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TOPIC: ROLE OF TNF AND IL-1 IN OSTEOCLAST FORMATION AND FUNCTION

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Excessive osteoclastic bone resorption results in osteoporosis and destroys joints of rheumatoid patients. It is induced by pro-inflammatory cytokines, such as RANKL, TNF and IL-1, but of these only RANKL is required for osteoclastogenesis during embryonic development. We have found that TNF and IL-1 induce osteoclast formation independent of RANKL/RANK signaling when c-Fos or NFAT 1 or 2 are force-expressed in NF-kB-deficient osteoclast precursors. NF-kB mediates these effects in wt osteoclast precursors initially through c-Fos and later through NFAT 1 or 2. TNF and IL-1 also increase c-Fos and their own expression in vitro and of c-Fos in vivo in osteoclasts. The resorption they induce is enhanced by increased c-Fos expression in osteoclasts. We propose that TNF and IL-1 induce an NF-kB -dependent vicious cycle in which their expression in inflammation induces osteoclast formation, which promotes aggressive bone resorption and enhances osteoclast expression of these cytokines to up-regulate the cycle. PTH +/- IL-6 which are elevated in CKD patients does not have this direct effect on osteoclast precursors when c-Fos is forced expressed in osteoclast precursors. However, transient or sustained increases in TNF or IL-1 in CKD patients could potentially induce bone loss by stimulating osteoclastogenesis through this mechanism. We have also found that TNF, but not IL-1, induces Smurf1 expression leading to degradation of Runx2 in osteoblasts resulting in reduced ALK Phos expression and decreased mineralizing nodule formation in vitro. Thus, TNF could induce bone loss by stimulating osteoclasts and inhibiting osteoblast function.