Receptor activator of NF-κB ligand (RANKL) plays a critical role in osteoclast differentiation and osteoclastic bone resorption. To understand the molecular mechanisms by which RANKL controls osteoclastogenesis, in this study, we investigated the role of JNK/c-Jun signaling in RANKL-regulated osteoclastogenesis. We found that the transgenic mice expressing dominant-negative c-Jun specifically in osteoclast lineage show osteopetrotic phenotype associated with impaired osteoclast development (Fig. 1). Blockade of JNK/c-Jun signaling using siRNA technology and dominant-negative approach diminished RANKL-dependent osteoclast differentiation in vitro (Fig. 2). Interestingly, RANKL/TRAF6/c-Jun signaling is implicated in activation of NFAT family and induction of NFAT2 expression. Furthermore, introduction of constitutively-active NFAT1 failed to promote osteoclast differentiation of spleen cells isolated from the dominant-negative c-Jun transgenic mice (Fig. 3). Our results indicated that JNK/c-Jun signaling is essential for regulation of NFAT family that is critical for RANKL-regulated osteoclast differentiation.

Critical Roles of c-Jun Signaling in Regulation of NFAT Family and RANKL-regulated Osteoclast Differentiation

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Autophagy Defends Cells against Invading Group A Streptococcus

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Macrophagy, commonly referred to simply as autophagy, mediates the bulk degradation of cytoplasmic components in eukaryotic cells. Degradation of exogenous materials, on the other hand, is mediated by endocytosis or phagocytosis. During autophagy, regions of cytoplasm and organelles are engulfed by autophagosomes, and then they eventually fuse with lysosomes for the non-selective degradation.

Streptococcus pyogenes (also known as group A Streptococcus, GAS) is the etiological agent for a diverse collection of human diseases. Although GAS can effectively attach to and invade pharyngeal and skin epithelial cells, the fate of invaded GAS into host cells has not clearly understood. We found that intracellularly invaded GAS was selectively acquired by the autophagosome-like compartments and degraded by fusion with lysosomes in non-phagocytic cells (Fig. 1). In the autophagosome formation-deficient Atg5−/− cells, such compartments were not formed and the number of intracellular GAS markedly increased. Our results indicate that the autophagic machinery is not only for degradation of subcellular components, but also for a second security system against the intracellular pathogens (Fig. 2).