A Novel Countermeasure Against Ionizing Radiation-Induced Bone Loss

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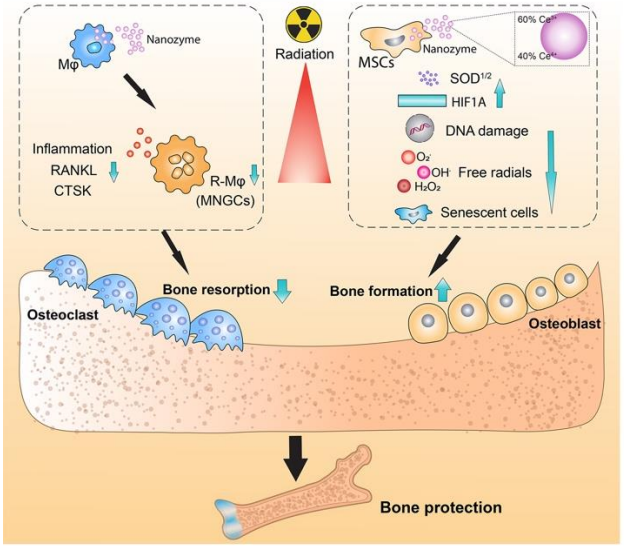
The disability, mortality and costs due to ionizing radiation (IR)-induced osteoporotic bone fractures are substantial and no effective therapy exists. Ionizing radiation increases cellular oxidative damage, causing an imbalance in bone turnover that is primarily driven *via* heightened activity of the bone-resorbing osteoclast. We demonstrate that rats exposed to sublethal levels of IR develop fragile, osteoporotic bone. At reactive surface sites, cerium ions have the ability to easily undergo redox cycling: drastically adjusting their electronic configurations and versatile catalytic activities. These properties make cerium oxide nanomaterials fascinating. We show that an engineered artificial nanozyme composed of cerium oxide, and designed to possess a higher fraction of trivalent (Ce^{3+}) surface sites, mitigates the IR-induced loss in bone area, bone architecture, and strength. These investigations also demonstrate that our nanozyme furnishes several mechanistic avenues of protection and selectively targets highly damaging reactive oxygen species, protecting the rats against IR-induced DNA damage, cellular senescence, and elevated osteoclastic activity *in vitro* and *in vivo*. Further, we reveal that our nanozyme is a previously unreported key regulator of osteoclast formation derived from macrophages while also directly targeting bone progenitor cells, favoring new bone formation despite its exposure to harmful levels of IR *in vitro*. These findings open a new approach for the specific prevention of IR-induced bone loss using synthesis-mediated designer multifunctional nanomaterials.



Schematic diagram highlighting the mechanistic avenues of protection provided by CeONPs against irradiation-induced bone loss. Radiation polarizes macrophages into radiation-associated macrophages (R-Mφ), the formation of multinucleated giant cells (MNGCs), with high expression of osteoclastogenesis- and inflammation-related markers and osteoclast activity. These were all significantly repressed following CeONP treatment *in vitro*. Further, CeONP treatment neutralized the highly damaging $O_2^{\bullet-}$, H_2O_2 and $OH^{\bullet}$, decreased DNA damage, increased bone-promoting (and anti-osteoclast) HIF1α protein levels, increased anti-inflammatory, pro-osteogenic and anti-osteoclastogenesis SOD expression, bone mineral deposition and reduced cell senescence thereby liberating osteoblastogenesis *in vitro* and significantly protecting bone against IR-induced bone fracture *in vivo*. The nanozyme designed to possess an increased relative fraction of Ce^{3+} surface sites, provided superior protection *in vitro.* This may be due to the enhanced SOD-mimetic activity, higher adsorption towards H/OOH and H/OO/H, an increase in interaction with ROS on the predominant {111} surfaces, as well as the selective and significant increase in both cytosol and mitochondrial *SOD1* and *2* gene expression.