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Mechanism of Osteoclastic Bone Resorption: A New Hypothesis

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Summary. Osteoclastic bone resorption involves the solubilization of the mineral salts and the degradation of noncollagen bone matrix and collagen fibrils. As no recognizable collagen fibrils have ever been reported within cytoplasmic vacuoles in osteoclasts, it is generally assumed that the collagen fibrils are digested extracellularly in the resorption zone. The extent to which lysis occurs extracellularly and whether or not the osteoclasts phagocytose the degradation products remain to be established.

In the present communication, a hypothesis is presented suggesting the possibility that osteoclastic resorption of bone involves the participation of two different cell types. According to this hypothesis, osteoclastic bone resorption is initiated by osteoclasts that demineralize areas of bone and degrade noncollagen bone matrix. After the osteoclasts have moved away or become partially detached from the demineralized site, the exposed collagen fibrils are phagocytosed by mononuclear, fibroblast-like or monocyte-derived cells.

Key words: Osteoclasts — Bone — Resorption.

Introduction

Resorption of bone involves removal of bone mineral and degradation of the organic bone matrix. The cell type thought to be primarily responsible for bone resorption is the osteoclast [1–3], although macrophages [4, 5] and osteocytes [6] also are known to be capable of resorbing bone.

The mechanism by which the osteoclast is thought to achieve resorption has been the subject of many investigations [2, 3]. It is not known whether degradation of noncollagenous organic bone matrix components precedes or follows mineral removal, although it is generally accepted that the solubilization of the mineral salts precedes the breakdown of collagen fibrils. Since no recognizable collagen fibrils have ever been found within cytoplasmic vacuoles in the osteoclast, it is generally assumed that the collagen fibrils are digested extracellularly in the resorption zone. The extent to which lysis occurs extracellularly and whether or not the osteoclasts phagocytose the degradation products still remain to be established.

In the present communication, a hypothesis is presented suggesting the possibility that osteoclastic resorption of bone involves participation of two different cell types. According to this hypothesis, osteoclastic bone resorption is initiated by osteoclasts that demineralize areas of bone and degrade noncollagen bone matrix. The collagen fibrils thus exposed are subsequently phagocytosed and digested by mononuclear, fibroblast-like or monocyte-derived cells. This occurs after the osteoclast has moved away or has become partly detached from the demineralized site.

Discussion

The first indication that osteoclastic bone resorption might be a two-phase process came from the results of experiments concerning the endocrine regulation of bone resorption. Bone resorption, as is generally accepted, can be stimulated by parathyroid hormone (PTH) and inhibited by calcitonin. In agreement with this general belief, it was shown [7–10] that calcitonin inhibits PTH-induced resorption of mineralized bone matrix. However, these same authors demonstrated that PTH-induced resorption of nonmineralized osteoid is not inhibited by calcitonin. These results suggest that degradation of mineralized bone is

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regulated differently from resorption of nonmineralized and demineralized bone matrix.

That cell types with different hormone responsiveness exist in bone tissue is suggested by results obtained by Wong and Cohn [11] and Luben et al. [12]. These authors were able to isolate populations of cells with osteoclast-like properties from bone that respond to both PTH and calcitonin, and other populations, in some respects similar to osteoblasts, that respond exclusively to PTH.

When taken together, these observations suggest that dissolution of mineral may be accomplished by one cell type, presumably the osteoclast, which is responsive to both PTH and calcitonin. Since cell types exclusively responding to PTH do occur in bone, such cell types could be responsible for resorption of demineralized or nonmineralized bone collagen. Responsiveness of osteoclasts in situ to PTH and calcitonin has been demonstrated [13, 14].

Histological evidence certainly does not exclude the possibility that osteoclastic bone resorption involves participation of two cell types. Observations made by Irving and Handelmar [15] in a light microscope autoradiographic study on the resorption of ^{3}H-proline-labeled implanted bone strongly suggested that no labeled material was phagocytosed by osteoclasts. On the other hand, labeled material was ingested by small round mononuclear cells. Also of interest in this regard is the observation that osteoclastic bone resorption generally does not remove unmineralized matrix [16]. Similarly, odontoclasts, which probably are not fundamentally different from osteoclasts, do not resorb nonmineralized dentin (I.A. Mjör, *personal communication*).

Mononuclear cells are often found in close association with osteoclasts in Howships lacunae [17; *personal observations*]. It is of course impossible to determine in routine histological sections whether these cells are actually involved in collagen degradation. In view of the great mobility of osteoclasts observed in time-lapse microcinematography of resorbing bone in vitro [18–20], the extremely rapid changes that take place in the ultrastructural cytology of osteoclasts [3], and the likelihood that communications exist between the extracellular resorption zone and the regular extracellular space [21], it seems possible that demineralized bone collagen is accessible to such cells. This possibility is further strengthened by the observation of Gaillard [18, 19] that at times bone matrix is seen to disappear after a giant osteoclast has moved away from a resorbing area.

The mononuclear cell types involved could be either macrophages or fibroblast-like cells. Collagen-containing vesicles have been described in macrophages in the wall of the involuting uterus [22–24], and in fibroblasts in such varying locations as the periodontal ligament [25–28], healing bone fractures [29], arthritic lesions [30], and healing wounds [31]. The evidence indicates that under suitable conditions both macrophages and fibroblasts are capable of phagocytosing and degrading collagen.

In support of a role for macrophages in the resorptive process, Mundy et al. [32] demonstrated that resorbing bone produces a substance that is chemotactic for human monocytes. Further supporting a role for the macrophage is the demonstration of contact-mediated bone resorption by human monocytes in vitro [33] and the previously mentioned observations of Goldhaber [4] and Mundy et al. [5].

Evidence that fibroblast-like cells may be associated with osteoclasts during the resorption of bone can be derived from the recent electron microscopic observations of Garant [34]. He noticed that fibroblasts in the vicinity of osteoclasts in periodontal ligament contained many intracellular collagen fibrils associated with lysosome-like structures, whereas osteoclasts lacked such profiles. Garant has interpreted his observations as representing phagocytosis and subsequent digestion of unanchored periodontal ligament collagen fibrils that were detached as a result of resorption of alveolar bone. However, the observations could also be interpreted as indicating that the cells had resorbed bone collagen fibrils exposed by osteoclast activity.

Evidence for the absence of collagen-degrading systems in osteoclasts and the presence of such systems in other cell types in bone tissue is provided by the recent observations of Sakamoto et al. [35]. These authors examined a resorbing system in vitro using immunofluorescence techniques and found that all cells except the osteoclasts were stained by an anti-collagenase antibody. In this connection we should point out, however, that the role of collagenase in either intracellular or extracellular digestion of bone matrix collagen is not clear. The results of Sakamoto et al. [36] suggest that synthesis and release of bone collagenase correlate with PTH-induced bone resorption. However, Lenaers-Clays and Vaes [37] could find no significant correlation between bone resorption and the amounts of either collagenase or procollagenase accumulated in culture fluids of resorbing bones. Furthermore, Lenaers-Clays and Vaes [38] were able to demonstrate that the addition of calcitonin to the culture fluids had no effect on the release of collagenase or procollagenase, although calcitonin decreases significantly the release of lysosomal enzymes β-glucurodinase [9, 38] and N-acetyl-β-glucosaminidase [38] in such systems.

There is in fact evidence which supports the hypothesis that osteoclastic bone resorption is a process requiring the activity of two cell types. According to this theory, solubilization of the mineral component and the digestion of the noncollagen bone matrix are accomplished by osteoclasts, whereas the demineralized collagen fibers subsequently are degraded through the action of mononuclear, presumably fibroclast-like or monocyte-derived, cells.

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