Ezh2, a novel target in detection and therapy of breast cancer

In 2013, 232,340 new cases of invasive breast cancer and 39,620 breast cancer deaths were estimated among US women. Currently, one in eight women in the US will develop breast cancer in her lifetime, and breast cancer is the second leading cause of cancer death among women. Despite many therapeutic advances over the last 20 years, metastatic disease remains a major cause of death for breast cancer patients, elucidating a crucial problem in the overall management of patients. The 5-year survival rate for metastatic breast cancer is currently estimated as <25%. The primary molecular subtypes of breast cancer have been identified by molecular markers: luminal tumors that are estrogen receptor and progesterone receptor positive, HER-2 positive tumors, and triple-negative breast cancer (TNBC) in which all markers are negative. As expected, these different cancer phenotypes have varying behaviors and prognoses, with the luminal type being well differentiated and the HER-2 and TNBC types being poorly differentiated. Furthermore, TNBC, which accounts for about 20% of all breast cancers, does not benefit from currently available endocrine and HER-2-targeted therapies. Given the more aggressive disease course and poor prognosis, including higher likelihood of brain and lung metastasis, it is important to identify novel therapeutic strategies for this subtype.

Enhancer of Zeste Homolog 2 (Ezh2), is a Histone-lysine N-methyltransferase enzyme that is encoded by the EZH2 gene. Ezh2 is a member of the polycomb group, a family of proteins that act as suppressors of transcription. Ezh2’s suppressor function occurs via the addition of three methyl groups to Lysine 27 of histone 3, a modification leading to chromatin condensation. Ezh2 is overexpressed in a number of human malignancies, including breast cancer, and its overexpression leads to oncogenesis by decreasing the expression of tumor suppressor genes. Ezh2 is of interest as a therapeutic target in TNBC, as TNBC has been shown to overexpress this protein. Targeting Ezh2 might provide an alternative treatment option to cytotoxic chemotherapy, the current standard of care for TNBC patients.

Multiple studies have confirmed the overexpression of Ezh2 in TNBC, as its presence has been associated with high tumor cell proliferation and features of aggressive breast cancer, including high nuclear grade and HER-2 positivity. In contrast, low-grade estrogen receptor-positive breast cancers, which generally have much better prognoses, have shown low Ezh2 expression. Consequently, studies have shown impaired tumor cell proliferation and metastasis after knockdown of Ezh2. Ezh2 overexpression has been associated with increased tumor size and disease stage, younger age of disease onset, negative hormone receptor status, and poor survival. Furthermore, overexpression of Ezh2 has been associated with poorly differentiated...
histologic features, particularly the TNBC phenotype, and thus, worse prognosis.

Not only has Ezh2 overexpression been confirmed in TNBC, but also it has been shown to be crucial in the self-renewal of TNBC cells. Studies have established the presence of a subpopulation of cells within a tumor that have the ability to self-renew and initiate tumor formation, whereas the majority of tumor cells are unable to self-renew. These cells, called as cancer stem cells (CSCs), are long lived and have been shown to be resistant to chemotherapy, and promote tumor reoccurrence and metastasis. CSCs are present in TNBC, with Ezh2 having been identified as playing an important role in the self-renewal of breast CSCs.

Increased expression of Ezh2 has been shown to be associated with transformation of breast epithelial cells to neoplasia, including atypical ductal hyperplasia, ductal carcinoma in situ, and inflammatory breast cancer (IBC). In morphologically normal breast tissue, Ezh2 is a molecular marker for precancerous states. Ezh2 has also been found to be a marker for aggressive breast cancer, as increased expression has been associated with disease progression. Ezh2 has been shown to repress the expression of E-Cadherin, enhance p38-kinase signaling, and prevent DNA repair, and these are likely the main mechanisms contributing to tumorigenesis and disease progression.

In addition to contributing to tumorigenesis, Ezh2 also appears to increase the risk of distant metastasis in patients with familial early-stage breast cancer. Ezh2 knockdown was shown to inhibit the migration and invasion of IBC cells. Additionally, Ezh2 knockdown suppressed the angiogenesis and tumor growth of IBC in vivo. Analysis of a cohort of 400 human tumors found Ezh2 to be overexpressed in clinically challenging types of breast cancer, such as basal-like, triple-negative disease, and HER-2-enriched tumors.

As the work on developing a targeted inhibitor of Ezh2 continues, our team is investigating the effects of eradication of Ezh2+ cells in vivo. Preliminary data in animal models appear very promising (F Farassati, unpublished data April, 2017), supporting our efforts to elucidate the future of Ezh2 as a novel target for therapy.

Disclosure
The authors report no conflicts of interest in this work.

References