

Breast Microcalcifications: A Focus

Manuel Scimeca*, Chiara Antonacci and Elena Bonanno

Anatomic Pathology Section, Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Via Montpellier 1, Rome 00133, Italy

Editorial

Microcalcifications are localized deposits of calcium in breast tissues within the most clinically significant abnormality of the gland and are considered an early mammographic evidence of breast cancer [1].

Increasing evidences suggest that the morphological appearance and the molecular structures of microcalcifications could be related to patient's prognosis.

Mammary microcalcifications have been characterized according to their molecular composition as type I composed of calcium oxalate (CO) and type II composed of calcium hydroxyapatite (HA) [2]. CO calcifications are associated with benign breast conditions or at most lobular carcinoma in situ, whereas HA deposits are associated with both benign and malignant breast tissue [2].

Despite the importance of mammographic mammary microcalcifications for early detection of breast cancer and their potential prognostic value, limited research has been carried out to determine how and why these mammary microcalcifications take place within the tumor microenvironment. Traditionally, they are related to cellular degeneration since their close relationship with comedo necrosis [3].

Recently, we characterized the elemental composition of microcalcifications by Energy Dispersive X-ray (EDX) microanalysis [4] describing for the first time the presence of magnesium-substituted hydroxyapatite (Mg-HAp) in breast microcalcifications [5]. It is important to underline that the complex forms of calcification (HA and Mg-HAp) are strictly related to malignant lesions whereas CO is mainly reported in benign lesions. Mg-HAp microcalcifications were mainly detected in breast cancers. The capability of HA to bind to bivalent ions such as magnesium (Mg) [6], may confer carcinogenic properties on HA since a Mg-depleted microenvironment can influence the DNA repair processes and the control of proliferation and apoptosis [7]. These data on microcalcifications composition let to speculate about an active deposition of calcium minerals in breast carcinogenesis, since such complex form of minerals cannot be due to a mere degenerative process but rather resemble a process of mineralization similar to that of bone. At the same time, the presence of complex forms of calcification raises an interesting question: how can breast epithelial cells produce HA?

Recent studies have [8,9] investigated the molecular mechanisms of the microcalcification process in breast cell cultures and demonstrated that mineralization could be comparable to that observed in physiological bone formation.

Thus, such mineralization phenomenon in the context of the breast microcalcifications suggests the existence of cells able to produce HA. The morphological characterization of cells surrounding the mineralized core displayed numerous cells exhibiting a mesenchymal phenotype surprisingly similar to osteoblasts [6]. These Breast Osteoblast-Like cells (BOLCs) presented electrondense bodies in their cytoplasmic vesicles whose content consisted of hydroxyapatite, a typical feature of osteoblast intracellular vesicles [10,11]. Here, for the first time, we propose to call them "Breast Osteoblast-like Cells" (BOLCs).

Observations of mesenchymal cells into mammary ducts (BOLCs) [6] could be explained by the occurrence of epithelial to mesenchymal phenomenon. Indeed, mammary cells, under specific stimuli, Tumor Growth Factor- β (TGF β) and Bone Morphogenetic Proteins (BMPs), may acquire mesenchymal characteristics transforming themselves into cells with an osteoblast-like phenotype. Our previous data on expression of mesenchymal markers (i.e. vimentin and β -catenin translocation) in breast provided evidence of a strong relationship between epithelial to mesenchymal transition (EMT) phenomenon and microcalcifications made of HA and/or Mg-HAp.

The presence of BOLCs in breast lesion suggests the existence of a kinship between bone and breast tissues. In this regards, several studies have demonstrated the expression of typical bone markers in breast cells [12,13], so it is not difficult to believe at this connection. In addition, breast cancers represent a clear example of neoplasms that display an extraordinary inclination to grow in bone [14]. About 10% of all breast cancer patients, without evidence of bone metastases at the time of diagnosis, will have a first relapse in bone within five years of their primary diagnosis. Furthermore, approximately 65–75% of patients with advanced breast cancer will develop bone metastases [14].

In conclusion, microcalcifications, now considered an early diagnostic marker of breast cancer, revisited as a result of a complex biological process like the EMT, could become a prognostic marker. In fact, the presence of HA in a benign breast lesion could represent a higher risk to develop a breast cancer mediated by EMT phenomenon. Moreover, the finding of a specific elemental composition associated with radiological characteristics of microcalcifications could enhance imaging technologies to discriminate microcalcifications in vivo, and thus represent a helpful tool in breast cancer screening. Raman spectroscopy of mammary microcalcifications represents a novel non-invasive procedure that could be used in conjunction with mammography to aid in the detection of breast cancer. It has been a useful tool to distinguish between hydroxyapatite found in benign breast tissue and hydroxyapatite associated with malignant breast cancer.

Despite, it is not able to identify important subtype of HA such as Mg-HAp. All together these considerations could be new prospective in breast cancer therapy. In fact, epithelial cancer associated to EMT often show MultiDrug Resistance.

***Corresponding author:** Manuel Scimeca, Anatomic Pathology Section, Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Via Montpellier 1, Rome 00133, Italy, E-mail: manuel.scimeca@uniroma2.it

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