Commentary

MELK kinase holds promise as a new radiosensitizing target and biomarker in triple-negative breast cancer

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Breast cancer remains the most common malignancy diagnosed in women and is one of the leading causes of cancer death among women. Breast cancer has accounted for ~29% of new cancer cases among women in the United States in 2015 and approximately 40,000 women per year are expected to die from the disease (1). The major subgroups of breast cancer, based on combined expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) have important implications in breast cancer etiology, the systemic therapies prescribed, the effectiveness of such therapies, and in outcome, both recurrence and survival (2,3). ER-positive patients have the best prognosis, due to effective targeted hormonal therapies and a more indolent disease phenotype. Prior to targeted therapy, HER2+ tumors portended some of the worst prognoses, but the development of a targeted treatment (trastuzumab) (4,5) has resulted in marked improvement in outcome (6). The triple negative breast cancer (TNBC) subtype (defined as ER-negative, PR-negative, and HER2-negative) comprises 10–30% of all invasive breast cancers, but the incidence varies by age and race/ethnicity. TNBCs have recently emerged as a distinctly highly aggressive subtype, which arises at an earlier age, is particularly prevalent among African-American and pre-menopausal females (7), has no available effective targeted therapies, and generally portends a poor outcome. Moreover, TNBCs tend to be resistant to radiation therapies (8). Thus, there is a great need to develop more effective therapies and to identify new biomarkers that might identify patients who would be responsive or resistant to current therapies.

A recent study by Speers *et al*. (9) may have significant clinical impact for this difficult and important challenge. In this study, the authors focus on the maternal embryonic leucine zipper kinase, or MELK, which had been previously implicated as an oncogenic kinase important for proliferation in basal-like breast cancer (10). MELK has also been shown to be important for mitosis and replicative stress in glioma stem cells (11,12), and was shown to protect glioma stem cells from radiation induced cell death (13). Previous work by the same group had identified MELK as overexpressed in TNBC (14), suggesting that it might be a potential target for this breast cancer subtype. Thus, in this recent study, the authors hypothesized that MELK may impact sensitivity of TNBC cells to radiation.

In the current study (9), Speers and colleagues validate the finding that MELK is overexpressed in TNBC, and show that MELK overexpression induces radioresistance in a large panel of 21 breast cancer cell lines. They go on to demonstrate that siRNA knockdown of MELK delays repair of double strand breaks from ionizing radiation *in vitro*, and that stable knockdown of MELK reduces growth of TNBC cells in mouse xenografts. Additionally, they show that combining radiation with MELK knockdown synergistically inhibits tumor growth *in vivo*. Importantly, the authors also take advantage of a recently developed MELK inhibitor, OTSSP167 (15), and show that MELK inhibition synergizes with radiation therapy to inhibit TNBC xenografts. This finding raises the possibility of radiosensitization of TNBC tumors with MELK inhibitors as a combinatorial neoadjuvant therapy to improve outcomes in these patients.

In addition to these significant findings, Speers *et al*. (9) also demonstrate that MELK can be used as a strong biomarker of risk of local recurrence for early stage

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breast cancer patients treated with adjuvant radiation in two large, independent datasets. Thus, women with high MELK expression would potentially derive less benefit from radiation therapy alone and might benefit from more aggressive treatments and/or combination therapies with MELK inhibitors.

Currently there are Phase I clinical trials recruiting for solid (NCT01910545) and hematological (NCT02795520) malignancies to test the safety and efficacy of MELK inhibitors. Thus, while TNBC remains one of the most difficult challenges for treatment of breast cancers, the recent findings regarding radiosensitization of these tumors via inhibition of MELK may provide new hope for patients suffering from this disease.

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Footnote

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