RIG-I and cGAS mediate the antimicrobial and inflammatory responses of primary murine osteoblasts and osteoclasts to *Staphylococcus aureus*.

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Staphylococcus aureus is the primary causative agent of osteomyelitis. It is now apparent that osteoblasts and osteoclasts play a significant role in the pathogenesis of such infections. Their responses can be protective or exacerbate inflammatory bone loss, mediated by the recognition of microbial motifs by various host receptors. We have reported that osteoblasts respond to *S. aureus* challenge, producing type I interferons, which can reduce the number of viable bacteria harbored within infected cells. Here, we demonstrate that *S. aureus* viability and invasion is necessary for maximal inflammatory cytokine and type I interferon responses of osteoblasts and osteoclasts. Importantly, we show that bone cells constitutively express the cytosolic nucleic acid sensors, retinoic acid inducible gene-I (RIG-I) and cyclic GMP-AMP synthase (cGAS) and demonstrate their upregulation following *S. aureus* invasion. RIG-I and cGAS functional status in bone cells was confirmed by showing that specific ligands for each can elevate their expression and induce cytokine responses. We have verified the specificity of such responses and have begun to establish the biological significance of RIG-I and cGAS-mediated bone cell responses with the demonstration that their attenuation increases *S. aureus* burden in infected cells, suggesting a potentially protective role for these sensors in osteomyelitis.

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