Deepening on Breast Cancer Metastasis: The ERα-Mediated Modulation of KISS/KISS1R System

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Breast cancer is one of the most important diseases worldwide with an annual global fatality of almost 800 000 and the primary cause of cancer mortality in women (1). The risk of breast cancer is age dependent. The probability of developing breast cancer is equal to 0.04% per year for average risk women between age 30 and 39 and increases to more than 10% per year in those over 80 years (2). Breast cancer in women under 40 years is not a common condition. However, a dramatic increase in the number of breast cancers diagnosed in premenopausal women has been reported in several countries. In the United States, 5.5% of breast cancers occur in women younger than the age of 40 years. Approximately 1 in 40 women diagnosed with early breast cancer is very young (<35 y). Breast cancer in young women is associated with a positive family history and gene mutations more frequently than in older women (3).

However, the mainly cause of deaths is not the primary tumors itself but also the result of metastasis to others organs (4). The biological mechanisms of metastasis development have been studied for more than 100 years. However, knowledge of all the cellular and molecular mechanisms that trigger it is still unclear. Further research is necessary to better understand this process, discover solutions for its prevention, and provide patients with a longer life expectancy.

The steps involved in the process of metastasis are often described as the "metastatic cascade," where single tumor cells or small tumor cell aggregates first detach and leave the primary tumor; next, the cells infiltrate the surrounding stroma (invasion) and enter into the circulatory system (intravasation); and finally, they travel to distinct sites where they establish secondary tumor growth (extravasation) (5–9). This seemingly simple process is one of the main concerns of current biomedical science, so when an interesting finding providing hope is encountered, nature itself appears to be illustrating its inherent complexity.

In this difficult path toward understanding this complex process, Cvetkovic et al (10) have opened a new door that will give rise to new research in the near future. They have focused their research in Kisspeptin receptor (KISS1R), also known as GPR54. This is a G protein-coupled receptor that binds kisspeptins (Kps). Kps are neuropeptides encoded by KISS1 and are the natural ligands of the KISS1R. These were initially described as metastasis inhibitors in melanoma (11). Later it was demonstrated that loss-of-function mutations in KISS1R cause absence of puberty and low LH and FSH levels in humans (12, 13). Therefore, the major role for the KISS/KISS1R system is to regulate the gonadotropic axis at puberty and during adulthood via tight modulation of GnRH secretion (14).

KISS/KISS1R is also expressed outside of central nervous system and seems to play a pivotal role in metastatic pathways. Loss of KISS1 expression has also been correlated with increased metastasis and/or cancer progression in malignant pheochromocytoma (15), esophageal squamous cell carcinoma (16), bladder (17), ovarian (18), gastric (19), and pancreatic (20) tumors. Moreover, specific animal studies examining KISS1 in breast cancer clearly demonstrated suppression of metastases in vivo (11, 18, 21, 22).

In contrast, Martin et al (23) found KISS1 messenger elevated in node-positive breast tumors in comparison with node-negative samples, yet no differences were observed in KISS1R, and other authors indicate that KISS1R signaling may correlate positively with breast tumor progression and metastatic potential (24, 25). A possible explanation for this paradox could be the associations of Kps

ISSN Print 0013-7227 ISSN Online 1945-7170
Printed in U.S.A.

Received March 27, 2013. Accepted March 28, 2013.

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Abbreviations: EGFR, epidermal growth factor receptor; ER, estrogen receptor; KISS1R, Kisspeptin receptor; Kp, kisspeptin; MMP, matrix metalloproteinase; TAM, tamoxifen.

to matrix metalloproteinases (MMPs), whose significance in tumor invasion and metastasis formation has been documented (26). It was reported that KISS1 negatively regulates MMP-9 expression in ovarian tumor (27) and hepatocellular carcinoma (28). Moreover, KISS1 protein forms a stable complex with pro-MMP-2 and pro-MMP-9 affecting the proteolytic processing of Kp, without affecting the pro-MMP processing (29). Consequently, it is conceivable that KISS/KISS1R system can have an important role in regulating extracellular matrix-linked growth substances via the regulation of the urokinase type plasminogen activator/plasmin/MMPs/tissue inhibitors of metalloproteinases system, as it has been shown in different models of metastasis, neoplasias, and pathophysiological conditions. Therefore, it seems possible that there is a balance between the metastasis-suppression KISS1 gene and the invasion-related urokinase type plasminogen activator/plasmin/MMP/tissue inhibitors of metalloproteinases genes. In this sense, Cvetkovic et al (10) showed that Kp-10/KISS1R signaling stimulates migration and invasion inducing a mesenchymal phenotype, because the expression of KISS1R induced an epithelial-to-mesenchymal transition-like event, resulting in the acquisition of an invasive phenotype, both in the presence as well as absence of the ligand. Moreover, they showed that KISS1R localizes to the leading edge of cell membranes where it colocalizes with Ras GTPase-activating-like protein IQGAP1, an oncogene that promotes tumorigenesis and binds human epidermal growth factor receptor (EGFR)2, in lamellipodia in motile cells, suggesting that KISS1R may play a dynamic role in cell migration. EGFR is overexpressed in breast cancer, and Cvetkovic et al (10) showed that the complex EGFR-KISS1R regulates EGFR endocytosis (30). Therefore, it seems possible that KISS1R could increase invasiveness of breast cancer cells via an EGFR-dependent mechanism.

On the other hand, a body of evidence supports the notion that estrogen receptor (ER)α-mediated pathways play a critical role in breast carcinogenesis (31). ERα level is consensually used as a prognostic marker of breast tumors and of the response to endocrine therapy (31). Some year ago, Marot et al (24) showed regulation of the expressions of KISS1 and its receptor through estrogen signaling pathways in breast tumor cell lines. Conversely, tamoxifen (TAM) administration up-regulated KISS1 and KISS1R expression in ER-positive breast tumor cells. The findings of Cvetkovic et al (10) indicate that ER-mediated regulation of KISS1 transcription predominates in the complex transcriptional context of mammary tumor progression. In their recent paper, the authors found that the ERα status of breast epithelia critically regulates the ability of KISS1R to induce an invasive phenotype and that level of KISS1R is regulated negatively by estradiol. Therefore, these findings seems to suggest that KISS1 expression level appeared to be an attractive molecular marker for predicting TAM responsiveness of ERα-positive breast cancers, mainly in postmenopausal women. The high KISS1 expression in ERα-positive breast tumor cells with poor prognosis may also reflect hormonal resistance to estradiol, impeding the beneficial action of TAM treatment in these patients.

Thus, resistance to antiestrogens is one of the major challenges in the treatment of ER-positive breast tumors (32). In addition, with gene expression assays recently proposed to predict tumoral responses to TAM (33–35), everything seems to indicate that an evaluation of KISS1 and its receptor's tumoral mRNA levels could be important for the clinical management of breast tumors. Additionally, KISS1 levels appear to be an interesting new marker for distinguishing breast tumors from normal mammary tissues.

In summary, Cvetkovic et al (10), in their last work, have proposed a new model for ERα-mediated modulation of KISS/KISS1R signaling, in which ERα expression is lost in breast epithelia as breast cancer progresses, and the brake keeping KISS/KISS1R signaling in check is removed, resulting in increased signaling through KISS1R, as well as increased induction of epithelial-to-mesenchymal transition in the mammary epithelial cells and acquisition of a mesenchymal phenotype, required for metastasis. This model is very interesting and opens new expectations, in which signaling KISS1/KISS1R could become a potential therapeutic target.

Acknowledgments

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Disclosure Summary: The author has nothing to disclose.

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