Genomic Dissection of Patient-Derived Xenograft Breast Cancer Liver Metastasis Models

J. Chuck Harrell, PhD
Assistant Professor, Department of Pathology
Virginia Commonwealth University

This year more than 230,000 women will be diagnosed with one of five major types of genetically distinct breast cancer; estrogen-sensitive (ER+; Luminal A, Luminal B), estrogen-insensitive (ER-/Triple Negative; Basal-like, or Claudin-low), or HER2+. Most of these patients undergo a lumpectomy or mastectomy, which are both surgeries that remove the primary tumor mass. Localized radiation around the site of the primary tumor is also often administered to kill any remaining cells. In some of these patients from that point onwards they are cured and never get breast cancer again. However, many patients are not so fortunate, and at the time of diagnosis or shortly thereafter, the cancer cells are found growing in a vital organ far away from where the tumor was first found. The spread and growth of cancer cells in a secondary site is termed metastasis, and diagnosis of metastatic disease conveys a bad prognosis. For over one-hundred years, it has been known that the first site that breast cancer spreads to is often the liver, however only limited liver metastasis research has been performed due to the inherent difficulty in developing the appropriate models. Therefore, the proposed studies that this grant will fund aim to develop better methods, models, and genomic insights that are geared to eradicate liver metastases.

Liver metastases often start asymptomatic, then progress to cause nausea, pain in the abdomen, weight loss, fevers, and jaundice. Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and ultrasounds can all be used to visually identify liver metastases. These tests combined with liver function assays and liver biopsies nearly always confirm metastatic growth. We previously identified four public databases where these types of clinical tests were used to identify the presence of liver metastasis in a total of 855 breast cancer patients. In addition to this clinical information, each sample in this dataset was screened (with gene expression microarrays) so that we could understand the genetic blueprint of each tumor. In this dataset, 107 out of 773 (14%) patients had liver metastases as their first site of relapse. Strikingly, 28% of HER2+ tumors and 14% of Basal-like tumors spread first to the liver. Of the HER2-enriched tumors that spread to the liver, we found that those cancer cells that expressed genes that were normally found only in liver cells (fibrinogen) were the ones that were the aggressive at colonizing the liver. Thus, the cancer cells that had liver-like properties may trick the liver into allowing it to reside there. Interestingly, fibrinogen is a clotting factor, so perhaps these cancer cells are more ‘sticky’ and allow them to adhere to and colonize the liver.

The experiments within this proposal aim to further develop a newer biological tool to specifically research liver metastasis. We will use breast cancer samples that were directly taken from a patient and grafted into a mouse. Unlike cancer cell lines which are grown in a plastic dish, these patient-derived xenografts (PDX) maintain the genetic and phenotypic characteristics found in the patient they were isolated from. We will use two HER2+ (or “HER2-Enriched”) and two Triple Negative (Basal-like) PDX models, and grow them in an immune-deficient (preventing host rejection of foreign cells) mouse and characterize the genetic differences that arise when the PDX lines are grown in the breast or the liver. We will then isolate the cancer cells that were capable of growing as liver metastases and grow them repeatedly in recipient mouse livers in an attempt to purify out those cells with the most aggressive liver metastasis characteristics. Through genetic tests of the original and liver-seeking cancer cells, we will be able to determine the pathways the liver-tropic cells rely on for their aggressive liver growth characteristics. Also, since chemotherapies are the most common type of liver metastasis treatment, we aim to understand why some cancers do not respond, or lose responsiveness, to chemotherapy when growing as liver metastases, compared to primary tumors. Therefore, genetic tests will be performed on liver metastases and mammary tumors undergoing chemotherapy treatment, with the goal of ascertaining mechanisms through which the liver microenvironment contributes to therapeutic efficacy.

Important for this funding mechanism, part of the goal of this proposal is to generate liver-tropic models that can be shared with collaborating investigators in accordance with organizational Materials Transfer Agreements.