DNA methyltransferase 3a regulates osteoclast differentiation by coupling to an S-adenosylmethionine– producing metabolic pathway

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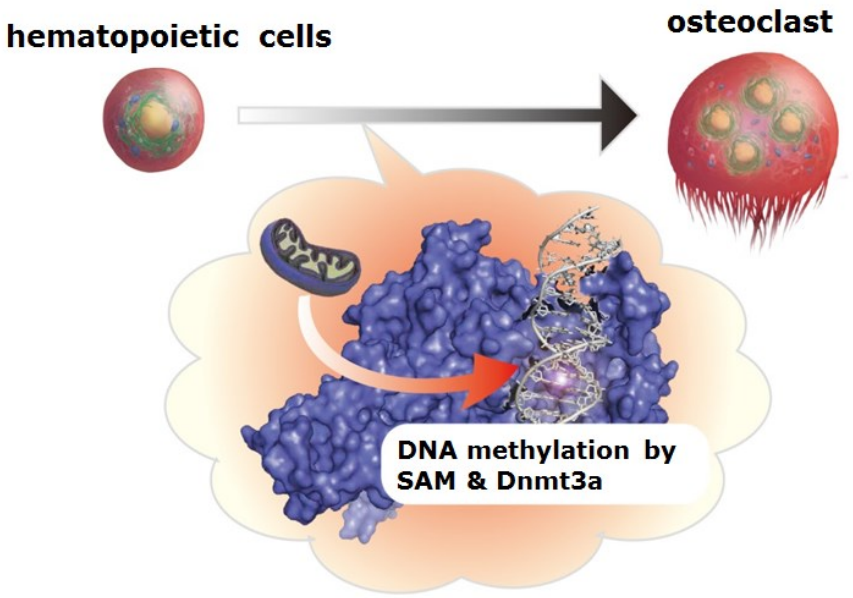
Keywords

Osteoclast, Differentiation, Cellular metabolism, Epigenetics

Abstract

Metabolic reprogramming occurs in response to the cellular environment to mediate differentiation, although the fundamental mechanisms linking metabolic processes to differentiation programs remain to be elucidated. During osteoclast differentiation, a shift toward oxidative metabolic processes occurs3. In this study we identified the de novo DNA methyltransferase Dnmt3a to be a transcription factor that couples these metabolic changes to osteoclast differentiation. Receptor activator of nuclear factor-κB ligand (RANKL) is an essential cytokine for osteoclastogenesis that induces a metabolic shift toward oxidative metabolic processes, accompanied by an increase in S-adenosyl methionine (SAM) production. We found that SAM-mediated DNA methylation by Dnmt3a regulates osteoclastogenesis via epigenetic repression of the anti-osteoclastogenic gene and that Dnmt3a-deficient osteoclast precursor cells do not undergo osteoclast differentiation efficiently. The importance of Dnmt3a in bone homeostasis was underscored by the observation that mice with an osteoclast-specific deficiency in Dnmt3a exhibit a high bone mass phenotype due to a smaller number of osteoclasts.

Furthermore, inhibition of DNA methylation by theaflavin derivative abrogated bone loss in models of osteoporosis. Thus, this study reveals the role of epigenetic processes in the regulation of cellular metabolism and differentiation, which may provide the molecular basis for a new therapeutic strategy.



Conceptual figure

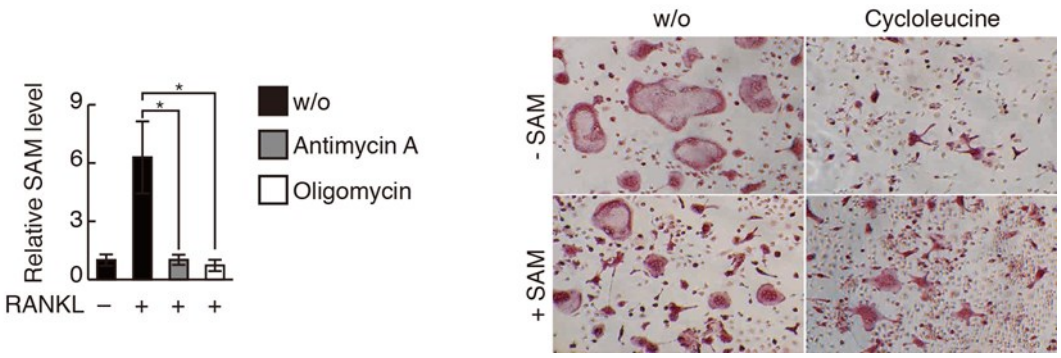


Figure 1. Effect of the respiratory chain inhibitors antimycin A (100 nM) and oligomycin (1 nM) on Irf8 expression and SAM levels in BMMs stimulated with or without RANKL.

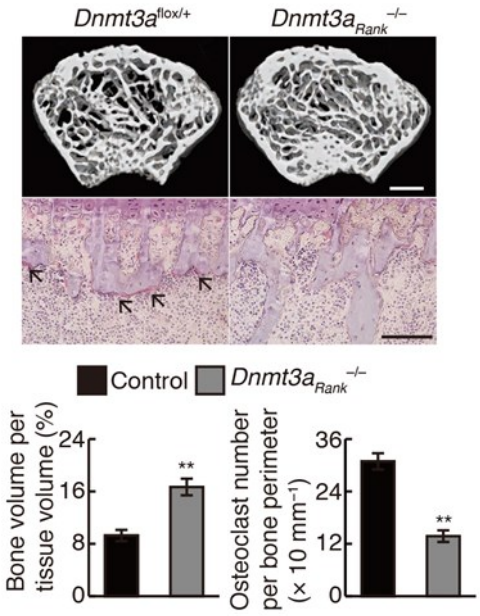


Figure 2. Histological analysis of the proximal tibias of 10-week-old control, Dnmt3aCtsk $^{-/-}$, and Dnmt3aRank $^{-/-}$ male mice.

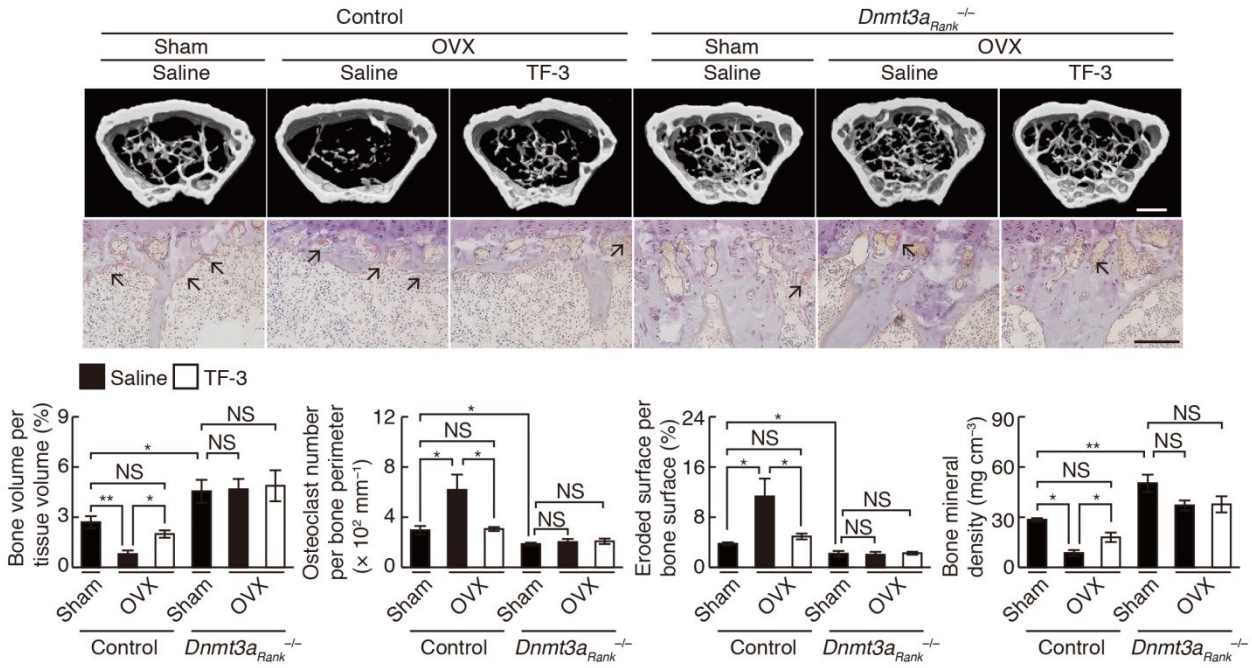


Figure 3. The therapeutic effect of the Dnmt3a inhibitor TF-3 on ovariectomy (OVX)-induced bone loss.