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RAGE-deficiency results in reduced PPAR-α nuclear translocation, proinflammation and altered bone metabolism.

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Receptor for advanced glycation end product (RAGE) is a multiligand receptor of the immunoglobulin superfamily. RAGE was first described as a receptor for advanced glycation end products (AGEs). AGEs are products of non-enzymatic glycation of proteins, lipids, and nucleic acids that are formed during the normal aging process, but also at a faster rate under diabetic conditions. Interaction of RAGE and its ligand has been shown to cause activation of proinflammatory transcription factor NF-κB and tissue perturbation. Consequently, the receptor has been implicated in various diseases, including complications of diabetes and inflammatory diseases.

Although, the pathologic role of RAGE has been reported, however, its physiologic function remains to be fully elucidated. In this study, we investigated the physiologic role of RAGE in bone metabolism and the molecular mechanisms involved using $RAGE^{-/-}$ mice as a model.

Morphometric analysis of bones from $RAGE^{-/-}$ mice revealed a 20% reduction in osteoblast surface area and a 35% reduction in bone volume when compared to the age-matched wild type. Furthermore, a 30% reduction in bone specific alkaline phosphatase activity was also observed in bones from $RAGE^{-/-}$ mice indicating an altered bone phenotype.

Using RT-PCR, ELISA and Western blot techniques, we investigated whether the alterations in the bone phenotype of $RAGE^{-/-}$ mice could be explained by inflammatory markers. Our results indicated that relative to age-matched wild type mice, a higher mRNA and protein expression of proinflammatory cytokines IL-6, IL-1β and TNF-α was observed in whole bone and in isolated osteoblasts from $RAGE^{-/-}$ mice. In addition, electrophoretic mobility shift assay (EMSA) demonstrated that CEBPβ and NF-κB nuclear activity in bones and in isolated osteoblasts from RAGE deficient mice were increased, thus indicating a proinflammatory phenotype in RAGE deficiency.

The increase in proinflammatory factors and cytokines lead us to evaluate the expression of PPAR-α-an anti-inflammatory transcription factor. Our result shows that, the expression and nuclear activity of PPAR-α was significantly reduced in RAGE deficient bones and in isolated osteoblasts when compared to age-matched wild type mice. We further investigated whether the reduction of PPAR-α in bones from RAGE deficient mice is involved in the shift towards proinflammatory phenotype. Treatment of cultured RAGE deficient osteoblasts with PPAR-α agonist WY14643 increased PPAR-α expression and its nuclear activity.

Interestingly, CEBPβ and NF-κB nuclear activity was reduced in WY14643 treated RAGE deficient osteoblasts. Cytokine profile of the treated cells indicated that the expression of IL-6 was significantly reduced, while the expression levels of IL-1β and TNF-α were not affected, suggesting that among the cytokines screened, IL-6 appears to be the primary proinflammatory cytokine affected by the RAGE-PPAR-α crosstalk in mouse bone.

From our observation we can conclude that loss of RAGE leads to suppression of PPAR-α and a proinflammatory phenotype which in turn, contributes to a low bone forming activity of the osteoblasts and consequently a low bone mass in femora from RAGE deficient mice. RAGE therefore may represent an inflammatory master switch with a patho-physiologic relevance.