Substance P augments the inflammatory immune response of resident bone cells during staphylococcal osteomyelitis

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Osteomyelitis is a serious infection of bone that is associated with progressive inflammatory tissue damage. *Staphylococcus aureus (SA)* is the principal causative agent of osteomyelitis and can enter bone via the bloodstream or surrounding tissues following injury or surgery, resulting in disease that is often refractory to treatment such as debridement or antibiotic treatment. Bone-forming osteoblasts and bone-resorption osteoclasts have increasingly been recognized to play an important role in the initiation and progression of detrimental inflammation at sites of SA infection due to the production of inflammatory mediators. Our lab and others have shown that osteoblasts and osteoclasts release factors that promote leukocyte recruitment and osteoclastogenesis following bacterial challenge, further promoting the dysregulated bone homeostasis and inflammation observed during staphylococcal osteomyelitis. Additionally, we have previously described elevated levels of proinflammatory cytokines and osteoclastogenic factors by SA-infected osteoblasts and osteoclasts following the introduction of the neuropeptide substance P (SP). SP has a known role in nociception and neuroinflammation and interacts preferentially with neurokinin 1 receptor (NK1R) expressed by osteoblasts and osteoclasts. We hypothesize that SP augments the inflammation and dysregulated bone remodeling driven by resident bone cells during staphylococcal osteomyelitis and can be a potential target for therapeutic intervention. In the present study, we describe elevated production of neutrophil chemoattractants by SA-challenged osteoclasts in the presence of SP. Interestingly, we have demonstrated that the introduction of a pharmalogical inhibitor of NK1R, aprepitant, reduces the observed SP-induced augmentation by SA-infected osteoblasts and osteoclasts in vitro. Importantly, we have also demonstrated reduced levels of pro-inflammatory cytokines and chemokines in the bone tissue following prophylactic treatment with aprepitant in a murine model of post-traumatic staphylococcal osteomyelitis. As such, these studies demonstrate that SP augments the production of inflammatory mediators by SA-infected resident bone cells and suggests the therapeutic potential for aprepitant to attenuate SP-induced augmentation during staphylococcal osteomyelitis.