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COMMENTARY

Iron-Mediated Control of *Pseudomonas aeruginosa-Staphylococcus aureus* Interactions in the Cystic Fibrosis Lung

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Communication is an important factor for bacterial survival, growth, and persistence. Much work has examined both inter- and intraspecies interactions and their effects on virulence. Now, researchers have begun to explore the ways in which host-modulated factors can impact bacterial interactions and subsequently affect patient outcomes. In this issue, two papers discuss how the host environment alters interactions between the pathogens *Pseudomonas aeruginosa* and *Staphylococcus aureus*, largely in the context of cystic fibrosis.

MICROSCOPIC SOCIETY

Just as macroscopic creatures must communicate in order to survive and thrive in the macroscopic world, so too do microorganisms "talk" with each other at the microscopic level. Instead of audio calls and visual cues, bacteria instead rely on the language of signaling molecules. As this method of cellular communication involves large numbers of cells coming to a "consensus" on subsequent group actions, researchers dubbed this behavior "quorum sensing." Classical quorum sensing has been largely focused on autoinduction, wherein a single species produces a signaling molecule unable to induce gene expression until the population grows to a threshold concentration. This phenomenon was first characterized in bioluminescence produced by *Aliivibrio* (formerly *Vibrio*) *fischeri* and has since been identified in a variety of clinically relevant human pathogens. More recent cell-cell communication research has revealed that other kinds of molecules, including metabolites and nutrients present in the growth environment, serve as cues that impact bacterial interactions (1–3). Additionally, interactions between different species have been found to occur in polymicrobial infections where they often form synergistic, virulence-enhancing relationships (4).

MICRONUTRIENTS/MICROORGANISMS

As pathogenic bacteria prey upon their host as a living source of nourishment, it is not surprising that available nutrients in the host environment can have a major impact on microbial gene expression. It also follows, then, that such an important regulatory factor might also affect the ways in which bacteria interact within the host. Therefore, a key question is whether the *in vitro* systems primarily used to study microbial interactions provide relevant insights into the ways in which microbes interact in the host.

This issue of the *Journal of Bacteriology* features two papers that explore the impact of host-provided nutrients further in the context of iron's ability to modulate *Pseudomonas aeruginosa*/*Staphylococcus aureus* interactions in the cystic fibrosis (CF) lung. Iron is a micronutrient vital for bacterial growth but relatively scarce in most infection sites, acting as a limiting factor (5). In contrast, iron levels have been found to be high in CF sputum and correlate negatively with patient outcomes (6). Additionally, pathogen lung colonization in CF patients displays a conserved pattern of succession, with *S. aureus* predominating early on before being displaced by *P. aeruginosa* (7). Although it has been previously demonstrated that *P. aeruginosa* harvests iron via killing of *S. aureus* (8), the exact dynamics of this hostile takeover remain unclear. Here, Filkins et al. (7) put forward an interesting hypothesis regarding progressional acquisition, along with supporting *in vitro* experiments. Based on gene expression data from bacteria cocultured on CF bronchiolar epithelial cells, these researchers discovered that the presence of *P. aeruginosa* drives *S. aureus* toward fermentative metabolism. This feat is accomplished via sabotaging *S. aureus*'s aerobic metabolism with a combination of factors, including the excretion of the potent staphylococcal respiratory chain inhibitor 2-heptyl-4-hydroxyquinoline *N*-oxide along with iron-scavenging siderophores. The shift proves detrimental to *S. aureus* growth rates and fitness, while these conditions are more than hospitable for *P. aeruginosa*, which preferentially feeds on the lactate that its victim produces (7). Relevant to this model, Nguyen et al. also demonstrate that free iron levels regulate *P. aeruginosa*'s inhibition of *S. aureus* in coculture (9). This group had previously shown that *P. aeruginosa*'s production of specific 2-alkyl-4(1*H*)-quinolones, antimicrobial compounds capable of killing *S. aureus*, is increased in low-iron environments (5). Here, they further demonstrate that this particular environmentally mediated form of bacterial cross-species inhibition occurs over a variety of *P. aeruginosa* strains, including those isolated from CF patients. Additionally, when *P. aeruginosa* is grown in monoculture, high iron levels are able to suppress production of the antimicrobials that target *S. aureus*. Moreover, when these two bacteria are grown together in coculture, iron's ability to suppress antimicrobial production is restored to CF isolates previously thought to be defective for this activity. These findings suggest that bacterial iron-regulated pathways become altered in polymicrobial infections and may contribute significantly to pathogenesis (9).

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HOST-PATHOGEN-PATHOGEN INTERACTIONS

As antibiotic resistance rates skyrocket and the threat of a postantibiotic era looms, the importance of alternative treatment modalities in clinical microbiology is clear. This is especially relevant in the context of polymicrobial infections, which display inherent resistance to traditional antibiotics (4). One promising method may be the development of therapeutics that target specific bacterial virulence factors, which have been proposed to reduce morbidity and mortality without promoting antimicrobial resistance through direct fitness selection. However, in order for these targeted therapies to become a reality, much needs to be learned regarding the exact mechanisms leading to virulence and poor patient outcomes. The two papers presented here give some of the first evidence regarding how host micronutrients impact interactions of two prevalent CF pathogens and provide insights into the mechanism controlling *P. aeruginosa*-mediated succession in the CF lung. The control of such host-modulated bacterial interactions is thus a largely unexplored field that may one day prove a fertile ground for medical innovation.

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