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Microbial Triad Of Periodontitis: Evidence So Far And The Shortfalls

Komal V[1], Geetha Ari[2], Sathish Rajendran[3], Jaideep Mahendra[4], Ambalavanan Namasivayam[5]

[1]*postgraduate Student, Department Of Periodontics, Meenakshi Ammal Dental College And Hospital, Chennai, Tamil Nadu, India.*
[2]*professor, Department Of Periodontics, Meenakshi Ammal Dental College And Hospital, Chennai, Tamil Nadu, India.*
[3]*associate Professor, Department Of Periodontics, Meenakshi Ammal Dental College And Hospital, Chennai, Tamil Nadu, India.*
[4]*professor And Head, Director Of Postgraduate Studies, Department Of Periodontics, Meenakshi Ammal Dental College And Hospital, Chennai, Tamil Nadu, India. Email Id:*
[5]*professor, Department Of Periodontics, Meenakshi Ammal Dental College And Hospital, Chennai, Tamil Nadu, India.*

Abstract:
Periodontal disease is a multifaceted infection that initiates with the disturbance of bacterial balance. Research shows that periodontitis isn't caused by a single organism but rather by diverse microbial communities working together. In essence, it's not merely an infectious condition but rather a dysbiotic disease, linked to changes in the composition of microbial communities compared to their normal state. Porphyromonas gingivalis, a significant member of oral microbial communities, is the primary pathogen responsible for periodontitis. Recent extensive research on this organism has revealed its increasingly apparent link to systemic diseases. Additionally, Treponema denticola inhibits fibroblast proliferation, increases collagen phagocytosis by gingival fibroblasts, and activates both the classic and alternative pathways of the human complement system. Whereas, Tannerella forsythia is a crucial and consistent component of microbial biofilms found in diseased periodontal areas. However, there is currently limited evidence explaining its colonization strategy for interactions with other microorganisms and host cells or tissues. There is limited concrete information regarding whether the red complex consortium is merely a consequence of environmental changes during the periodontal disease process or if it actively contributes to the initiation and progression of tissue-destructive events through synergistic mechanisms.

Keywords: *Biofilm, periodontitis, red complex, virulence factor*

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I. Introduction:

Periodontal disease is a complex infection that begins with disruption of bacterial homeostasis. It induces a host inflammatory response, characterized by persistent inflammation of connective tissue breakdown and alveolar bone destruction. It is now well established that periodontitis is not caused by a single or selective organisms but rather by polymicrobial communities of indigenous microbes acting in concert. In other words, periodontitis is not an infectious condition, but rather a dysbiotic disease, that is, associated with an alteration in the abundance of individual species within the polymicrobial community, relative to their abundance or influence in health.[1,2]

II. Community Substructure In Periodontium:

- Local environmental constraints also determine the nature of the associated microbial communities.
- For example, the epithelial cells of the gingival epithelium continually turn over **(shedding surfaces)**, and hence the microbial communities have less time to develop and tend to be less complex than those on the **non-shedding surfaces** of the teeth.
- Additionally, to avoid loss following host cell death, many bacterial colonizers of the junctional epithelium invade the tissues and internalize within epithelial cells, where they can spread to adjacent cells.
- Polymicrobial communities can also develop intracellularly, a location that will protect them from the action of many immune effector molecules.

- On tooth surfaces, a layer, or pellicle, of molecules derived from saliva is rapidly deposited, and it is to these salivary molecules that primary colonizers such as the oral streptococci and actinomyces adhere. (Figure 2)[3]

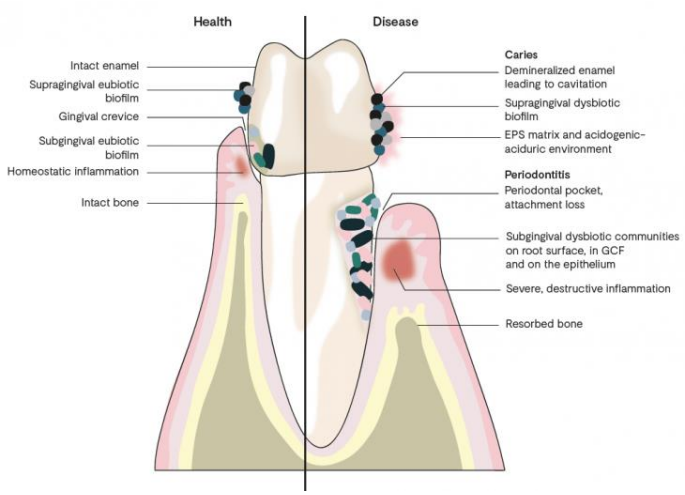

Figure 2: Dysbiosis leading to microbial invasion of the mucosa and further development of subgingival biofilm, involving colonisation by "red complex" pathogens including *P. gingivalis* and *T. denticola*, leading to inflammation and destruction of tooth-supporting tissues.

Currently, based on the research of Socransky team stands out specific groups of bacteria (called complexes) with particular importance in the pathogenesis of periodontitis. *Porphyromonas gingivalis* creates with the species of *Tannerella forsythia* and *Treponema denticola* so called **red complex**, which appears to be associated with disease symptoms in chronic periodontitis. The second important group of bacteria forms an **orange complex**, comprising 13 species, including *Fusobacterium nucleatum* and *Prevotella intermedia*. Orange complex bacteria are an **essential link** in allowing the colonization of periodontal tissue by a red complex. (Figure 3)[4]

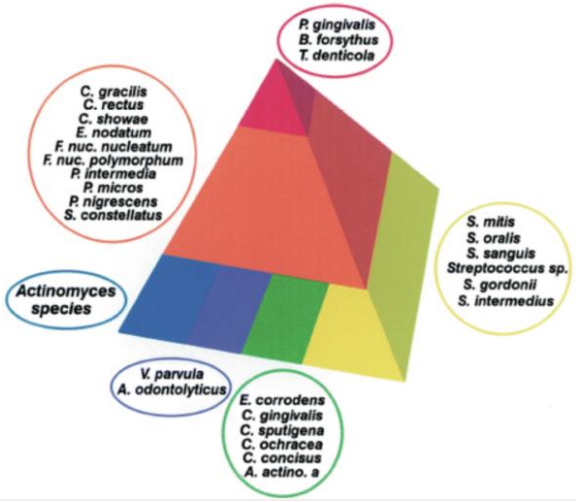

Figure 3: Pyramid of periodontitis complexes (Sockransky, 2002)

III. Microbiome In Chronic Periodontitis

Porphyromonas gingivalis

- Gram-negative, anaerobic, nonmotile, black pigmented bacteroides.
- Virulence factors- collagenase, endotoxin, IgA, proteases, and low-molecular weight compounds including hydrogen sulfide and ammonia which induce bone resorption, destroy connective tissue, induce a variety of cytokines, and inhibit host protective mechanisms. (Figure 4)[5]

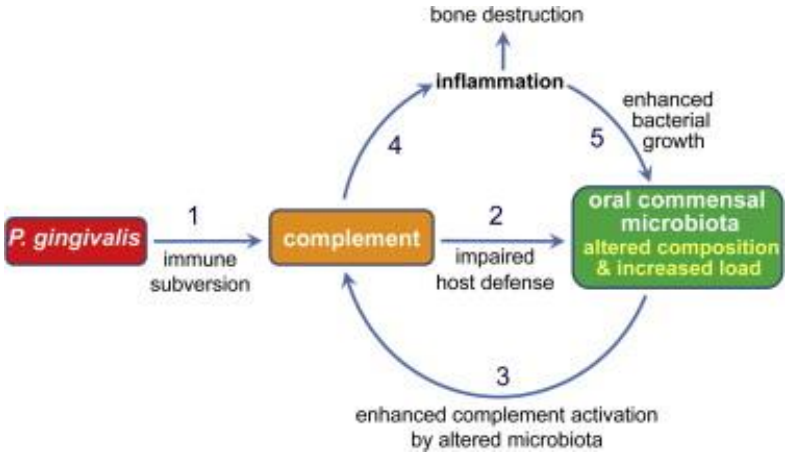

Figure 4: Mechanism of *P.gingivalis*

Gingipain- *P.gingivalis* lipopolysaccharide.

- The "trypsin-like" enzymes cleave polypeptides at the C-terminal after arginine or lysine residue. These proteinases are commonly known as gingipains, namely gingipain R and K that cleave after arginine and lysine, respectively.
- Inhibits osteoblastic differentiation and mineralization in periodontal ligament stem cells which participate in periodontal tissue regeneration.
- Capacity to degrade antibacterial peptides, such as neutrophil-derived α-defensins, complement factors, such as C3 and C4, T cell receptors, such as CD4 and CD8.[6]

Current Status Of P. *Gingivalis* And Its Systemic Impacts: (Figure 5)[7]

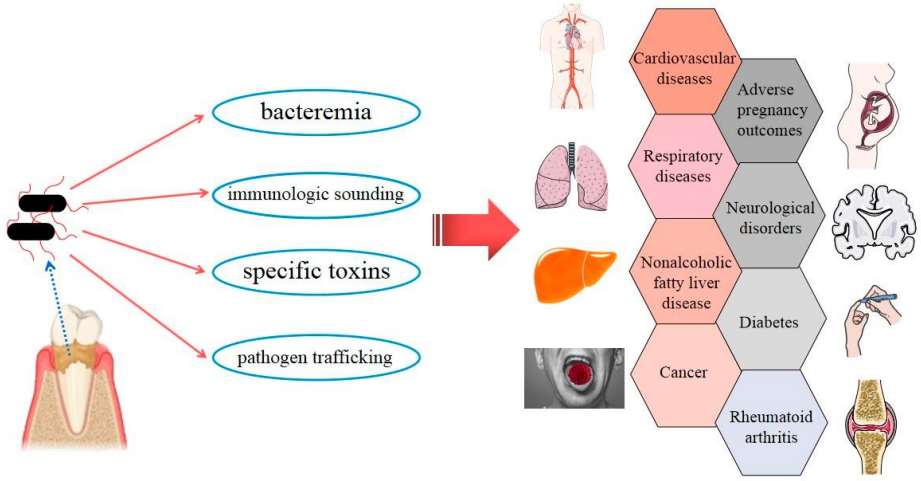

Figure 5: Schematic representation of *P.gingivalis*-associated systemic diseases.[7]

Atherosclerotic Cardiovascular Diseases (ACVDs)

- Much evidence has linked periodontitis to an increased risk of ACVDs (Humphrey 2008).[8]
- Periodontal treatment has been shown to improve the endothelial function and reduce CRP, IL-6, TNF-α of atherosclerotic disease, particularly in individuals already suffering from CVDs.[9]
- In-vivo experiment: Infection with *P. gingivalis* exacerbated atherogenesis in apolipoprotein E (ApoE)-deficient mice, and proximal aortic lesion size in *P. gingivalis*-inoculated mice was 2-fold larger than in control mice (Li, 2002). These results strongly suggest that *P. gingivalis* may enter the lesion area and promote the development of ACVD.[10]
- *P. gingivalis* invades endothelial cells via the autophagic pathway while suppressing apoptosis-through the NF-kB or p38 MAPK pathway, its fimbria and LPS upregulates the expression of various adhesion molecules in endothelial cells, such as VCAM-1, ICAM-1, monocyte chemoattractant protein, P-selectin, and E-selectin.[11]
- Furthermore, the proteolytic activity of Rgp and Kgp shown to induce lipid peroxidation and changes the expression of LDL and HDL to foam cell formation from macrophages. (Figure 6)[12]

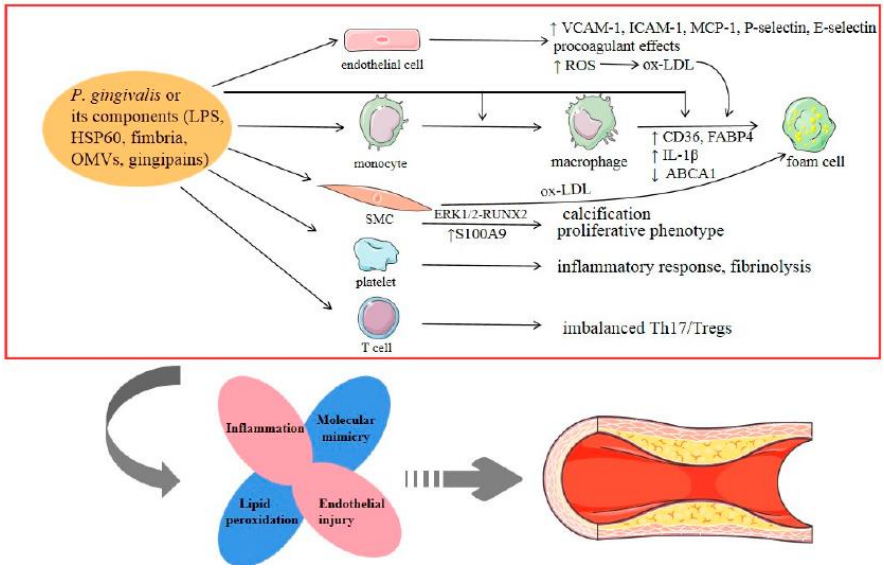

Figure 6: *Porphyromonas gingivalis*-induced stimulation of accelerated atherosclerosis.[7]

Myocardial Infarction (MI)

- A recent meta-analysis detected presence of periodontal bacteria in atherosclerotic plaque specimens from MI patients revealed that *P. gingivalis* was the most frequently detected species, with an average prevalence of 40%.[13]
- Further in-vivo evidence proved that experimental *P. gingivalis* bacteremia induced myocarditis/MI in mice causes progression of MI through direct action with cardiomyocytes.
- Promoting cardiomyocyte apoptosis by activating Bax and increases MMP-9 activity by enhancing oxidative stress, thereby exerting a strong detrimental effect on the healing process of the infarcted myocardium and subsequently leading to cardiac rupture after MI.[14]
- Lastly, *P. gingivalis*-associated production of IL-17A might play an essential role in the pathology of MI, as IL-17A was found to exacerbate ventricular remodeling after acute MI in mice.[15]

Hypertension

- In-vivo studies have shown that intraperitoneal injection of *P. gingivalis* exacerbated the hypertensive response to angiotensin II in mice, suggesting an adverse effect on hypertension.[16]
- Repeated exposure of live *P. gingivalis*/LPS induced the release of pro-inflammatory CKs and angiotensin II in human coronary artery endothelial cells, together with *P. gingivalis*-associated mediators like CRP, IL-6, TNF- α, contributing to both endothelial dysfunction and development of arterial hypertension.[17]
- Recent animal study supported the hypothesis that the Th1 immune response induced by *P. gingivalis* antigens is response for elevated BP. Moreover, *P. gingivalis* can induce high expression of ECAM, platelet aggregation, thus impairing vasomotor function.[18,19]

Oral cancer

- A meta-analysis revealed that periodontitis increased the risk of OSCC by nearly 2-fold.[20]
- In vivo experiments further confirmed the negative effect of *P. gingivalis* in OSCC and found that *P. gingivalis* accelerated OSCC progression in an immune microenvironment through the secretion of C-C motif chemokine 2, chemokine (C-X-C motif) ligand 2, IL-6, and IL-8 from infected oral dysplastic keratinocytes to recruit myeloid-derived suppressor cells.[21]
- Large studies explored the mechanisms of *P. gingivalis* in OSCC- (Figure 7)

○ epithelial–mesenchymal transition (EMT) of oral epithelial cells
○ inhibition of epithelial cell apoptosis
○ promotion of immune evasion
○ proliferation/invasion of tumor cells.

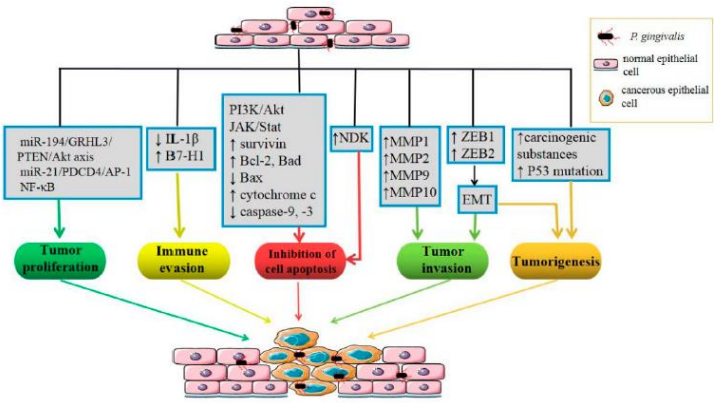

Figure 7: Cancer-associated processes in which *Porphyromonas gingivalis* may be implicated.

Diabetes

- *P. gingivalis* increases systemic inflammation, especially in adipose tissue, through the induction of endotoxemia, alteration of gut microbiota, an impaired regional adaptive immune response, resulting in insulin resistance.[22-24]
- A recent study by Tian 2020 indicated that *P. gingivalis* aggravated high-fat diet (HFD)-induced insulin resistance in mice via its biosynthesis of branched-chain amino acids, which activates the mammalian target of rapamycin and downstream genes, which leads to the dephosphorylation of insulin receptor substrate 1.[25]
- *P. gingivalis* loaded with gingipains and translocated to the liver in mice, leading to the attenuation of insulin sensitivity and inhibition of hepatic glycogen synthesis, partly by attenuating the Akt and GSK-3 pathway.[26]
- Ilievski 2017 in an experimental study gave oral administration of *P. gingivalis* induced the translocation of *P. gingivalis*/gingipains to the pancreas in mice, leading to significant changes in islet architecture and cell apoptosis, which may be involved in the development of prediabetes.[27]

Treponema denticola

- Gram negative, obligatory anaerobic bacteria.
- Virulence factors- Suppresses fibroblast proliferation, enhancement of collagen phagocytosis by gingival fibroblasts, and activation of both the classic and the alternative pathways of human complement, and evidently exacerbates the damage to the supporting periodontal tissues.[28]

Bacterial coaggregation and bacteria–host interactions:

- *T. denticola* interacts with *P. gingivalis* and *F. nucleatum*. This coaggregation likely plays a role in the progression of periodontal disease (biofilm formation), since Kigure et al reported that these two members of the red complex occurred physically related in the forming biofilm.[29]
- In a recent study, Hashimoto et al investigated the binding of *P. gingivalis* fimbriae to *T. denticola* dentilisin. *P. gingivalis* fimbriae mediate attachment to host cells, as well as participating in the coaggregation between several different plaque-forming bacterial species.[30]

Effects on host innate and immune mechanisms:

- Weinberg & Holt and Baehni et al showed that when human gingival fibroblasts exposed to *T. denticola* the fibroblasts underwent significant cytoskeletal rearrangement, characterized by cell rounding, the formation of surface blebs and detachment from the cell surface.[31]
- Several investigators compared the effect of *T. denticola* on the viability of both human epithelial cells and gingival fibroblasts; approximately 50% of the fibroblasts underwent an apoptotic process.[32]

Tannerella forsythia

- Gram negative, anaerobic fusiform organism.
- *T. forsythia* possesses a surface-layer (S-layer) consisting of serrated structural subunits (about 10 nm wide and 10 nm high) in either oblique or tetragonal lattices and lacks surface appendages such as fimbriae.
- The S-layer is composed of at least two high molecular weight glycoproteins of 220 and 210 kDa size encoded by the tfsA and tfsB genes, respectively.
- A unique O-linked oligosaccharide decorates the bacterium's cell surface proteins and was shown to modulate the host immune response.

- Friedrich et al 2016 investigated the biosynthesis of the nonulosonic acid (NulO) present at the terminal position of this glycan. (Figure 9)[33]

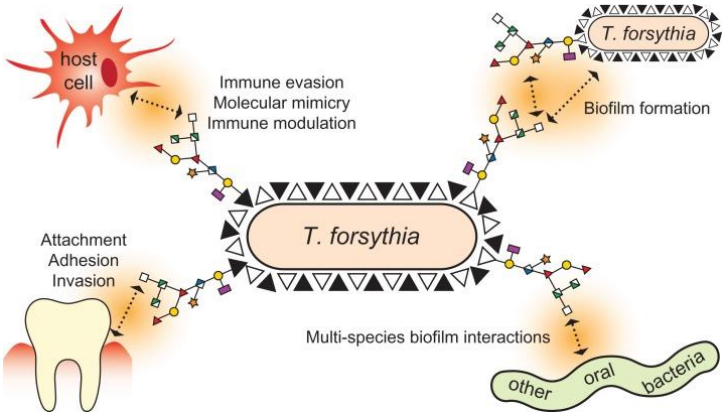

Figure 9: *Tannerella forsythia* strains display different cell-surface nonulosonic acids: biosynthetic pathway characterization and first insight into biological implications

Bacterial coaggregation and bacteria–host interactions:

- *T. forsythia* is an important and consistent member of the microbial biofilm at diseased periodontal sites. However, currently there is minimal evidence detailing its colonization strategy for interacting with other microorganisms and/host cells/tissues.
- The lrrA gene of *T. denticola* codes for the LrrA protein that binds to a portion of the T. forsythia leucine-rich repeat protein, BspA, through an N-terminal region, supporting an additional strategy for colonization and providing some molecular mechanism for the consortium relationship of these species.[34]

Proteinases and degradation of host tissue structure:

- *T. forsythia* produces an enzymatic peptidase activity that degrades benzoyl-DL arginine-naphthylamide (BANA), the activity of which appears related to sites of periodontal tissue destruction and was originally described as a trypsin-like protease.
- In a screen of a genomic library from *T. forsythia* ATCC 43037, Hughes et al were able to identify two glycosidase genes that encode for an a-Dglucosidase and an N-acetyl-b-glucosaminidase (sialidase). (Figure 10)[35]
- The latter enzyme exhibits some homology to a similar enzyme from *P. gingivalis* and could contribute to undermining basement membrane integrity in periodontal pockets.

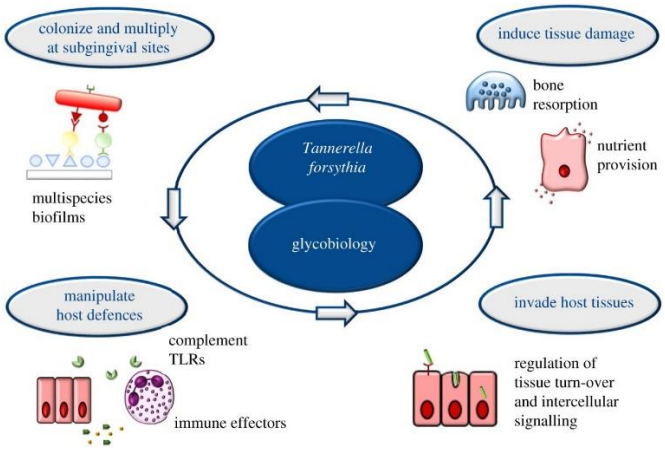

Figure 10: Glycobiology underpins the pathogenicity of the oral bacterium *Tannerella forsythia*. The unique protein-linked O-glycan of the bacterium was found to be involved in (i) the bacterium's establishment in oral plaque, (ii) manipulation of host defence mechanisms, (iii) adhesion to and invasion of host tissues and, eventually, (iv) tissue damage.

T. forsythia and apoptosis activity:

- In a recent study, Arakawa et al examined the effects of cell extracts from *T. forsythia* to induce cytolytic activity against HL-60 and other human leukemic cells.[36]
- Apoptotic inducing indicators:
  - loss of both mitochondrial membrane potential and membrane integrity
  - damage to the cell cytoplasmic membrane
  - DNA ladder formation
  - activation of caspase-3
- The effect of the *T. forsythia* cellular extracts on peripheral white blood cells and lymphocytes was also examined.
- Flow cytometry for annexins revealed when treated with culture supernatant, the levels of normal white blood cells and lymphocytes were approximately 2 and 8 times higher than those of the control cells, respectively, supporting the suggestion that both the *T. forsythia* culture supernatant and bacterial extract had the ability to induce apoptosis.[37]

T. forsythia and the murine abscess model:

- Yoneda et al have studied the effects of mixed infections of *P. gingivalis* and *T. forsythia* in a murine abscess model.
- While several other bacterial combinations studied in the murine abscess model resulted in tissue destruction, the combination of *P. gingivalis* and *T. forsythia* showed a synergistic effect on abscess formation. This coinfection with *P. gingivalis* and *T. forsythia* resulted in the formation of larger abscesses than did monoinfection with either species.
- This cooperative effect appeared to be the result of a synergism rather than an additive effect.[38]

Shortfalls- long-term challenges for developing an understanding of structure–function relation and dynamics in microbial communities (MCs):

The need to include evolutionary processes

- Traditionally, evolution has been ignored in ecological models, as it is assumed to occur only on long timescales. While this assumption might hold for animal and plant communities, ecological and evolutionary timescales can coincide in some MCs, because of their short generation times, large population sizes and high rates of gene transfer.[39]
- The intermixing of ecological and evolutionary dynamics is strikingly demonstrated by long-term growth experiments with *Escherichia coli* in glucose-limited chemostats. Here, genetic diversification produces two genotypes, which cross-feed; that is, it leads to a new ecological interaction. Functional diversification at the genome level is maintained by the novel ecological interaction and vice versa (Little et al, 2008).[40]

Community assembly and historical contingency

- Community assembly, or the mechanism by which a community forms, is a widely studied topic in macro-ecology, but has been relatively little addressed for MCs (Woodcock et al, 2007).[41]
- For some MCs it is known, however, that historical contingency—the order in which different species arrive in the community—can have a strong impact on community composition; examples include oral communities (Teles et al, 2012) and gut microbiota (David et al, 2014).[42]

The importance of spatial structure

- Indeed, densely packed aggregates, which may be free-floating or in the form of surface-attached biofilms, are believed to be the predominant mode of life for many microbes in the natural environment.
- Within these microbial aggregates, driving factors for spatial organisation include (i) metabolite gradients caused by consumption/production, diffusion (ii) physical adhesion and (iii) motility.[39]

IV. Future Directions And Conclusion:

Comprehending the impact of interbacterial interactions on the pathogenesis of periodontitis aids in the creation of innovative treatment approaches, including antagonist-based adherence inhibition, passive immunization, replacement therapy, virulence modulation through non-pathogenic bacterial level regulation, probiotics, and disruption of signalling mechanisms. The disruption of the harmonic relationship between the host and commensal microorganisms is considered to be an important factor for the development of oral pathologies. Certain organisms are antagonistic to periodontopathogens. With regard to the red complex, *Staphylococcus aureus* and *Streptococcus mutans* isolates inhibited the growth of *T. denticola* and *P. gingivalis*. *S. sanguinis*, *S.*

cristatus, S. salivarius, S. mitis, *Actinomyces naeslundii* inhibited the adhesion of standard *P. gingivalis* strains in vitro. *S. cristatus* arginine deiminase repressed FimA, a major subunit protein of the long fimbriae, and inhibited biofilm formation by *P. gingivalis*.[43]

The future of research in this area should direct some effort into moving from cataloguing the biofilm consortia towards defining the crucial mechanisms that underpin these purported in vivo pathogenic assets. This will likely require more creative use of animal models and more sophisticated human studies to critically evaluate the cause-and-effect nature of these relationships.

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