



# Breast and bone: A story of hidden similarities

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## Abstract

Several clinical and biological evidences, such as breast calcifications and breast metastasis to bone, suggest a deep relation between bone and breast tissues. Tangible proofs of great similarities between these tissues bring to light how complex phenomena, as breast micro calcifications and bone metastasis, could be the result of a tight correlation between apparently different organs. The fine characterization of breast micro calcifications could be a helpful tool in breast cancer screening, since it could help imaging technologies to discriminate micro calcifications in vivo. Also, the recent finding of cells involved in the formation of breast micro calcifications, the BOLCs, evokes a new vision about the "breast-bone" affinity. Indeed, the identification of breast cancer cells with highly affinity for bone environment can shed new light on prevention and therapy of bone metastasis from breast.

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## Short Review

Several clinical and biological evidences, such as breast calcifications and breast metastasis to bone, suggest a deep relation between bone and breast tissues.

Indeed, recent studies have actually demonstrated the expression of typical bone markers in breast cells [1-3], so it is easy to think about the possible connection between them. The issue emerged not so many years ago, even because the origins of these two components are completely far from one another.

The clearest expression of it concerns the Bone Morphogenetic Proteins and Wingless (Wnt) pathways. Bone morphogenetic proteins (BMPs) are cytokines belonging to the transforming growth factor- $\beta$  (TGF- $\beta$ ) super-family. They play multiple functions during development and tissue homeostasis, including regulation of the bone homeostasis [4]. About 20 different human BMPs have been found and grouped into subfamilies, according to their sequence similarity and known functions [5]. The effects of BMPs depend upon the target cell type, differentiation stage, local concentration of BMPs, as well as interactions with



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other secreted proteins [6]. For a long time BMPs have been considered only in relation to bone but now it is clear they are also involved in other organs, including breast. Recent studies have demonstrated that BMPs can promote oncogenic behavior by affecting apoptosis, migration, invasion and angiogenesis [7], initiate micro calcification in breast tumor models [8], promote the epithelial to mesenchymal transition (EMT) phenomenon [9]. The canonical Wnt signaling activity promotes bone formation [10-11] but it is also implicated at several stages of mammary gland growth and differentiation, and it has recently been linked to human breast cancer [12].

Combining these data, it is hard to escape the idea that bone and breast are not involved with each other. From a clinical point of view, the proof of this relation is provided by two important facts: the first is that about 80% of advanced breast cancers develops bone metastasis [13], the second one concerns the presence of breast micro calcifications, localized deposits of calcium species such as hydroxyapatite in breast tissue, considered an early mammographic sign of breast cancer [14].

The term breast micro calcification refers to calcifications of whom diameter is inferior to 1 mm, knowing that current spatial resolution mammographs make small objects to be detected without magnification for a size ranged between 100 and 200  $\mu\text{m}$  [15]. Mammary micro calcifications are calcium deposits within the breast tissue and their mammographic appearance was first described in 1951 [16]. They are classified according to their mammographic morphology, i.e. density and distribution [17], and by their physical and chemical properties [18]. The Breast Imaging Reporting and Data system (BI-RADS) developed by the American College of Radiology, allow us to classify breast micro calcifications according to their appearance. It was developed in order to standardize the description and recommendations for the care of anomalies detected by mammography, and as a result, facilitate communication between radiologists and referring physicians. Currently micro calcifications are classified according to BI-RADS, Madame Le Gal and Re.Co.R.M. methods [19]. Several studies suggest that the morphological appearance of mammographic micro calcifications is associated with patient prognosis, since breast cancer patients presenting with small tumors and mammographically detected casting type calcifications have a poor survival rate for this tumor size category [20]. There is also more recent evidence that invasive ductal carcinoma presenting with calcifications has a larger tumor size, increased lymph node involvement and decreased 8-year patient survival [20].

It is possible that the molecular structures of micro calcifications are a more important factor related to patient prognosis. Two types of mammary micro calcifications have been identified and characterized on a molecular level; type I composed of calcium oxalate (CO) and type II composed of hydroxyapatite (HA) [21]. Calcium oxalate is associated with benign breast conditions or at most lobular carcinoma in situ, whereas hydroxyapatite is associated with both benign and malignant breast tissue [22]. A new subtype of complex HA form, Mg-Hap was found by Scimeca et al. in 2013 [22]. Despite the importance of mammographic mammary micro calcifications for the initial detection of breast cancer and their potential prognostic value, limited research has been carried out to determine how and why these mammary micro calcifications are formed within the tumor microenvironment and it has been traditionally thought they are formed by cellular degeneration.

Nevertheless, recent studies have demonstrated an active

role of the epithelial cells of mammary tissue in their formation [22], since invasive mammary cell lines are capable to produce hydroxyapatite in vitro when exposed to an osteogenic cocktail [23]. Liu et al. [8] actually proved that, at least in a syngeneic model system, BMP-2 is sufficient for inducing high levels of micro calcification in breast carcinoma. In addition, Scimeca et al. [24] recently discovered the presence of Breast Osteoblast-Like Cells (BOLCs) surrounding calcium deposits. BOLCs are cells with morphological characteristics typical of mesenchymal cells and osteoblasts such as cytoplasm rich in vesicles containing electron-dense granules similar to the intracellular vesicles of the osteoblasts [25]. Due to their characteristics, BOLCs could be the junction ring among mammary epithelial cells, the complex micro calcifications and the development of bone metastasis.

Scientific dissertation here reported highlights the main cellular and molecular mechanisms of the breast-bone affinity. Tangible proofs of great similarities between breast and bone tissues bring to light how complex phenomena, as breast micro calcifications and bone metastasis, could be the result of a tight correlation between apparently different organs. The fine characterization of breast micro calcifications could be a helpful tool in breast cancer screening, since it could help imaging technologies to discriminate micro calcifications in vivo. Also, the recent finding of cells involved in the formation of breast micro calcifications, the BOLCs, evokes a new vision about the "breast-bone" affinity. Indeed, the identification of breast cancer cells with highly affinity for bone environment can shed new light on prevention and therapy of bone metastasis from breast.

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#### Conflict of Interest Statement

There are no potential conflicts of interest relating to the manuscript (for each authors), and there were no extramural sources supporting this research (excluding sources already declared). The study is original and the manuscript has not been published yet and is not being considered for publication elsewhere in any language either integrally or partially except as an abstract. All authors have agreed with the submission in its present (and subsequent) forms.

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