INTRODUCTION:

Bone loss is a universal feature of aging. This skeletal fatigue is a direct result of combined defects in osteoblasts and osteoclasts and underlies many orthopaedic disorders. The NFκB signaling axis is a crucial mediator of cell survival, a primary regulator of osteoclasts and has recently been shown to influence osteoblasts. The transcriptional activity of NFκB is suppressed by the histone deacetylase Silent Information Regulator T1 (SIRT1), of the sirtuin family of longevity-associated genes. The well-conserved sirtuins regulate lifespan in lower organisms and are strongly linked to proliferation and survival. Pharmacological regulation of SIRT1 also affects bone cells in vitro.

We hypothesize that SIRT1-NFκB levels alters with age to influence osteoblasts and osteoclasts, and represent and underlying mechanisms governing the onset and progression of age-related bone loss.

METHODS:

We assessed changes in NFκB activity using an NFκB-luc reporter mouse model and correlated these findings with SIRT1 expression from young (<2eth) and old (>16eth) animals. We also analyzed the bone phenotype of mutant mice with elevated NFκB activity (IκBα) by μCT and histomorphometric analysis, molecular and protein studies and purified immortalized macrophages. In addition, SIRT1 flx mice were obtained from Jackson Laboratories and knockout cells generated by adenoviral transfection of a cre-recombinase gene construct (Ad-Cre) and osteoblast- and osteoclast-SIRT1 deletion models generated using the 2.3kb Col1α1 and Lysozyme M Cre models respectively.

RESULTS:

The activity of NFκB from bone samples isolated from old mice was significantly increased but interestingly, there was no coupled increase (9.2%±0.3 Vs 15.4%±1.6) IκBα+/−. Immortalized macrophages from IκBα− mouse models was also striking.

DISCUSSION:

These studies suggest that SIRT1-NFκB interactions regulate bone cells and elevated NFκB uncouples osteoblasts and osteoclasts. These findings identify a novel molecular link between aging, osteoclast and osteoblast function and bone loss.

SIGNIFICANCE:

These studies indicate that a loss of SIRT1 leads to an uncoupling of the normal bone remodeling process, to favor enhanced resorption and impaired formation. Along with decreased SIRT1 expression in old age, these findings suggest that declining levels of SIRT1 with age may predispose the skeleton to the musculoskeletal deterioration associated with increased lifespan.

REFERENCES: