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Cross-respiration between oral bacteria leads to worse infections

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Researchers determined that two bacterial species commonly found in the human mouth and in abscesses, cooperate to make the pathogenic bacterium, *Aggregatibacter actinomycetemcomitans*, more infectious. Key to the cooperation is that the harmless partner provides the pathogen with an oxygen-rich environment that helps it flourish. The findings, published this week in *mBio*, an online open-access journal of the American Society for Microbiology, could lead to better ways to fight the majority of bacterial infections that play out within complex communities of bacteria.

"Historically, we tend to think of infections as caused by a single organism, but many diseases are caused by multiple species," explains Apollo Stacy, a graduate student in Molecular Biosciences at The University of Texas at Austin and lead author of the study. "We wanted to ask, what effect do these multiple species have on each other during infections?"

Working with professor Marvin Whiteley, Stacy and his colleagues used a laboratory model of two oral bacteria, *A. actinomycetemcomitans* (Aa) and *Streptococcus gordonii* (Strep), which live together in human mouths and are also found in abscesses in the lungs and brain. Aa is one of the main culprits of periodontal disease and can also travel to and infect heart valves. However, the Strep species is considered commensal and does not generally cause problems for its human host. Previous work by Whiteley's group had shown that these two bacteria alone do not cause severe disease, but together they were highly infectious.

"In this study, we asked what are all the genes that Aa needs to survive with and without the commensal Strep bacteria?" says Stacy.

To do that, Stacy first made mutant strains of Aa, in which each gene in its genome had been disrupted by pieces of DNA called transposons (Tn). Next, he placed the Aa mutants alone or with Strep into abscesses on the thighs of mice. Then, using a technique called Tn-Seq, he cataloged which genes were required for Aa survival either alone or with its Strep partner.

The first list revealed which processes or functions Aa needs to survive alone. Comparing that to the second list told Stacy which of those processes Strep's presence could compensate for. He discovered that when Strep is present it shifts Aa from an anaerobic metabolism to a more aerobic metabolism.

"Strep is increasing the availability of oxygen in the infection," says Stacy. "And that's important because Aa can use oxygen to make more energy and grow better."

Other researchers in the Whiteley lab had already shown that Strep produces a waste product, L-lactate, which turns out to be one of Aa's favorite foods. Furthermore, Aa must be able to use the L-lactate made by Strep, a process known as cross-feeding, for the two species to cause severe infection. However, Aa cannot effectively use L-lactate as a food source unless there is enough oxygen around for aerobic respiration. Stacy's findings provide the key connection.

"It's pretty amazing that these bugs have evolved these interactions," notes Whiteley. "Not only is Strep going to feed Aa, but it gives it what it needs, the knife and fork, to eat it, too." By providing oxygen to Aa, a process the team dubbed cross-respiration, Strep allows the pathogen to grow to much higher levels, resulting in a worse infection.

"Now we are starting to understand that a lot of modern infections are caused by a community of organisms," says Whiteley, director of the John Ring LaMontagne Center for Infectious Disease in Austin. "These two bacteria have evolved to live together, so they give us a way to explore these highly intricate relationships."

Provided by American Society for Microbiology

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