Discovery of a Novel PPARγ Agonist, KR62980 with New Indication of Osteoporosis Treatment

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Osteoporosis is the most common metabolic bone disorder and remains an increasingly significant problem in domestic as well as worldwide circumstance. Bone homeostasis is maintained by a balance between bone resorption by osteoclasts and bone formation by osteoblasts, and a balance shift for an excess of resorption over formation leads to the bone loss and increased propensity to fracture that is characteristic of osteoporosis.

Peroxisome proliferator-activated receptors (PPARs) are a member of nuclear receptor superfamily that acts as a transcription factor upon activation. Of the three PPAR isoforms identified so far (PPARα, δ/β, γ), PPARγ has been an attractive target for anti-diabetic thiazolidinediones such as rosiglitazone and pioglitazone by regulating glucose and lipid homeostasis. Recent reports suggest that thiazolidinediones has been implicated in regulation of osteoclast and osteoblast differentiation and function. Those compounds were shown to inhibit osteoclast formation and bone resorption in vitro, whereas rosiglitazone enhances also bone marrow adipogenesis and born resorption in ovariectomized rats, thus causing bone loss in vivo.

Initially to develop novel anti-diabetic agents targeting PPARγ, we discovered KR62980 with novel structure of non-thiazolidinedione. KR62980 showed in vivo glucose lowering effect with little weight gain. KR62980 also induced little adipogenesis in mesenchymal stem cells, which stimulated the investigation on the effects of KR62980 on osteoblast differentiation. As expected, KR62980 stimulated differentiation of preosteoblasts as well as bone marrow stromal cells to osteoblasts, accompanied by increased alkaline phosphatase, Runx-2, and BMP expression. The in vivo bone formation effects by KR62980 were confirmed by mouse calvaria implantation model. Consistent with previous findings on PPARγ-induced osteoclast inhibition, KR62980 inhibited osteoclast differentiation and formation of resorption pit concurrent with NF-κB inactivation. Taken together, these results suggest that KR62980 has dual beneficial effects on osteoporosis treatment, namely osteoblast stimulation and osteoclast inhibition. Based on the present study, KR-62980 may have great potential for the development of novel anti-osteoporotic agents.