Dr Justin Merritt, from the Oregon Health & Science University, studies disease-causing bacteria at mucosal sites in humans, especially in the mouth. His latest research on bacteria that cause tooth decay offers interesting and very novel insights into the processes that can trigger disease.

The human mouth harbours more than 700 unique microorganisms that live on the teeth and oral mucosa. This so-called oral microbiome performs diverse functions for its host, for instance in food digestion, detoxification of environmental chemicals or immune responses. An imbalanced microbiome (termed dysbiosis) can have strong effects on health, with one example of this being dental caries (tooth decay). This is a major health problem worldwide, affecting 60–90% of schoolchildren and more than 95% of adults. In cases of advanced dental caries, few alternative options exist other than removing the tooth completely.

**BACTERIA CAUSE TOOTH DECAY**

Tooth decay is caused by dental plaque, which mainly consists of bacterial biofilm, forming on and around the teeth. A biofilm is an aggregate of microorganisms and other (secreted) substances that can adhere to surfaces. One major contributor to this biofilm forming on teeth is a bacterium called Streptococcus mutans (S. mutans). S. mutans has specialised receptors that allow it to stick more readily to the tooth surface and it can grow on a wide variety of carbohydrates. However, in the presence of sucrose (table sugar), it starts converting this sugar type into long, sticky polymers called glucans, which adhere to teeth. On its surface, S. mutans has proteins that bind glucan (glucan-binding proteins or Gbp) thereby greatly facilitating its biofilm formation and the resulting dental plaque.

Sucrose is the only sugar that can be metabolised to form these sticky molecules. However, S. mutans can also catabolise sucrose and many other sugars for energy, producing lactic acid as a by-product. This creates an acidic environment in the mouth, leading to the dissolution of the calcium-rich tooth enamel. Simultaneously, S. mutans thrives in this acidic environment, outcompeting numerous other microorganisms that are not so tolerant of the acidity. In the long run, this allows S. mutans to dominate within the biofilm.

**What is it that makes Streptococcus mutans so successful at colonising the mouth, compared to all other bacterial species sharing its habitat?**
or oral microbiome, leading to tooth decay. Consuming sugar therefore aids S. mutans in creating the perfect conditions for its survival and success.

However, what is it that makes S. mutans so successful at triggering tooth decay, compared to all other bacterial species sharing its habitat? How exactly does it regulate biofilm formation and could that be prevented? These are the key questions that Dr Merritt and his team have asked in their bid to improve oral health.

HOW BACTERIA BECOME HARMFUL
Bacteria can adjust to their environment through regulatory networks, which allow them to regulate the activity of their genes. In this way, they can quickly respond to changes in the environment such as stress or particular nutrient availability. This is one of the reasons why bacteria can live in so many different niches on earth and how initially harmless bacteria can cause diseases. Dr Merritt and his team at the Oregon Health & Science University have discovered pathways within bacteria that cause oral diseases, such as tooth decay. In one branch of their research, the Merritt team shed light on a peculiar regulatory system that can control many disease-associated processes in S. mutans.

FINING UNEXPECTED ANSWERS
The Merritt lab discovered a key gene in the disease-causing process — the irvA gene. Despite its name, the irvA gene is not active under normal environmental conditions, meaning it produces no mRNA. The reason for this is that a protein called GbpC in S. mutans blocks RNase degradation of the irvA mRNA, thus preventing the irvA gene from being translated into a protein. The Merritt lab then hypothesised that if they could find a way to block the action of GbpC, they could then activate the irvA gene to produce a protein that would help the bacteria to become more harmful.

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WHAT MAKES STREPTOCOCCUS MUTANS AN INTERESTING MODEL FOR STUDYING DISEASES AT MACROSCALE SITES IN GENERAL AND GENE-REGULATORY PATHWAYS IN PARTICULAR?
S. mutans is a pathogenic species that causes dental caries and contributes to periodontal disease. It is known for its ability to form biofilms and produce a variety of virulence factors, including enzymes that degrade host extracellular matrix components and adhesins that facilitate colonization of tooth surfaces. The irvA gene, which encodes an iron-regulated surface protein, plays a crucial role in virulence. The irvA gene is induced by iron limitation and its expression is controlled by the regulation system, which is activated by iron availability. This system is important for the adhesion and colonization of S. mutans on tooth surfaces, allowing the bacteria to establish a stable foothold and resist host defenses.

BROADENING THE VIEW
Bacteria have a vast variety of gene regulatory strategies even among similar species. The Merritt lab is dedicated to exploring completely unknown regulatory mechanisms in harmful bacteria. One example of this is a new mechanism they have discovered in S. mutans, termed the LytTR regulatory systems (LRS). This system appears to be involved in both the initiation of S. mutans cell death as well as its secretion of toxic substances that prevent growth of competing bacteria. Studying disease-related processes in harmful bacteria will not only advance our understanding of those microorganisms, but could ultimately deliver novel therapeutic targets to tackle illnesses.

We are interested in finding the Achilles’ heel of particular species for targeted therapeutics

WHAT LED YOU TO STUDY GENETIC REGULATORY MECHANISMS IN PATHOGENIC BACTERIA?
I have always been fascinated by pathogenesis, but never imagined myself devoting so much effort to the study of gene regulation. However, this changed dramatically during my graduate studies in S. mutans. Here was an organism that exists as part of the normal flora in virtually all adults and yet it possesses a conditional ability to trigger disease. This seemed so counterintuitive and ultimately piqued my curiosity to understand how members of the flora like S. mutans regulate processes that can result in pathology to the host.

WHAT MAKES STREPTOCOCCUS MUTANS AN INTERESTING MODEL FOR STUDYING DISEASES AT MACROSCALE SITES IN GENERAL AND GENE-REGULATORY PATHWAYS IN PARTICULAR?
There are a couple of qualities of S. mutans that I think make it a wonderful model organism. Firstly, it is an obligate member of the human microbiome. The human oral cavity is its only known natural habitat and therefore it is a relevant model organism for studies of human dysbiotic disease. Secondly, S. mutans is a relatively small genome and has an amazingly robust genetic system. It literally takes only several days from start to finish to create all types of mutant strains. Consequently, we are always willing to test unconventional ideas.