LPA1 inhibition induces metastatic dormancy in mouse models of breast cancer

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A lysophosphatidic acid receptor 1 (LPAR1) inhibitor, known as Debio-0719, suppresses the development of metastases in mice by inducing cancer cell dormancy, according to a study published August 21 in the *Journal of the National Cancer Institute*.

Metastasis is a main contributor to mortality in cancer patients. Patients with "triple negative" breast cancer (tumor cells that are hormone receptor negative and express normal levels of the HER2 oncogene) are known to be at high risk for metastatic progression.

In addition, breast and prostate cancers are known for having variable but possibly long periods of dormancy, where the disease is silent. Factors inducing or breaking a dormant state are poorly understood, but extending dormancy is considered a therapeutic goal.

To determine the effects of LPA1 inhibition on metastatic dormancy, Jean-Claude A. Marshall, MSc., Ph.D. of the Women's Cancers Section, Laboratory of Molecular Pharmacology, Center for Cancer Research, NCI, and colleagues analyzed primary tumor size, distant metastases and their molecular characteristics in two model systems of aggressive "triple negative" breast cancer metastasis, the murine 4T1 mammary carcinoma model and human MDA-MB-231 human breast carcinoma model. Debio-0719 or shRNA knockdown of LPA1 significantly inhibited metastasis formation without affecting primary tumor size. Tumor cells found in distant organs, such as the lungs and liver of Debio-0719 treated mice, had ceased proliferation and exhibited other molecular

hallmarks of dormancy. LPA1 inhibition represents one of the first compounds to induce dormancy in metastatic sites in triple negative breast cancer.

The authors point out that LPA1 inhibition had no effect on the growth of the primary tumors in either model system. As such, it would not normally be considered further for drug development. Their data suggest that alternative drug development approaches may identify compounds with novel activities, such as metastatic dormancy.

The authors point out that their study did not determine the duration of tumor dormancy, and that Debio-0719 and other LPA1 inhibitors should be tested in additional model systems. However, they conclude: "With such inhibitors in hand, the interaction of dormancy pathways and standard of care therapeutics, radiation therapy, patient stress, and other important factors can be determined to develop a deeper picture of potential preventative and therapeutic scenarios."

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