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Vaccines and early breast cancer

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Our recent work has cast an exciting new light on the expression of cancer/testis (CT) genes in breast cancer and its precursor lesions. Cancer/testis (CT) genes, normally expressed only in the human germ line but activated in various malignancies, are immunogenic in cancer patients. Their tumor-restricted expression pattern makes these proteins promising clinical reagents for anticancer immunotherapy.[1] Although the overall frequency of CT gene expression in breast cancer is low, our previous data demonstrated that the expression of CT genes such as NY-ESO-1 and members of the MAGEA family is high in a subset of estrogen receptor (ER)-negative, high-risk carcinomas.[2-4]

Immunotherapy strategies can potentially induce or amplify pre-existing responses to eliminate transformed cells. The development of successful immunotherapy against tumors starts with the identification of tumor antigens (TA), preferably those that are tumor-specific, such as those derived from the CT genes. To evaluate CTs as therapeutic cancer vaccine targets, multiple clinical trials worldwide have been performed or are underway using either MAGEA3 or NY-ESO-1. Adjuvant therapy with MAGEA3-based cancer vaccine in a double-blinded, randomized, placebo-controlled, proof-of-concept phase II study in 182 patients with completely resected stage IB or II non-small cell lung carcinoma (NSCLC) yielded encouraging results.[5] A phase III clinical trial (MAGRIT), expected to enroll more than 2000 patients from 400 participating institutions in 33 countries, promises to be the most statistically meaningful adjuvant immunotherapeutic clinical trial for NSCLC to date.[5] Nonetheless, such a clinical environment may not be the ideal therapeutic context for cancer vaccines, as immune responses are not infrequently blunted in advanced or end-stage malignancies. The occurrence of CT-expressing ductal carcinoma in situ (DCIS) may thus offer a more appropriate therapeutic opportunity.

In our most recent study, published in *Oncoscience* in January 2014,[6] the frequency of expression of certain CT genes and the related pathology was studied in 40 patients with breast lesions, including DCIS, lobular carcinoma in situ (LCIS), and atypical proliferative lesions. In recent years, molecular and clinical observations have corroborated the hypothesis that DCIS is a precursor of invasive breast cancer (IBC).[7] Our study discloses a group of ER-negative DCIS for whom CT expression and other characteristics are similar to those found in overt breast cancers. Of the CTs studied, MAGEA3 was only found to be expressed in ER-negative DCIS, and its expression was marginally associated with an immune response as evidenced by high CD8+ lymphocytic infiltration. Our study was not designed to ascertain if the CT genes could be markers of progression; this is the subject of our ongoing work. Although current data suggest that ER-negative DCIS are more likely to progress, other markers such as those of EMT or the cell cycle need to be incorporated in the quest of defining more clearly indices of progression. Assuming that the expression of CT genes could identify and/or is associated with lesions that are more likely to progress, cancer vaccines based on CTs might have a real impact on the treatment of DCIS patients in the postoperative adjuvant setting.

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