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Interactions of Staphylococcus aureus with Osteoclasts and Osteoblasts

Emily Goering
Washington University in St. Louis

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Mentor: Deborah Veis

Osteomyelitis is infection-driven inflammatory disease of the bone primarily caused by *Staphylococcus aureus* (*S. aureus*), which results in pathological bone loss. Historically, *S. aureus* was thought to be an extracellular pathogen, yet new research has shown that *S. aureus* is internalized into many cells. To investigate the behavior of intracellular *S. aureus* in bone cells, we used an in vitro gentamicin protection assay to examine intracellular bacterial survival in osteoblasts, the cells that build bone, and osteoclasts, the cells that destroy bone, over several time points. We found that *S. aureus* persists in differentiated osteoblasts but is unable to replicate over the course of infection. However, in differentiated osteoclasts intracellular *S. aureus* is able to proliferate over time, whereas it is eliminated in osteoclast precursors. We next examined the intracellular location of *S. aureus* in osteoclasts to determine how *S. aureus* avoids elimination and replicates in these cells. We used fluorescence-based confocal microscopic imaging of the fluorescent dye Lysotracker, which marks acidified intracellular vesicles, with GFP-labelled *S. aureus* during *in vitro* infection of osteoclasts. We found that intracellular *S. aureus* is localized to lysosomes early in infection but not late in infection in osteoclasts, indicating a role for lysosomes in mediating clearance of intracellular *S. aureus*. Finally, to determine if the NLRP3 inflammasome affects intracellular *S. aureus* pathogenesis in osteoclasts, we utilized NLRP3 knockout osteoclasts in the *in vitro* gentamicin protection assay. Initial results suggest that loss of NLRP3 results in increased levels of intracellular bacteria over time, suggesting a role for the NLRP3 inflammasome in limiting bacterial growth in osteoclasts. Overall, the ability of *S. aureus* to persist within osteoblasts and osteoclasts and avoid progression of endocytic vesicles to lysosomes may provide a niche in which *S. aureus* can escape professional phagocytes and extracellular antibiotics, mediating the pathogenesis of osteomyelitis.