Development of a Humanized Mouse Model of Breast Cancer Liver Metastasis

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Breast cancer is one of the most frequently diagnosed cancers in women, with few effective therapies for advanced-stage metastatic disease. This malignancy is a major health threat worldwide because of its high incidence rate, and frequent occurrence of metastasis to secondary organs. In particular, liver metastasis was found in over 60% of late stage breast cancer patients based on autopsy analysis, and is a major cause of death for the patients.

Animal models of breast cancer metastasis to the lung, bone and brain have provided much insight into the spread of breast cancer to these tissues, however, a clinically relevant, liver specific model of metastasis is still lacking and the molecular basis of liver metastasis remains poorly understood. Available models also do not adequately mimic human disease in order to identify liver metastasis genes or to evaluate new therapeutics for preventing or treating liver metastasis. In our preliminary studies in collaboration with Dr. Alexander Ploss, an expert in engineering “humanized” mice for liver disease research, we have generated a human liver chimeric mouse. This mouse model essentially grows a human liver following human liver cell transplantation into an immune-deficient strain of mice called FNRG. We have also found that if we inject the human breast cancer cell line MDA-MB-231 into these human chimeric mice, liver metastases readily develop and are more aggressive than in mice that are not engrafted with human liver cells (hepatocytes). These results suggest that the human liver presents a favorable environment for metastatic breast cancer cells and may serve as a useful model to identify the factors in the breast cancer cells and in the liver that drive metastasis to this organ.

In this proposal, we will determine if the human liver provides a more compatible environment compared to the mouse liver for the formation of liver metastasis. We will further use this system to isolate breast cancer cells with enhanced liver metastatic abilities and identify genes that may promote liver metastasis. These genes will be validated in follow-up experiments to confirm their role in the process of breast cancer metastasis to the liver as well as their clinical importance in predicting risk of liver metastasis in human breast cancer patients. The results of this study will have a direct impact on developing novel strategies to prevent or treat liver metastasis and subsequently reduce the mortality of patients from breast cancer.