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 Lab 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 coculture 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.
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/EBPβ 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 and Further Information:
James R Zanewicz
Chief Business Officer
zanewicz@tulane.edu

Find Us:
engage.tulane.edu
t: @zanewicz
t: @engagetulane