



Cancer Biology Breast Cancer

The Machado Lab: Understanding the Early Stages

Prior to the manifestation of breast cancer, breast tissue goes through several distinct premalignant stages. The earliest stage in which a premalignant lesion is considered *bona fide* cancer is ductal carcinoma in situ (DCIS). Detectable by mammography, these DCIS lesions are treated with surgery and often radiation and hormone therapy. However, only about half of these patients would actually develop invasive breast cancer if left untreated.

The laboratory of **Heather Machado** aims to illuminate what causes some DCIS lesions to progress to invasive cancer while others remain indolent. The ultimate goal is to identify biomarkers that predict which patients are at risk for developing invasive breast cancer, so that individualized patient care could be adopted. In particular, the lab studies the role of the breast stroma (especially the macrophage immune cell population) in DCIS progression.

Unique Mouse Models: Enabling Study of Early Stages

Most animal models used to study breast cancer do not replicate the early stages, including DCIS. The Machado lab utilizes transplanted mouse mammary epithelial cells lacking the p53 gene to recapitulate breast cancer development in its entirety in a living animal. In addition, Dr. Machado has helped to develop a unique human-in-mouse model of DCIS progression, in which some DCIS lesions become invasive where others remain non-invasive.

The lab also uses a matrigel-based cell culture system to culture DCIS cells with macrophages, allowing for a more mechanistic interrogation of DCIS-to-invasive-cancer progression. These unique model systems, when used in combination, allow the lab to identify potential biomarkers and treatment strategies that differentiate invasive DCIS from benign disease. Two of these targets, Gas6 and Axl, are currently being investigated by the lab both for their prognostic utility and for their specific mechanisms of action and importance in DCIS development and progression.

Small Molecule and Protein Regulators of p53

The Lu lab also explores the ability of existing drugs to regulate the behavior of p53, as well as the identification of novel cellular regulators and transcriptional targets. One example is Inauhzin, a drug that inhibits the activities of the proteins SIRT1, which deacetylates p53, and IMPH2, which is essential for GTP synthesis, leading to their inactivation.

Other work includes the novel p53 suppressor protein PHLDB3, which suppresses p53 activity by helping MDM2 mark p53 for degradation; the NGFR protein (which is normally found in neurons but is also overexpressed in cancers) which also suppresses p53 by stabilizing MDM2; and a novel target of the p53-related protein p63 called CCDC3, which is involved in lipid metabolism. With one lab studying several individual targets and regulators of p53, it is better positioned to understand how ribosomal stress and metabolism can influence p53 and its downstream transcriptional programs.

Normal Breast Development Biology

It has been recognized for decades that normal breast development spanning from puberty to gestation can affect a woman's risk for developing breast cancer. However, the specific mechanisms behind this interplay remain poorly understood.

The Machado lab is addressing this gap in knowledge by studying the stroma of the breast during the process of involution. After lactation ceases, the breast tissue undergoes this process, which involves a high rate of apoptosis in the breast tissue and creates a pro-inflammatory environment. Chronic and prolonged exposure to pro-inflammatory signals is known to be a prerequisite condition for carcinogenesis in a wide variety of solid cancer tumors.

By investigating this process and the role of the immune system and other cells in the breast stroma, the lab plans to identify novel therapeutic targets for the treatment of a specific type of breast cancer called post-partum-associated breast cancer. Specifically, they found that a gene called C/EBP β is an important mediator of breast remodeling during involution. Understanding the mechanisms that regulate this process may lead to better treatment strategies for high-risk patients.

Contact & Further Info:



James R Zanewicz, RTTP
Chief Business Officer
zanewicz@tulane.edu
504.919.3800 (m)



Claiborne M Christian, PhD
Business Development Assoc.
christian@tulane.edu
504.909.3905 (m)

engage.tulane.edu
t: @engagetulane

Tulane

SCHOOL OF MEDICINE

