Targeting Tumor Dormancy to Prevent Breast Cancer Recurrence

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Despite early detection and adjuvant therapy, breast cancer remains the leading cause of cancer mortality in women, largely due to distant, incurable recurrences arising years, or even decades, after treatment of the primary tumor. Recurrent, metastatic tumors arise from the pool of residual local and disseminated tumor cells (RTCs) that survive primary treatment and persist in the host in a presumed dormant state. We hypothesize that effectively disabling the survival mechanisms by which RTCs persist in breast cancer patients following treatment will deplete this critical reservoir of cells, reduce tumor recurrence, and thereby improve survival. Since RTCs constitute the reservoir from which recurrent cancers arise, understanding their biology is a critical priority in cancer research. At present, however, the mechanisms enabling these cells to survive in a dormant state and ultimately recur are poorly understood, and RTC-directed treatment approaches are in their infancy.

To address this need, we have developed genetically engineered mouse (GEM) models for human breast cancer that recapitulate key features of human breast cancer progression, including metastasis, residual disease, dormancy and recurrence. Investigation of these models using both genetic and pharmacological approaches has identified several mediators of dormant RTC survival and recurrence, demonstrated their relevance to pathways that contribute to therapeutic resistance in human breast cancers following targeted therapy or chemotherapy, and revealed that pharmacological targets for dormancy and recurrence may be unique to these stages of tumor progression. These findings have, in turn, led to the initiation of clinical trials to test the ability of targeted therapies to deplete the burden of RTCs in the bone marrow of breast cancer patients and thereby decrease risk of relapse. If successful, the ability to therapeutically target survival mechanisms utilized by RTCs would constitute a powerful approach to preventing cancer recurrence and the mortality associated with it.