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Inhibition of lipopolysaccharide - induced osteoclast formation and bone resorption in vitro and in vivo by cysteine proteinase inhibitors

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Abstract

Inflammation - induced bone destruction is a major treatment target in many inflammatory skeletal diseases. The aim of this study was to investigate if the cysteine proteinase inhibitors cystatin C, fungal cysteine proteinase inhibitor (E - 64), and *N* - benzyloxycarbonyl - arginyl - leucyl - valyl - glycyl - diazomethane acetate (Z - RLVG - CHN_2) can inhibit LPS - induced osteoclast formation. Mouse bone marrow macrophages (BMMs) were isolated and primed with receptor activator of NF - κ B ligand (RANKL) for 24 h, followed by stimulation with LPS, with and without inhibitors. Adult mice were injected locally with LPS and then treated with E - 64 and osteoclast formation assessed by the number of cathepsin K^+ multinucleated cells. Cystatin C inhibited LPS - induced osteoclast formation time and concentration dependently (IC_{50} = 0.3 μ M). The effect was associated with decreased mRNA and protein expression of tartrate - resistant acid phosphatase (TRAP) and cathepsin K and of the osteoclastogenic transcription factors c - Fos and NFATc1. LPS - induced osteoclast formation on bone slices was also inhibited by cystatin C, resulting in decreased pit formation and release of bone matrix proteins. Similar data were obtained with E - 64 and Z - RLVG - CHN_2. Cystatin C was internalized in BMMs stimulated by LPS but not in unstimulated BMMs. Osteoclast formation induced by LPS was dependent on TNF - α, and the 3 inhibitors abolished LPS - induced TNF superfamily 2 (gene encoding TNF - α; *Tnfsf2*) mRNA expression without affecting *Il1b*, *Il6*, or oncostatin M (*Osm*) expression. Formation of osteoclasts in the skull bones after local LPS stimulation was inhibited by E - 64. It is concluded that cysteine proteinase inhibitors effectively inhibit LPS - induced osteoclast formation in vivo and in vitro by inhibition of TNF - α expression. The targeting of cysteine proteinases might represent a novel treatment modality for prevention of inflammatory bone loss.