Bone apetit: How bacteria eat bone to sustain invasive infection

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Researchers from Vanderbilt University Medical Center have determined the metabolic pathway that *Staphylococcus aureus* use to survive in bones. Invasive *S. aureus* infections frequently occur in the bone and are notoriously resistant to antimicrobial therapy. The research is presented at ASM Microbe, the annual meeting of the American Society for Microbiology, held from June 7th to June 11th in Atlanta, Georgia.

"We found that S. aureus needs to synthesize certain amino acids itself, rather than relying on the host nutrients," said Jim Cassat, M.D., Ph.D., Associate Director, Vanderbilt Institute for Infection, Immunology, and Inflammation, the lead study author. The researchers focused on how S. aureus procures essential cellular building blocks from the host. All forms of life need up to 13 essential metabolites that are used to fuel cellular proliferation and form macromolecules like protein, nucleic acids, and lipids.

"Because these particular amino acid biosynthesis pathways are found only in microbes and plants, they might be particularly attractive targets for the development of new antimicrobial compounds," said Dr. Cassat. Collectively, this work sheds light on how bacterial pathogens obtain crucial nutrients from the host during invasive infection.

Staphylococcus aureus is one of the most important human bacterial pathogens, in part due to the ability to infect nearly every organ and cause significant tissue destruction. This tissue destruction makes

invasive staphylococcal infections particularly difficult to treat, as antibiotic penetration into the infection site is limited.

One of the most frequently affected sites during invasive S. aureus infection is bone, which is paradoxical when considering the tissue properties of the skeleton. Specifically, bone has low oxygen concentrations and is constantly being destroyed and reformed by osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells). Bone infection (osteomyelitis) is notoriously recalcitrant to antimicrobial therapy and causes substantial morbidity.

"For this reason, many patients with bone infection require surgeries to remove infected or damaged bone," said Dr. Cassat, "Our lab studies osteomyelitis with the goal of defining how bacterial pathogens survive in such a dynamic environment, how bone cells sense and respond to bacterial pathogens, and how immune responses crosstalk with bone turnover."

To test how *S. aureus* obtains these critical nutrients during osteomyelitis, the researchers used a large panel of bacterial mutants that are deficient in various metabolic pathways. They tested these mutants in a murine osteomyelitis model to determine which pathways contribute to survival in bone. To supplement these studies, the team developed an ex vivo assay in which Staph is forced to use bone as a sole nutrient source. These approaches revealed specific metabolic pathways that are absolutely necessary for bacterial survival in bone.

In previous studies, Dr. Cassat and the researchers used a special technique called "transposon sequencing" or "TnSeq" to identify S. aureus genes that contribute to osteomyelitis. However, these experiments involve a large number of bacterial mutants that may compete with one another, or perhaps even share nutrients during infection. Therefore, it can be difficult to understand exactly which

metabolic pathways are important for bone infection using only TnSeq.

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