

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

Overexpression of γ -glutamyltransferase accelerates bone resorption and causes osteoporosis

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Genetic studies in human patients as well as mutant mice have disclosed critical molecules involved in osteoclast development, including cytokines, intracellular signaling molecules, and nuclear transcription factors. Among these, the osteoclastogenic cytokines have received special attention, because they represent novel targets for the development of both diagnostic tools and antiresorptive drugs. For example RANKL, belonging to the TNF family, was identified as an essential cytokine for osteoclastogenesis, and mice deficient in RANKL were found to lack osteoclasts and to exhibit severe osteopetrosis. In an attempt to identify new cytokines that stimulate osteoclast differentiation, expression cloning was used and led to identify γ -glutamyltransferase (GGT) as such a stimulator. Mice deficient in GGT exhibit growth retardation, cataracts, and severe osteoporosis and die at 10–18 wk of age. Purified GGT is capable of inducing osteoclast formation in bone marrow cultures, which raises the possibility that its excess may also be involved in the bone and joint pathology characterized by enhanced osteoclastic bone resorption.

To examine its pathogenic role *in vivo*, transgenic mice were generated that overexpressed GGT. Systemic as well as local production of GGT accelerated osteoclast development and bone resorption *in vivo* by increasing the sensitivity of bone marrow macrophages to RANKL, an essential cytokine for osteoclastogenesis. Mutated GGT devoid of enzyme activity was as potent as the wild-type molecule in inducing osteoclast formation, suggesting that GGT acts not as an enzyme but as a cytokine. Recombinant GGT protein increased RANKL expression in marrow stromal cells and also stimulated osteoclastogenesis from bone marrow macrophages at lower concentrations.

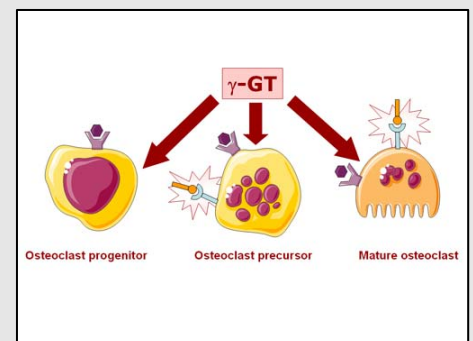
Thus, GGT is implicated as being involved in diseases characterized by accelerated osteoclast development and bone destruction and provides a new target for therapeutic intervention.

1. Hiramatsu K et al. *Endocrinology*. 2007;148: 2708–2715.

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GGT acts not as an enzyme but as a cytokine, and may provide a new target for therapeutic intervention.



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