TRANSGENIC MOUSE MODEL FOR REDUCING OXIDATIVE DAMAGE IN BONE

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Exposure to musculoskeletal disuse and radiation result in bone loss; we hypothesized that these catabolic treatments cause excess reactive oxygen species (ROS), and thereby alter the tight balance between bone resorption by osteoclasts and bone formation by osteoblasts, culminating in bone loss. To test this, we used transgenic mice which over-express the human gene for catalase, targeted to mitochondria (MCAT). Catalase is an anti-oxidant that converts the ROS hydrogen peroxide into water and oxygen. MCAT mice were shown previously to display reduced mitochondrial oxidative stress and radiosensitivity of the CNS compared to wild type controls (WT). As expected, MCAT mice expressed the transgene in skeletal tissue, and in marrow-derived osteoblasts and osteoclast precursors cultured *ex vivo*, and also showed greater catalase activity compared to wildtype (WT) mice (3-6 fold). Colony expansion in marrow cells cultured under osteoblastogenic conditions was 2-fold greater in the MCAT mice compared to WT mice, while the extent of mineralization was unaffected. MCAT mice had slightly longer tibiae than WT mice (2%, $P<0.01$), although cortical bone area was slightly lower in MCAT mice than WT mice (10%, $p=0.09$). To challenge the skeletal system, mice were treated by exposure to combined disuse (2 wk Hindlimb Unloading) and total body irradiation ^{137}Cs (2 Gy, 0.8 Gy/min), then bone parameters were analyzed by 2-factor ANOVA to detect possible interaction effects. Treatment caused a 2-fold increase ($p=0.015$) in malondialdehyde levels of bone tissue (ELISA) in WT mice, but had no effect in MCAT mice. These findings indicate that the transgene conferred protection from oxidative damage caused by treatment. Unexpected differences between WT and MCAT mice emerged in skeletal responses to treatment.. In WT mice, treatment did not alter osteoblastogenesis, cortical bone area, moment of inertia, or bone perimeter, whereas in MCAT mice, treatment increased these parameters. Taken together, this typically catabolic treatment (disuse and irradiation) appeared to stimulate cortical expansion in MCAT mice but not WT mice. In conclusion, these results reveal the importance of mitochondrial ROS generation in skeletal remodeling and show that MCAT mice provide a useful animal model for bone studies.