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Review

Microcalcifications in breast cancer: Lessons from physiological mineralization

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ABSTRACT

Mammographic mammary microcalcifications are routinely used for the early detection of breast cancer, however the mechanisms by which they form remain unclear. Two species of mammary microcalcifications have been identified; calcium oxalate and hydroxyapatite. Calcium oxalate is mostly associated with benign lesions of the breast, whereas hydroxyapatite is associated with both benign and malignant tumors. The way in which hydroxyapatite forms within mammary tissue remains largely unexplored, however lessons can be learned from the process of physiological mineralization. Normal physiological mineralization by osteoblasts results in hydroxyapatite deposition in bone. This review brings together existing knowledge from the field of physiological mineralization and juxtaposes it with our current understanding of the genesis of mammary microcalcifications. As an increasing number of breast cancers are being detected in their non-palpable stage through mammographic microcalcifications, it is important that future studies investigate the underlying mechanisms of their formation in order to fully understand the significance of this unique early marker of breast cancer.

Contents

Abbreviations: ALP, alkaline phosphatase; ASARM, acidic serine- and aspartate-rich MEPE-associated motif; BI-RADS, breast imaging reporting and data system; βG, β-glycerophosphate; BMP2, bone morphogenic protein 2; BSP, bone sialoprotein; Ca, calcium; DMP1, dentin matrix protein 1; DSPP, dentin sialophosphoprotein; DPP, dentin phosphoprotein; DSP, dentin sialoprotein; ECM, extracellular matrix; G, glycerol; HA, hydroxyapatite; MEPE, matrix extracellular phosphoglycoprotein; MMP, matrix metalloproteinase; MMs, mammary microcalcifications; NPP1, nucleotide pyrophosphate phosphodiesterase 1; OPN, osteopontin; OSC, osteocalcin; OSN, osteonectin; PFA, phosphonoformic acid; Pi, inorganic phosphate; PPi, inorganic pyrophosphate; SIBLING, small integrin-binding ligand N-linked glycoprotein.

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Introduction

Breast cancer is a worldwide public health problem and is the most common cause of cancer deaths, accounting for approximately 16% of cancer deaths in adult women [1]. Mammography is used for the early detection of breast cancer and 30–50% of non-palpable breast cancers are detected solely through the appearance of microcalcifications during a mammogram scan [2]. Mammary microcalcifications are calcium deposits within the breast tissue and their mammographic appearance was first described in 1951 [3]. Mammary microcalcifications can be classified according to their appearance on a mammogram based on the Breast Imaging Reporting and Data system (BI-RADS) developed by the American College of Radiology. Some of the typical classifications include powdery, crushed stone-like and casting type calcifications, as shown in Fig. 1 [4].

There is mounting evidence to suggest that the morphological appearance of mammographic microcalcifications is associated with patient prognosis. Several studies have shown that breast cancer patients presenting with small tumors and mammographically detected casting type calcifications have a poor survival rate for this tumor size category [4–6]. There is also more recent evidence that invasive ductal carcinoma presenting with calcifications have a larger tumor size, increased lymph node involvement and decreased 8-year patient survival [7]. In addition, this study demonstrated that tumors with casting type calcifications were associated with worse survival rates than those with non-casting type calcifications [7]. Studies have also suggested that clustering of microcalcifications could be used as a diagnostic tool to distinguish between benign and malignant lesions of the breast [8–10]. However, not all studies are in agreement that clustering of microcalcifications or casting type calcifications are related to patient outcome [11–13]. It is possible that the molecular structures of microcalcifications are a more important factor related to patient prognosis.

Two types of mammary microcalcifications have been identified and characterized on a molecular level; type I composed of calcium oxalate and type II composed of hydroxyapatite [14]. 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 [14–17]. Raman spectroscopy has been a useful tool to distinguish between hydroxyapatite found in benign breast tissue and hydroxyapatite associated with malignant breast cancer [17]. The carbonate content of hydroxyapatite is reduced significantly when progressing from benign to malignant breast disease [18]. 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 [19].

Despite the importance of mammographic mammary microcalcifications 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 microcalcifications are formed within the tumor microenvironment and it has been traditionally thought that they are formed by cellular degeneration. However, the process of physiological mineralization resulting in the hydroxyapatite deposition in bone is well documented and accepted as an active cell-mediated process [20]. This review brings together existing knowledge from the field of physiological mineralization and juxtaposes it with our current understanding of the genesis of mammary microcalcifications in order to better understand the significance of this unique early marker of breast cancer.

Models of mineralization

Physiological mineralization is widely considered to be a regulated process and is restricted to specific sites in skeletal tissues, whereas pathological mineralization occurs in soft tissue [21]. It has been suggested that the mechanisms regulating pathological mineralization might be similar to those regulating physiological mineralization [21–23]. As limited research has been carried out on the molecular mechanisms involved in pathological mammary mineralization, lessons from other mineralization studies may be useful to establish whether a similar mechanism is taking place for mammary cells. In

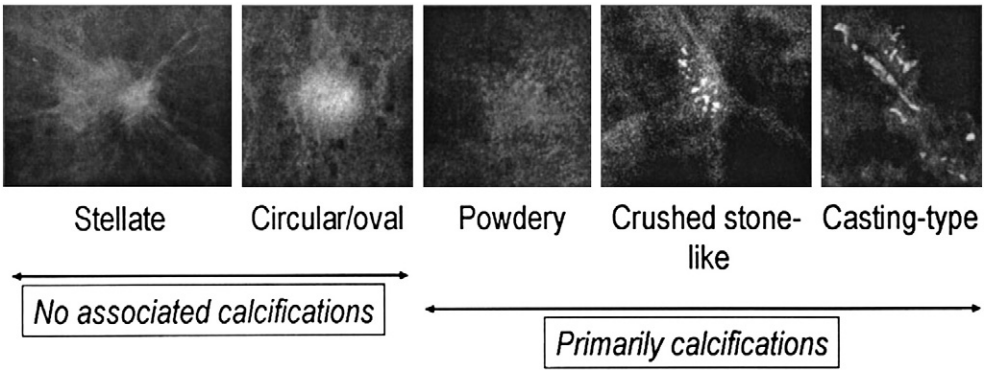

Fig. 1. Mammographic features from samples that were histologically proven, 1–14 mm invasive breast carcinoma cases. Primary calcifications are visible as powdery, crushed stone-like and casting type calcifications taken from Tabar et al. [4].