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LAY ABSTRACT

Breast cancer (BC) is the most commonly diagnosed cancer, and the second leading cause of death in women because of tumor cell metastasis. There is an urgent need to understand further, why some cancers become metastatic and develop safe and effective treatments for metastatic BC. Our research has shown that a protein called "RAGE" increases BC malignancy and metastasis in animal models. RAGE is a receptor present on the surface of BC and immune cells, and gets switched on by many of the inflammatory proteins produced in cancer. We are especially interested in how RAGE activates BC cells, and how it makes cancer worse by recruiting a normal cell type from the blood known as myeloid-derived suppressor cells (MDSCs). MDSCs have recently been shown to be major regulators of the amount of inflammation and immunosuppression in a tumor and how aggressive BC can become. MDSCs also affect how cancer responds to anti-cancer therapy including chemotherapy and immunotherapy. We have shown that by reducing the expression of RAGE in highly metastatic BC, both in the tumor and non-tumor cells, we can prevent BC metastasis in mouse models. Human studies have revealed increased RAGE protein levels in aggressive breast cancers, and higher levels of RAGE are predictive of worse breast cancer outcomes, especially in TNBC. Furthermore, we have shown that drugs that specifically block RAGE make BC cells less metastatic in mice. While RAGE drives metastasis, it is not known if inhibiting RAGE will lead to the regression of established metastatic disease. Therefore, further preclinical testing and validation of RAGE inhibitors are critical before translation to people with metastatic breast cancer. We will test whether RAGE drives metastatic disease using BC animal models and with drugs against RAGE. We will also examine whether the combination of RAGE inhibitors with low-dose chemotherapeutics and immunotherapies synergize to eradicate metastatic disease in mice. We will also explore the importance of RAGE expression in tumor cells versus expression in normal tissues using genetic deletion of RAGE in either the tumor or normal cells. Completion of the aims of this study not only holds great promise for understanding metastatic disease but also, more importantly, the development of a novel treatment for breast cancer metastasis. Together with the experience of Dr. Lippman in translating scientific findings to the clinic, the initiation of clinical trials is feasible after the completion of this proposal. The results of this study are likely to have a significant impact on the clinical practice and treatment of metastatic breast cancer. The testing and development of RAGE-targeted inhibitors that are both safe and effective in treating metastatic BC have the potential to make a significant difference in the lives of breast cancer patients.