

Dimethyl fumarate prevents osteoclastogenesis by decreasing NFATc1 expression, inhibiting of erk and p38 MAPK phosphorylation, and suppressing of HMGB1 release.

Abstract

Osteoclasts are multinucleated bone-resorbing cells derived from monocyte/macrophage progenitor cells. Excessive formation and resorbing activities of osteoclasts are involved in the bone-destructive pathologies of rheumatoid arthritis and osteoporosis. Recently, it has been found that nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor for anti-oxidative stress genes, functions in osteoclastogenesis. Dimethyl fumarate (DMF) is a potent activator of Nrf2 and has been shown to inhibit osteoclastogenesis. Here, we investigated the mechanisms of this inhibition by examining the activation of several signalling pathways during the differentiation of bone marrow-derived macrophages into osteoclasts. DMF inhibited the differentiation of osteoclasts in a dose-dependent manner and suppressed the bone-resorbing activity of osteoclasts. DMF treatment decreased the expression of nuclear factor of activated T-cells cytoplasmic-1, and significantly decreased phosphorylation of extracellular signal-regulated kinase and p38 mitogen-activated protein kinase in osteoclasts. We also found that DMF inhibited the extracellular release of high mobility group box 1, associated with an up-regulation of heme oxygenase-1, likely mediated through Nrf2 activation. Our results indicate that DMF inhibits osteoclast differentiation through multiple pathways.