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Integrin aV?3 is important for bone resorption

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Keywords

aV?3 integrin, bone resorption, knockout, osteoclasts

Context

Osteoclasts are the primary cells responsible for bone resorption. Dysregulation of osteoclast activity has been linked to major diseases such as arthritis, osteoporosis, osteopetrosis, and metastatic tumor invasion into bone. Osteoclasts derive from a monocyte/macrophage lineage, and acquire a multinucleated, bone-resorbing phenotype after stimulation by two essential molecules: osteoclast differentiation factor (ODF or OPGL/RANKL/TRANCE) and macrophage colony stimulating factor (M-CSF). With proper stimulation and contact with bone, these polykaryons undergo cytoskeletal changes directing their bone-resorptive organelle (the ruffled membrane) to the point of contact. Matrix attachment molecules may direct these cytoskeletal changes. Prior studies using peptide inhibitors of the aV?3 integrin showed that these peptides could inhibit the resorptive capacity of osteoclasts. It is possible that similar integrins such as aV?5 could also be involved in resorption or even have overlapping function with aV?3. To further explore the role of aV?3 in resorption, these investigators generated ?3-/- mice and examined them for defects in osteoclast function, bone structure, and bone metabolism. Regulation of aV?5, a closely related integrin, was also examined in the ?3-/- mice.

Significant findings

BMM from both wild-type and ?3-/- mice differentiated into TRAP positive multinucleated osteoclasts in ST2 coculture. However, the ?3-/- osteoclasts failed to spread in culture, as compared to ?3+/+ and ?3+/- osteoclasts. Induction of aV?3 surface expression in BMMs using interleukin (IL)-4 was eliminated in ?3-/- mice. Expression of aV?5 integrin was not upregulated in ?3-/- mice. Stimulation of BMMs with M-CSF/ODF failed to show upregulation of ?5 mRNA in ?3-/- osteoclasts. Granulocyte M-CSF (GM-CSF) equally inhibited ?5 mRNA expression in ?3+/+, +/-, and -/- osteoclasts, which further demonstrated lack of ?5 upregulation in ?3-/- mice. Before 6 months of age, bone development in ?3-/- mice appeared to be unimpaired. However, after 6 months, these mice developed osteosclerosis, as determined by radiographs of sex-matched littermate tails. Histology of femurs from these mice also revealed increased cortical and trabecular bone mass after 6 months. Despite their osteosclerotic phenotype, mutant mice had increased numbers of osteoclasts. These cells exhibited defective ruffled

membrane formation and actin ring organization suggestive of impaired bone resorptive capacity. This impairment was demonstrated *in vitro* using bone resorption assays in which mutant osteoclasts formed shallow, poorly defined resorption lacunae on bone.

Comments

This study provides definitive proof for the role of ?3 integrin as an important, yet nonessential molecule for osteoclast-mediated bone resorption. Currently, it is unknown how osteoclasts target and bind bony surfaces to initiate resorption. This paper implicates the aV?3 integrin in this process, although it is not the sole receptor mediating this event, and it is likely that other surface molecules work together with ?3 integrin to mediate osteoclast targeting and attachment to bone. Identification of other matrix attachment molecules responsible for targeting the osteoclast to bone will offer new therapeutic modalities for the treatment of bone metabolism disorders.

Methods

The ?3-/- mice were generated using a phosphoglycerate kinase (PGK)-neo gene cassette to replace a genomic fragment spanning part of the ?3 promoter to exon II by standard homologous recombination in embryonic stem (ES) cells. Osteoclasts were generated using a coculture system in which bone marrow macrophages (BMMs) were either cultured with ST2 stromal cells, 1,25-dihydroxyvitamin D, and glucocorticoids, or stimulated with ODF and M-CSF. Northern blotting was used to examine compensatory upregulation of aV?5 mRNA in response to the absence of aV?3. Osteoclasts were identified by positive tartrate-resistant acid phosphatase (TRAP) staining of multinucleated cells. Osteosclerosis was determined by radiography. Ruffled membrane formation was examined using transmission electron microscopy and actin cytoskeletal organization was detected using confocal microscopy with rhodamine phalloidin dye. *In vitro* bone resorption assays were performed by culturing osteoclasts on whale dentin slices for 7-10 days and then using scanning electron microscopy to measure lacuna depth.

Additional information

(Engleman *et al, J Clin Invest* 1997, **99:**2284-2292 [Abstract])

References

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