

Debate

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Roles of hyaluronan in bone resorption

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Published: 29 April 2004

Received: 27 February 2004

BMC Musculoskeletal Disorders 2004, 5:12

Accepted: 29 April 2004

This article is available from: <http://www.biomedcentral.com/1471-2474/5/12>

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Abstract

Background: Hyaluronan, an unsulfated glycosaminoglycan, while being closely linked to osteoclast function several years ago, has received little attention lately. Given recent new knowledge of hyaluronan's possible cell binding abilities, it is important to re-examine the role of this polysaccharide in bone homeostasis.

Discussion: Previously published data demonstrating a linkage between induction of hyaluronan synthesis and osteoclast-mediated bone resorption are reviewed. Suggestions are made involving the cell binding ability of hyaluronan and its potential to mediate osteoclast binding to bone surfaces and its potential to serve as a diffusion barrier and participate in the sealing zone required for osteoclast-mediated bone resorption.

Summary: This brief article summarizes previous studies linking HA to bone resorption and suggests roles for hyaluronan in the process of bone resorption.

Background

Hyaluronan (HA) is an unsulfated glycosaminoglycan consisting of a single repeating disaccharide unit (1,4-glycuronic acid- β -1,3-N-acetylglucosamine- β). HA is about 1–10% of cartilage glycosaminoglycans, but it is also widely distributed in other tissues, *e.g.* in the skin, the eye, and in most body liquids [1]. HA is an important component of connective tissue matrices where its functions include promoting matrix assembly and tissue hydration and viscosity of some fluids, and modulating cell-cell or cell-matrix interactions [1]. Recently, additional roles for HA in cell signaling have been elucidated which involve cellular hyaladherins such as CD44 and RHAMM (CD168) that have specific downstream signaling pathway(s) which can mediate HA-dependent functions [2].

Linkage of hyaluronan synthesis to bone resorption

Several studies [3-5] demonstrated that treatment *in vivo* with parathyroid gland extract (PTE) resulted in increased bone synthesis of hexosamine-containing compound(s). Based on such findings, Severson et al. [6] used organ cultures of neonatal mouse calvaria, treated with PTE and then labeled with ^3H -glucosamine (glcN), to demonstrate that PTE caused a 4-fold increase in papain-resistant macromolecular material that was identified as hyaluronic acid, now called hyaluronan (HA). Luben and coworkers provided data that clearly linked parathyroid hormone (PTH)-induced synthesis of HA to bone resorption. Using organ cultures of bones pre-labeled *in vivo* with $^{45}\text{Ca}^{++}$, they demonstrated that *in vitro* treatment with PTH followed by radiolabeling with ^3H -glcN resulted in a 3–4-fold increase in HA synthesis [7]. This increase was detectable by 4 h and was maximal at 24 h. Changes in $^{45}\text{Ca}^{++}$ release followed a parallel course but with a delayed onset

(24 h) and peak (48 h). Addition of HA, hyaluronidase or glucosamine to the culture medium in the absence or presence of PTH had no significant effect on $^{45}\text{Ca}^{++}$ release. Using a similar system to assay calcium release and HA synthesis, Luben and Cohn [8] also found that addition of calcitonin to PTH-stimulated cultures caused HA synthesis and, subsequently, calcium release to return to control levels. After 24 h in the presence of both hormones, an "escape" phenomenon [9] was observed, i.e., the rate of HA synthesis and calcium release again increased, with the former preceding the latter. These data strongly linked induction of HA synthesis to osteoclastic resorption, prompting the authors to suggest "that a change in hyaluronate synthesis is a metabolic prerequisite for demineralization". Luben et al., [7] speculated that the role for HA in bone resorption could be to act as a calcium binding agent, to act as a barrier to the diffusion of enzymes away from the resorption site or to regulate the mobility of osteoclasts or osteoclast precursor cells. To our knowledge, none of these possibilities has been proven nor excluded and all deserve additional exploration.

Thus, though HA's role was not known, sufficient evidence existed linking HA to bone resorption that Wong and coworkers [10,11] utilized PTH stimulation of HA synthesis as a specific marker during the purification of osteoclastic cells. The studies cited above and others prompted Stern and Raisz [12] to comment in a discussion of markers of bone resorption that "hyaluronic acid seems to be the most appropriate for study because, unlike the other biochemical changes, it has been clearly linked to bone resorption."

Discussion

Role of HA in cell binding

The requirement for osteoclasts to bind to bone surfaces prior to assuming their resorptive role is well documented, though the means by which they do so is not. Recent work has suggested that osteoclasts utilize integrins, in particular the vitronectin receptor, $\alpha_v\beta_3$, to bind to one or more of the cell adhesion proteins, e.g. osteopontin or bone sialoprotein [13,14], though such binding may not occur at the sealing zone as previously supposed [15]. Since osteoclasts have recently been shown to possess cell surface proteins capable of binding to HA [16], in particular CD44, a cell surface HA binding protein [17] capable of supporting cell adhesion [18], HA may also regulate the osteoclast's ability to bind to bone surfaces by acting alone or in conjunction with osteopontin, bone sialoprotein or other matrix proteins (likely synthesized by osteoclasts). Recent work by Spessoto et al., [19] supports this scenario and work by Suzuki et al., [20] confirms that osteoclasts from CD44^{-/-} mice are defective in bone resorption.

In addition, given the large hydrodynamic volume of HA, it seems possible that it could participate in forming a diffusion barrier underneath the osteoclast, presumably at the sealing zone. One could speculate that any HA present in the ruffled membrane area would be degraded by lysosomal enzymes secreted from the osteoclasts.

It is instructive to note that while little is known about the bone enzymes responsible for degrading HA, i.e., hyaluronidase (EC 3.2.1.35), β -D-glucuronidase (EC 3.2.1.31), and N-acetyl- β -D-hexosaminidase (EC 3.2.1.30), genetic deficiencies of β -D-glucuronidase (Sly syndrome, [21]) or N-acetyl- β -D-hexosaminidase (Sandhoff Disease, [22]), result in numerous skeletal deformities, suggesting that these enzymes have important roles in normal bone homeostasis.

On the other hand, an additional role of HA may be in modulating osteoblast adhesion to osteoid or bone surfaces. In their model of hormonal regulation of bone resorption, Rodan and Martin [23] suggested that PTH induces osteoblasts, which form a contiguous layer on the bone surface, to change shape, thereby allowing osteoclasts access to the bone surface, a prerequisite for bone resorption. Given that osteoblasts exhibit vectorial secretion, i.e., directed toward the underlying bone surface, and that HA has a large molecular size and hydrodynamic volume, HA synthesized by osteoblasts may prove to be a molecular lever of sorts, capable of prying osteoblasts from the osteoid surface or from one another, disrupting the continuity of the lining layer of cells. Thereafter, in such a scenario, the HA could serve as an adhesion substrate for incoming osteoclasts and, possibly, act as a diffusion barrier at the sealing zone. In this regard the recent findings of Midura et al., are pertinent – they found that HA content of bone extracellular matrix was substantially enhanced by PTH treatment and that this was a direct response to the peptide hormone [24].

Another scenario is suggested by the recent work by Fujii et al., [25] who demonstrated that ligation of osteoblast CD44 with HA regulates adhesion molecule expression of osteoblasts and increases their binding to macrophage-like cells. These authors suggested that the interactions of CD44 and HA may play a role in osteoclastogenesis.

Summary

1. HA synthesis is tightly coupled to onset of bone resorption
2. HA's roles in cell adhesion and in limiting diffusion suggest mechanisms for its involvement in osteoclast-mediated bone resorption

3. These mechanisms include cell binding, and/or acting as a molecular lever or diffusion barrier
4. Additional studies are needed to clarify the roles that HA has in bone metabolism in general and in bone resorption specifically.

Competing interests

None declared.

Author's contributions

CWP was solely responsible for the content of this article.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

<http://www.biomedcentral.com/1471-2474/5/12/prepub>

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