

An antagonist of osteoclast integrins prevents experimental osteoporosis.

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Editorial

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Osteoporosis is caused by a chronic negative balance between the rates of bone formation and bone resorption, with resorption exceeding formation. Bone resorption in osteoporosis is mediated primarily by a single cell type, the osteoclast. An understanding of the cytologic mechanism by which osteoclasts resorb bone, and recognition of the biological factors that regulate osteoclast resorptive activity, can lead to therapeutic control over osteoporosis.

The report by Engleman et al. in this issue of the *Journal*, provides new insight into the mechanism of osteoclast-mediated bone resorption (1). The Engleman et al. study is based on two related hypotheses: first, that the attachment of osteoclast membrane integrins, especially the $\alpha_v\beta_3$ integrin to underlying matrix molecules, e.g., fibronectin or osteopontin, is a critical step in activating bone resorption; and second, that metabolic probes, designed to resemble the RGD- (arginine-glycine-aspartic acid) containing sequence in these matrix integrin ligands, can be used to bind to osteoclast membrane integrins, thus replacing the natural ligands and downregulating osteoclast resorptive activity. Perhaps the most exciting finding in this report is the identification of a synthetic RGD mimetic peptide, β -[[2-[[5-[(aminoiminomethyl)amino]-1-oxopentyl]amino]-1-oxoethyl]amino-3-pyridine-propanoic acid, bis-trifluoroacetate (SC56631), that effectively binds the $\alpha_v\beta_3$ integrin. The report shows that SC56631, not only blocks bone resorption by osteoclasts in culture, but that it also prevents bone loss in the oophorectomized (OVX) rat model of osteoporosis.

SC56631 is not the first resorption-inhibiting compound to be identified as a possible antiosteoporosis agent. Bisphosphonates and calcitonin have been investigated and used clinically for their osteoclast-inhibiting and bone sparing properties (2, 3). Echistatin, an RGD-containing peptide from snake venom (somewhat resembling SC56631), has been shown to inhibit completely osteoclast-mediated bone resorption *in vivo* in thyroparathyroidectomized rats treated with PTH (4). However, SC56631, as described by Engleman et al., is apparently of low toxicity and even at a low dosage can block resorption by binding with the $\alpha_v\beta_3$ integrin on the osteoclast membrane. Therefore, SC56631 shows promise as a possible antiosteoporosis agent.

The Engleman et al. study provides an unexpected insight into the role of integrins in controlling osteoclastic resorption by showing that blocking of the $\alpha_v\beta_3$ integrin with SC56631 causes a significant reduction in the number of osteoclasts. This finding suggests that integrins may be involved primarily in the process of formation of osteoclasts rather than in the attachment of already formed osteoclasts to the bone surface. There is disagreement in the literature as to whether the $\alpha_v\beta_3$ integrin is concentrated at attachment zones of the osteoclast

plasma membrane (5) or actually is excluded from the attachment zones (6). If the latter is true, as most reports seem to indicate, then the $\alpha_v\beta_3$ integrin may be more involved in the cell-to-cell fusion process that is required for osteoclast formation, rather than in attachment of osteoclasts to the underlying bone matrix. The fact that Engleman et al. found a reduction in the number of osteoclasts in animals treated with SC56631, rather than a simple detachment of osteoclasts from bone surfaces, supports the hypothesis that $\alpha_v\beta_3$'s main function lies with the biogenesis of osteoclasts rather than in their attachment.

One wonders what type(s) of toxicity might result from the systemic treatment of animals or humans with SC56631. A possible complication of SC56631 treatment could be anticoagulation because of an inhibition of platelet aggregation by the agent. It has been shown that RGD-containing compounds, such as echistatin, bind to the $\alpha_{11b}\beta_3$ integrin of platelets, thus preventing platelet aggregation and potentially inhibiting coagulation (7). Although Engleman et al. have shown that SC56631 binds to the $\alpha_{11b}\beta_3$ platelet integrin, no bleeding was observed in rats treated with the compound for as long as 6 wk. This apparent lack of a platelet effect in the rats tested may have resulted from a reduced affinity of SC56631 for the rat $\alpha_{11b}\beta_3$ platelet integrin. However, the status of platelet aggregability and the coagulation potential of peripheral blood in treated animals will have to be followed closely in future studies.

In summary, the Engleman et al. report presents important new information suggesting a role for the $\alpha_v\beta_3$ in osteoclast differentiation as well as adhesion, and it indicates a possible new approach to osteoporosis therapy using SC56631 to block $\alpha_v\beta_3$ integrin and inhibit osteoclastic bone resorption.

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