Alpha-lipoic acid suppresses osteoclastogenesis despite increasing the receptor activator of nuclear factor kappaB ligand/osteoprotegerin ratio in human bone marrow stromal cells.
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Abstract
Growing evidence has shown a biochemical link between increased oxidative stress and reduced bone density. Although alpha-lipoic acid (alpha-LA) has been shown to act as a thiol antioxidant, its effect on bone cells has not been determined. Using proteomic analysis, we identified six differentially expressed proteins in the conditioned media of alpha-LA-treated human bone marrow stromal cell line (HS-5). One of these proteins, receptor activator of nuclear factor kappaB ligand (RANKL), was significantly up-regulated, as confirmed by immunoblotting with anti-RANKL antibody. ELISA showed that alpha-LA stimulated RANKL production in cellular extracts (membranous RANKL) about 5-fold and in conditioned medium (soluble RANKL) about 23-fold, but had no effect on osteoprotegerin (OPG) secretion. Despite increasing the RANKL/OPG ratio, alpha-LA showed a dose-dependent suppression of osteoclastogenesis, both in a coculture system of mouse bone marrow cells and osteoblasts and in a mouse bone marrow cell culture system, and reduced bone resorption in a dose-dependent manner. In addition, alpha-LA-induced soluble RANKL was not inhibited by matrix metalloprotease inhibitors, indicating that soluble RANKL is produced by alpha-LA without any posttranslational processing. In contrast, alpha-LA had no significant effect on the proliferation and differentiation of HS-5 cells. These results suggest that alpha-LA suppresses osteoclastogenesis by directly inhibiting RANKL-RANK mediated signals, not by mediating cellular RANKL production. In addition, our findings indicate that alpha-LA-induced soluble RANKL is not produced by shedding of membranous RANKL.
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