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> ONE MONTH, ONE PROTEIN <

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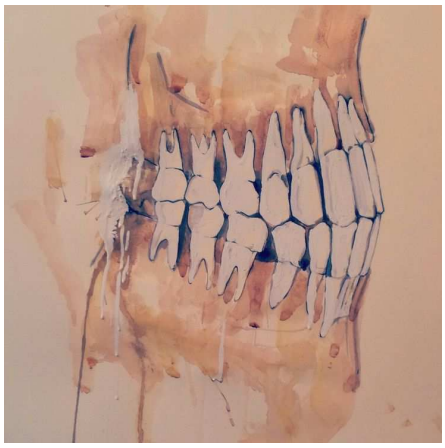
a loosening of habits

Vivienne Baillie Gerritsen

We are not alone. From the day we are born, we carry with us hordes of microorganisms which, if all is going well, live off us while giving something in return. This micro-universe which is an integral part of our physiology has been called the microbiome. In the recent years, scientists have demonstrated the importance a microbiome has on our overall health; how it can influence our well-being as it can be at the heart of a disease. Take our mouths for instance. A mouth is home to billions of microorganisms with whom we share our life on a daily basis. However, when the balance between them and us is perturbed, it can cause discomforts such as periodontal disease, also known as gum disease or periodontitis. Periodontal disease is probably the doing of a variety of microorganisms, but there is one bacterium that seems to have a major role in its development: *Porphyromonas gingivalis*. *P.gingivalis* has filaments – or fimbriae – that protrude from its outer membrane and help the bacterium adhere, among other things, to host cells. The molecular structure of fimbriae is gradually emerging, as are the roles of the proteins that are part of it.



watercolour, by Fayaz Adam Ibrahim

Courtesy of the artist

For many microorganisms, the mouth is a great place to be. Here is an environment that offers saliva to bathe in, whose temperature is not only warm but particularly stable – varying between 34 and 36°Celsius – and its pH, close to neutrality. These are ideal conditions in which to thrive. So much so that our mouths harbour a particularly rich microflora composed of fungi, mycoplasma, protozoa, bacteria and perhaps even viruses, that all live in relative harmony. However, when an imbalance of sorts occurs, then diseases such as caries and periodontitis appear. Scientists estimate that there are about six billion bacteria in our mouths, represented by over 700 species. The major pathogen for periodontitis is a bacterium known as *Porphyromonas gingivalis* to whom human mouths offer shelter. One of the triggering factors of periodontitis is a persistent biofilm that forms on our teeth and is brimming with bacteria. This results in an immune response, i.e. the production of molecules which in turn cause a local chemical imbalance. Inflammation of our gums ensues, and begins to affect the supporting tissue of our teeth, leading – in the worst scenario – to their loss. According to the World Health Organisation, 10 to 15% of the adult population suffers from periodontitis worldwide. In the US, one half of the population over 30 years of age suffer from the disease at different levels of severity.

In the past decades, much has been understood about the pathogenesis and natural history of periodontal diseases. From the 1930s up to the 1970s, bacteria had still not been identified as the pathogenic agents. The ongoing theory was one of ‘non-specificity’ where periodontitis was caused by a cocktail of microorganisms and not one in particular. In the late 1970s, however, it became obvious that periodontal diseases were caused by bacteria, the most pathogenic of which is *P.gingivalis*. *P.gingivalis* is an anaerobe bacterium that likes to wallow in the slim slit between our teeth and our gums. It is a black-pigmented bacterium – hence its name *Porphyromonas*, from the Greek ‘porphyro’ meaning purple, and ‘monas’ meaning unit – and produces many virulence factors that, if left to their own devices, will cause a tooth to lose its grip. One of the bacterium’s major virulence factors are its fimbriae.

Fimbriae are thin filamentous protrusions that are used as probes or anchors to interact with other cells. *P.gingivalis*' uses its fimbriae to adhere to host cells. Fimbriae are typically made of fibrous protein subunits: one or several tip subunits, structural subunits, and an anchor subunit – which is planted in the bacterium's membrane. Fimbriae are typically about 50Å wide, which is the width of an individual subunit, thus suggesting that the filaments are formed by a head-to-toe assembly of individual subunits. In *P.gingivalis*, there are two types of fimbriae: major fimbriae which can be impressively long (up to 1.6µm), and minor fimbriae that are far shorter (a maximum of 120nm). The major fimbriae have been extensively studied as they constitute the major virulence factor.

P.gingivalis' major fimbriae are composed of five different subunits – FimA, FimB, FimC, FimD and FimE – with specificities that make them either structural subunits, tip subunits or anchor subunits. Tip subunits are found at the distal end of fimbriae, while anchor subunits are found at its other end and are used to dock to the bacterium's membrane. Surprisingly, anchor subunits are the last subunits to be added and thus regulate fimbrium polymerization. Typically, fimbrium polymerization seems to follow a tip-to-base assembly involving a tip subunit to which is added a row of structural subunits, while an anchor subunit ends fimbrium extension.

On the molecular level, the role of each subunit is emerging. FimE is a tip subunit, has an adhesive role and is required for the assembly of subunits FimC and D. FimB is the anchor subunit and thus regulates fimbrium length. It has unique structural features, no doubt for its retention in the bacterial membrane. FimA, the major constituent of fimbriae, has been studied in most detail because it is proving to have a decisive role in *P.gingivalis* virulence. Its distribution is now known to be linked to environmental factors, human genetic predisposition and diseases such as obesity for example. Six FimA genotypes have been reported – types I-VI – though no distinction can be made with regards to morphological differences. Type I seems to be the most prevalent in *P.gingivalis* positive healthy adults. Type II seems to be the most prevalent in patients suffering from periodontitis. And types II and IV seem to be particularly aggressive, creating greater damage to tissues.

Much remains to be understood. Though *P.gingivalis* plays a huge part in periodontitis progression, there is little chance that it acts on its own, but with many other members of the microbiome. As such, a whole set of virulence factors from different bacteria are most probably acting in unison; unveiling each of these virulence factors is essential if effective therapies are to be developed, which will slow down, or indeed stop altogether, tissue destruction. In the same way, identifying the different genotypes will help to establish periodontal disease risk at the population level and fine-tune therapeutic approaches. A greater knowledge of fimbrial molecular architecture will also help to understand the interactions between host and microbe, and form a drug design basis for developing vaccines – something to look forward to when you know that, besides losing teeth, several studies have shown a possible connection between periodontitis and other human diseases such as cardiovascular disease.

Cross-references to UniProt

Major fimbrium subunit FimA type-1, *Porphyromonas gingivalis* : B2RH54
Major fimbrium anchoring subunit FimB, *Porphyromonas gingivalis* : A0PA81
Major fimbrium subunit FimC, *Porphyromonas gingivalis* : B2RH57
Major fimbrium tip subunit FimD, *Porphyromonas gingivalis* : B2RH58
Major fimbrium tip subunit FimE, *Porphyromonas gingivalis* : B2RH59

References

1. Yan How K., Peng Song K., Gan Chan K.
   Porphyromonas gingivalis: An overview of periodontopathic pathogen below the gum line
   Frontiers in Microbiology, doi: 10.3389/fmicb.2016.00053
   PMID: 26903954

2. Xu Q., Shoji J., Shibata S., Naito M., Sato K., Elsliger M.-A., Grant J.C., Axelrod H.L., Chiu H.-J., Farr C.L., Jaroszewski L., Knuth M.W., Deacon A.M., Godzik A., Lesley S.A., Curtis M.A., Nakayam K., Wilson I.A.
   A distinct type of pilus from the human microbiome
   Cell 165:690-703(2016)
   PMID: 27062925

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