Breast Cancer RESEARCH

VIEWPOINT

PTHrP and breast cancer: more than hypercalcemia and bone metastases

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Abstract

Parathyroid hormone-related protein (PTHrP) causes hypercalcemia in cancer patients. PTHrP is required for normal breast development and has been shown to promote bone metastases from breast cancers. However, whether the protein also contributes to the formation of primary tumors has been unclear. Two recent papers suggest it may. First, a report in *Nature Genetics* identified the PTHrP locus as a new breast cancer susceptibility gene. Second, a paper in *Journal of Clinical Investigation* demonstrated that PTHrP promotes tumor growth and metastases in MMTV-PyMT mice. These studies implicate PTHrP in the development and growth of primary breast tumors and underscore the need for further research.

Background

Parathyroid hormone-related protein (PTHrP) – also parathyroid-like hormone (PTHLH) – was discovered as the cause of a common paraneoplastic syndrome, humoral hypercalcemia of malignancy [1,2]. Both the *PTHLH* and parathyroid hormone genes descended from a common ancestor and both proteins bind and activate the same G-protein coupled receptor (type 1 PTH/PTHrP receptor). PTHrP is widely expressed in embryos and contributes to the development of many organs, including the breast [1,2]. PTHrP is produced by epithelial cells in the embryonic mammary bud, and the type 1 PTH/PTHrP receptor is expressed by the surrounding mesenchyme. Genetic disruption of either gene results in a failure of mammary development in mice and humans [2]. In the adult virgin breast, PTHrP is produced by myoepithelial cells and its receptor is expressed in the periductal stroma [2,3]. Overexpression of PTHrP in myoepithelial cells inhibits ductal extension, but postnatal disruption of the *PTHLH* gene in these cells has no effect [3]. During lactation, PTHrP is produced by alveolar epithelial cells and is secreted into milk and into the maternal circulation, where it participates in the mobilization of skeletal calcium for milk production [4]. PTHrP thus has important functions in normal breast development and physiology.

PTHrP also contributes to the pathophysiology of breast cancer. PTHrP production by tumor cells in the bone microenvironment has been shown to promote osteoclastic activity and contribute to osteolytic bone metastases [5]. The question of PTHrP's function in primary tumors has been less clear. Studies in cultured breast cancer cell lines have reported conflicting effects on tumor cell behavior [6,7]. Clinical studies have also shown disparate results; some smaller case series suggest that PTHrP expression predicts more aggressive behavior [8,9], while a large, well-controlled clinical study from Melbourne suggested that PTHrP expression was an independent predictor of a more benign clinical course [10]. Therefore, while PTHrP's participation in the development of bone metastases has been well established, what effects, if any, PTHrP has on the development or progression of primary tumors remained unclear. Now, two recent articles underscore the importance of PTHrP in primary breast cancers and call attention to the need for more studies to clarify the protein's functions in breast cancer biology.

The articles

First, in a recent paper published in *Nature Genetics*, Ghoussaini and colleagues combined several datasets encompassing 70,000 patients and 68,000 controls in order to perform genome-wide association studies to identify new breast cancer susceptibility loci [11]. One of the three new loci they identified, rs10771399, was in a 300 kb linkage disequilibrium block that contains only one gene, *PTHLH*.

Second, in work recently published in the *Journal of Clinical Investigation*, Li and colleagues examined the role of PTHrP expression in an animal model of breast cancer caused by PyMT [12]. The authors used the

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MMTV-Cre transgene to target the *PTHLH* gene in mammary epithelial cells, and found that while loss of PTHrP expression did not affect tumor incidence, it did dramatically prolong tumor latency, slow tumor growth and reduce metastases. Restraint of tumor growth correlated with reduced proliferation and increased apoptosis, perhaps due to alterations in cyclin D_1, protein kinase B 1 and 2, and B-cell lymphoma 2 expression. The reduction in metastases may have been related to reductions in the expression of CXC chemokine receptor 4 and the inhibition of angiogenesis. Finally, the authors developed a blocking antibody to PTHrP and demonstrated that it could inhibit primary tumor growth and lung metastases in a xenograft model. These data suggest that PTHrP powerfully promotes tumor formation in breast cancer.

Discussion

The report from Ghoussaini and colleagues focuses attention on PTHrP as a potential contributor to breast cancer susceptibility. If the *PTHLH* gene is confirmed to be causal in resequencing studies of the rs10771399 locus, then animal studies such as those described by Li and colleagues will be instrumental in understanding how PTHrP might alter disease susceptibility. Together, these two studies raise many interesting questions regarding the mechanisms by which PTHrP might alter the formation or progression of breast tumors. Perhaps the most perplexing involves the opposite results reported in a similar study by Fleming and colleagues demonstrating that disruption of the PTHrP gene increased the incidence of tumors in MMTV-Neu mice, results consistent with the clinical study from Australia [10,13]. The opposing results of these two transgenic mouse studies highlight an important issue for future research.

Clearly, the molecular context appears to be critical for determining PTHrP's actions. Although both MMTV-Neu and MMTV-PyMT are models of luminal-type cancer, their pathways to transformation vary in important ways, and other molecules also exert differing effects on tumor formation in these two strains [14,15]. Sorting out why PTHrP has opposite effects in these two models will probably provide important clues to understanding the molecular nature of its actions in breast cancer.

Abbreviations

MMTV, mouse mammary tumor virus; Neu, heregulin 2 gene; PTHLH, parathyroid-like hormone; PTHrP, parathyroid hormone-related protein; PyMT, polynoma middle T antigen.

Competing interests

The authors declare that they have no competing interests.

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