epimerase gene, usually involved in fatty acid synthesis during cell wall construction, or one of many Enoyl-[acyl-carrier-protein] reductase genes (*fabI*), respectively – both derived from the oral microbiome (37). There is evidence that the *fabI* gene has already made its way onto a transposon in *Staphylococcus* which is now selectable by triclosan (38). It is concerning that duplication or repurposing of metabolic genes within heterologous hosts can confer resistance to such common compounds. The high adaptive potential of the oral microbiome seems to be intrinsically linked to HGT and the mobilome, despite an apparent conserved taxonomic composition.

Taxonomic composition of the oral microbiome

In general, factors that lead to correlations in taxonomic composition between different sites in an individual’s mouth are stronger than those that could cause differences via local dispersal in the oral cavity. Thus, it is meaningful to talk about general differences in oral microbiome taxonomic composition. Individuals appear to have a stable oral microbiome ‘fingerprint’ over timescales of months (39) to a year (40), despite rapidly fluctuating proportional abundances on the time-scale of days (41). Oral viruses have also been shown to be personalized and persistent over similar timescales (42), consistent with known phage-bacteria interactions in the oral microbiome (43). The relative importance of all factors that could conceivably lead to individual-level differences is difficult to establish due to the complexity of

performing a comprehensive controlled analysis, although studies of various combinations allow some conclusions to be drawn.

The core oral microbiome

In line with being the first known human-associated microbiome, the oral microbiome has been extensively characterized compared to other microbiomes, as summarized in the Human Oral Microbiome Database (HOMD, www.homd.org) (44). HOMD provides a curated collection of full-length 16S rRNA gene sequences of common oral microbes, together with genome sequences where available. As of 2017 just 32% of taxa are estimated to remain uncultivated (44). The characterized oral microbiome is dominated by six major phyla making up 96% of the taxa (*Firmicutes*, *Proteobacteria*, *Bacteroidetes*, *Actinobacteria*, *Spirochaetes* and *Fusobacteria*) (45). These major phyla define the core oral microbiome determined by the common nature of the oral cavity across individuals – microbes subsisting on endogenous nutrients from the human host – with secondary differences in composition due to other factors. Differences between individuals at the sub-genus level do not appear to translate into larger-scale geographic differences across global scales (46).

Diet

The primary source of nutrients for oral microbes is saliva and gingival crevicular fluid rather than food ingested by the host (11), suggesting that diet may not be a key modulator of the oral microbiome in terms of its healthy composition. However, there have been many postulated associations between diet and oral disease, most notably dental caries (see below). The higher prevalence of oral disease in industrialized countries may be linked to diet-associated dysbioses in the oral microbiome (47). Chronic disorders like diabetes and inflammatory bowel disease have been linked to a ‘Western diet’ (48), and the oral microbiome may play a role in this interaction. Further insight into the possible interaction of diet and the oral microbiome over evolutionary timescales may come from investigations of ancient dental calculus (49), and it has been claimed that major shifts in composition are identifiable that correspond to the Neolithic and Industrial Revolutions (50).

Lifestyle

Smoking measurably affects the oral microbiome, with a study of 1204 American adults finding that current smokers had distinct oral microbiome composition from those who had never smoked, with lower levels of *Proteobacteria* and an increased abundance of *Streptococcus* spp. (51). Smokers experience higher susceptibility, severity, and faster progression of periodontal disease, although the mechanisms remain underlying the disease progression remain unclear (52). Other lifestyle factors may also influence the oral microbiome, whether through general health or indirectly through environmental exposure, although these are less well-studied.

Genetics and the environment

There are several ways that host genetics could conceivably affect the oral microbiome, including salivary composition, immune phenotype, or indirectly through gene-diet interactions as observed in the gut microbiome (53). Typically genetics is confounded with multiple other factors, most notably environment. Understanding the role of these factors in determining the oral microbiome is of particular relevance for conditions such as inflammatory bowel disease that show familial aggregation that could be driven by either genetics or shared environment

(54). While there is a generally observable correlation between human genetics and oral microbiome composition, given current limits on the cohorts available for study and therefore the ability to distinguish genetic effects on the establishment and maintenance of the oral microbiome, the role of genetics is still uncertain. Whatever this role, there is currently some evidence to support the conclusion that environmental effects are nevertheless dominant.

It is well-established that cohabiting individuals share overlapping oral microbiomes (55,56) – including in some cases, with their cohabiting dogs (57) – as is the case in other human microbiomes, including for unrelated individuals (58). Stahringer et al. (59) performed a longitudinal study of the salivary microbiome of twins over several years and concluded that “nurture trumps nature”, with the effect of shared upbringing larger than that of genetics. They observed that monozygotic and dizygotic twins did not have statistically more similar microbiomes, in agreement with observations on the gut microbiome (60), and that oral microbiome similarity decreased over time once twins no longer co-habited, pointing to the dominant effect of environment.

It has been suggested that there may be ethnic differences in the oral microbiome, possibly linked to differing susceptibilities to periodontitis (61,62). However, conclusions reached simply by comparing ethnic groups without any genetic evidence based on questionable assumptions of completely shared lifestyles and other confounders should be viewed with scepticism. A more rigorous analysis by Blekhman et al. (63) explicitly used human genetic information extracted from HMP samples from 93 individuals, and did find that host genetic variation correlated with the composition of the oral microbiome. Notably, the most significant association was between genes involved in the signalling pathway for leptin (64) and taxa in keratinized gingiva and subgingival plaque, suggesting a link between immunity and the oral microbiome at these sites.

It seems probable that associations with host genetic variation (or the corresponding lack thereof) in different oral environments may be due to differing relationships between different communities within the oral microbiome and the host immune system. For example, a recent study we conducted in a large family of related Ashkenazi Jewish individuals found no significant associations between host genetics and salivary microbiome composition, and identified shared household as the dominant variable (65). This analysis required SNP-based kinships instead of pedigree kinships, which can differ substantially from true genetic kinships. However, a similar study of the nasopharyngeal microbiome in Hutterite individuals (66) did find associations linked to mucosal immunity genes. The diversity of tissue types and microbial niches has a direct impact on host defense mechanisms and requires an array of immunological adaptations.

The oral microbiome and mucosal immunity

The immune system within the oral cavity usually maintains tissue homeostasis in combination with a stable microbial community, but in some individuals this balance is destabilised leading to a diseased state, or dysbiosis.

Oral immunity in health

As with almost all tissues the first line of immunity lies with the innate immune system, which consists of a number of diverse molecular and cellular components. In addition to the physical barrier of the mucous membrane, the mucosal surface and oral cavity is also bathed in saliva that contains a myriad of antimicrobial compounds. Saliva contains a whole host of antimicrobial peptides and proteins (e.g. defensins, histatins, lysozyme, bactericidal/permeability increasing protein (BPI), immunoglobulins A and G), as well as enzymes such as lactoperoxidase that generate bactericidal agents (e.g. hypothiocyanite (OSCN⁻)) (67,68). The importance of saliva for oral health is clearly evident in conditions such as primary Sjögren's syndrome and Aplasia of Lacrimal and Salivary Glands (ALSG), which are both characterised by hyposalivation (69,70). Hyposalivation results in xerostomia (dryness of the mouth), increased risk of dental erosion, dental caries, periodontal disease and oral infections.

The most prominent innate immune cells within the oral cavity are the tissue macrophages and dendritic cells, which act as sentinels for the immune system and reside predominately within the lamina propria. These cells express pattern recognition receptors (PPRs) such as Toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs), which recognise pathogen specific ligands such as lipopolysaccharide, viral RNA and bacterial DNA (collectively termed pathogen-associated molecular patterns (PAMPs)) (71). Activation of the PPRs results in a rapid and robust inflammatory response that recruits neutrophils and monocytes from the circulatory system and initiates the activation of the adaptive immune response.

A balance between pro-inflammatory T helper type 17 (Th17) cells and anti-inflammatory T regulatory (Treg) cells are now thought to play a major role in regulating the immune response within mucosal tissue (72). Over activation of the Th17 cells or a loss in Treg cells can lead to the development of immunopathology and auto-inflammatory disease. In oral inflammatory disease, Th17 cells and associated cytokines (IL-17A, -21 and -22) have been reported to play an active pathological role in primary Sjögren's Syndrome (73), chronic periodontitis (74) and oral lichen planus (75). Th17 cells play a critical role in protection against extracellular bacterial and fungal infections within the mucosal tissue, with accumulation driven by physiological damage from mastication (76), but dysregulation in their activation results in inflammation and autoimmune disease (77). Over the coming years the role of Th17 cells within the oral cavity will become clearer and may also lead to the development of targeted therapeutics for a range of diseases.

Tolerance between the microbiota and host

In all mucosal surfaces there is a continual balance between immunity and tolerance, which results in the development of an environment that supports the development of a relatively stable microbiota. This balance also has to enable the host to mount an adequate immune response upon infection. How the immune system coordinates this complex system and how much influence the microbiota has on this process is still poorly understood. In addition to pathogenic bacteria, our oral cavity is also home to probiotic bacterial species such as *Lactobacilli*, *Streptococci* and *Bifidobacterium*.

Probiotic species have been shown to shift the composition of the microbiota and directly influence the immune response in host tissue, providing hope that additional mucosal inflammatory diseases could be treated through the manipulation of the microbiota. There is a growing belief that probiotics have therapeutic potential in oral conditions such as gingivitis and periodontitis (78), although more randomized control trials are required (79).

Our current understanding of immune tolerance has mainly been developed from studies conducted in the gastrointestinal tract. Within this setting T regulatory cells (Tregs) form the foundation for tolerance in conjunction with the anti-inflammatory cytokines interleukin-10 (IL-10) and transforming growth factor- β (TGF- β). Alterations in the secretion of IL-10/ TGF- β and/or Treg activation results in a loss in tolerance and the initiation of an inflammatory response. Under normal circumstances once the threat has been eradicated by the immune response the tissue undergoes a resolution phase, which reestablished tolerance. Defects in these processes have been identified in a number of mucosal inflammatory diseases. What influence the oral microbiota plays in actively driving these diseases is still an area of considerable debate (80,81).

Diseases associated with alterations in the oral microbiome

There is a greater risk of microbial infection in individuals that are immune compromised either through genetic mutations, chronic infection, immunomodulatory treatments or pregnancy. A high proportion of these infections occur in the oral cavity. While there is debate about the direction of causation, it is clear that many oral diseases can be associated with specific bacterial populations and altered immune status. We discuss some prominent examples here.

Dental caries

Dental caries refers to tooth decay, which is caused by acids produced by oral bacteria (82). These acids are byproducts of the breakdown of oral carbohydrates (83). The association between dental caries and carbohydrates was first hypothesised by Miller in 1890 (84), and is now supported by extensive evidence (85). Reduced-sugar diets have been shown to be associated with lower amounts of dental caries (86), and it is known that cooked starches can act as a stimulus that produces elevated acidity and aciduric species at caries-prone sites (87). In response to this body of evidence, the World Health Organization has issued guidelines that free sugars in diet should provide <5% of total energy intake (88). Other important prevention strategies include oral hygiene (to prevent the buildup of aciduric biofilms) and dietary fluoride (to encourage the remineralisation of tooth enamel) (85).

Periodontitis

Periodontal disease involves bacterial derived factors that stimulate the inflammatory response in the gingivae (89). In general, after an earlier focus on specific pathogens that were identifiable by culture techniques, newer paradigms take a more ecological view where microbial communities enter a disrupted alternative stable state. This is due to synergistic feedback between bacteria and their environment, tipping the balance “from homeostasis to dysbiosis” (90). However, it is undoubtedly true that species such as *Porphyromonas gingivalis*, *Porphyromonas intermedia* and *Aggregatibacter actinomycetemcomitans*, which reside within plaque, are highly

important in activating the host immune response and driving a chronic inflammatory reaction within the gingivae. Tissue inflammation or gingivitis can lead to a cascade of events, resulting in osteoclastogenesis and subsequent local bone loss via the receptor activator of nuclear factor-kappa B (RANK)-RANK ligand (RANKL). Activation of RANKL drives macrophage differentiation into osteoclasts and bone reabsorption, which results in the development of periodontitis.

A recent study has demonstrated that the level of *P. gingivalis* within the subgingival plaque provides the most reliable indicator of the progression of chronic periodontitis (91). Interestingly, *P. gingivalis* expresses a range of virulence factors which facilitate survival within the oral cavity and avoidance of the host immune system (92). Rubrerythrin, a nonheme iron protein, protects the bacteria from neutrophil mediated oxidative killing and exasperates the local and systemic inflammation within the gingivae (93). The gingipains Kgp and RgpA are the major proteases involved in hemin acquisition, binding, and accumulation. They protect *P. gingivalis* from oxidative damage through the formation of an oxidative sink (92). Gingipains have also been shown to play a role in complement and immunoglobulin degradation, inactivation of cytokines and their receptors, platelet aggregation, attenuation of neutrophil antibacterial activities, and increasing vascular permeability, as well as, prevention of blood clotting.

In addition to the local oral inflammation there is a growing body of evidence linking the inflammation associated with periodontal disease with the development of cardiovascular disease (94). These findings highlight the potential role oral inflammation plays on our systemic health.

Oral lichen planus

Oral lichen planus (OLP) is a T-cell-mediated inflammatory disease of the oral mucosa with an unknown aetiology. A number of studies have looked at the microbiota composition in patients with OLP and identified evidence of dysbiosis (95–97). Wang *et al.* (96) reported that the overall structure of the salivary microbiome was not significantly affected by disease status. However, they did find evidence of variation in abundance of several taxonomic groups, observing that levels of *Porphyromonas* correlated with disease scores and salivary levels of IL-17 and IL-23, which are both associated with the activation of Th17 mediated immunity and mucosal inflammation. *Porphyromonas* has also been identified as a core genus in periodontal disease, and an elevation in periodontopathogens observed in OLP patients has been predicted to play an important role in its progression (98).

HIV infection

HIV infection has been associated with increased prevalence of oral mucosal infections and dysregulation of oral microbiota, including the overgrowth of *Candida albicans* and the development of candidiasis as in other immunosuppressed populations (99). Candidiasis results from the loss in neutrophil recruitment to the oral tissue through a depletion in number of mucosal associated Th17 lymphocytes. Oral manifestations have been reported in up to 50% of HIV-infected individuals, and up to 80% of those who have progressed to AIDS. Impaired oral immunity in HIV infection may predispose patients to periodontal diseases, potentially increasing the risk of cardiovascular disease (94). The precise effects HIV infection has on the oral microbiome are complicated by potential effects of the anti-retroviral

treatment. A study comparing HIV-positive individuals to controls found only minor differences in the composition of the salivary microbiome, although certain taxa including *Haemophilus parainfluenzae* were significantly associated with HIV-positive individuals e.g. (100).

Conclusion

Our understanding of the oral microbiome has improved significantly since Leeuwenhoek's pioneering work over 350 years ago, with next-generation sequencing methods providing us with a much fuller picture of its true taxonomic diversity. However, despite great success in establishing its composition and variation across different sites in the mouth and associations with various external factors, we still have much to discover about the interactions within oral biofilms; both in immune-associated dysbioses and also in the transfer of antimicrobial resistance genes.

Improving our understanding of this dynamic yet stable array of microbial communities will require the integration of information from different approaches as we go forward, combining the power of sequencing with imaging and improved culture techniques. We can also learn from the past; as experimental recovery of ancient DNA from dental calculus continues to improve, we will be able to map the large-scale effects of human activities over tens of thousands of years onto our oral microbiomes.

We can be certain that the complexity we transport daily within our mouths will continue to astonish us. As Leeuwenhoek wrote, "For my part, I judge from my own case, although I clean my mouth in the manner heretofore described, that there are not living in our United Netherlands so many people as I carry living animals in my mouth this very day" (1).

Summary Points

There is a conserved core human oral microbiome with fine-scale differences at an individual level.

Individuals who share an environment (e.g. household) tend to have a more similar human oral microbiome.

The adaptability and resilience of the human oral microbiome is likely due to constant reseeding from the environment and the adaptive ability of the resident bacteria.

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