The Role of Adipose Tissue in Capturing Human Diversity in Breast Cancer Preclinical Models

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Female breast cancer represents 15.2% of all new cancer cases in the United States with an estimated 297,790 new cases and 43,170 deaths in 2023[1]. Based on data collated by the American Cancer Society, female breast cancer incidence increased with a rate of 16.9 per 100,0000 women annually [2]. Data acquired by the National Breast Cancer Coalition and other entities evidenced variation in breast cancer incidence and mortality amongst different ethnic, racial, and age groups[3, 4]. Breast cancer is the leading cause of cancer-related deaths amongst African American and Hispanic women[3]. In particular, African American women are more susceptible to distant-stage breast cancer and high-grade tumors compared to other women[3]. African American women have the highest incidence rate for <40 years old and the highest mortality rate for ages 20-49 years old due to a higher proportion of triple negative breast cancer (TNBC) [3, 5]. White women have the highest incidence at ages 45-49 years old followed by Asian Pacific Islander (API) women whereas American Indian Alaska Native (AIAN) women have the highest mortality rate in women 70-75 years old [3, 5].

The statistics demonstrate the complexity of the disease and overwhelming evidence of diversity and heterogeneity in breast cancer etiology, progression, and treatment response. Application of these statistics becomes critical in the development of preclinical models for disease modeling and drug discovery. In 2020, the Pharmaceutical Research and Manufacturers of America reported that over 1,300 medicines, vaccine, and other immunotherapies for cancer treatment were in clinical trials, including 108 specific to breast cancer [6]. According to ClinicalTrials.gov, 1,421 studies are ongoing or currently recruiting for breast cancer drug intervention evaluation [7]. Many potential interventions and clinical trials are underway, yet an impact on patient mortality has yet to be realized. Given the complexity of the disease, current

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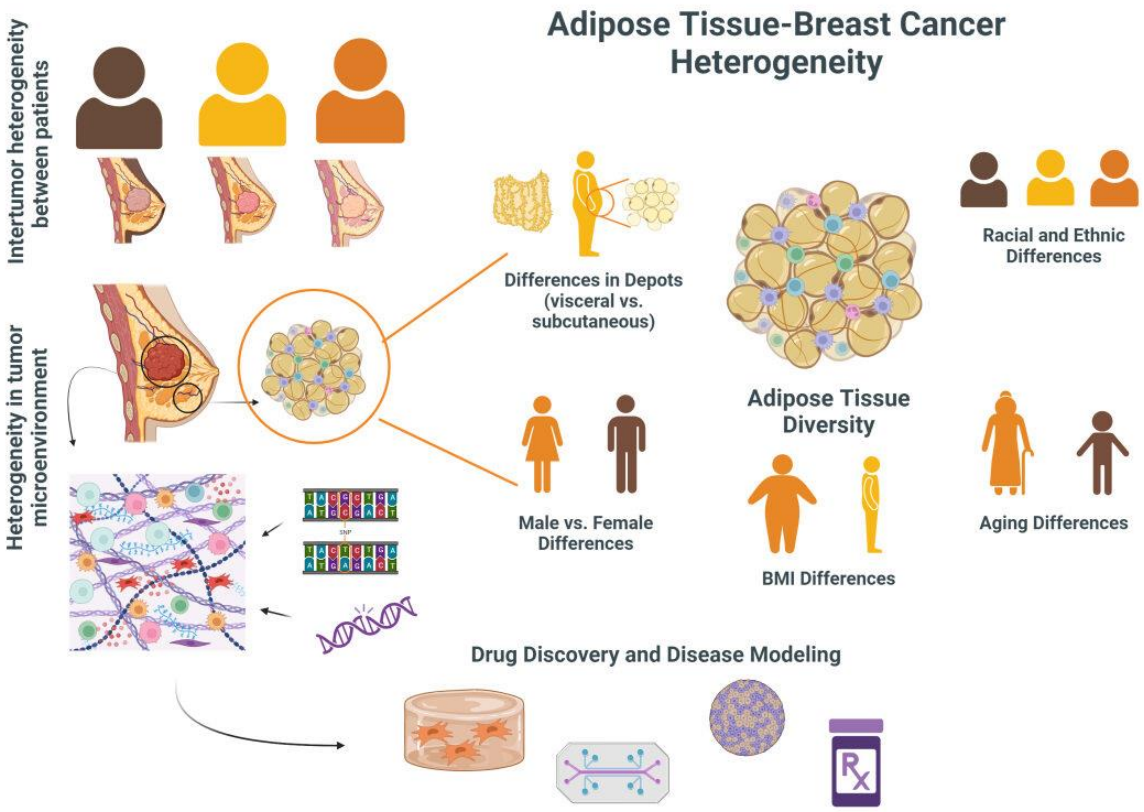

Figure 1. The generation of preclinical breast cancer models must expand beyond the MPS model design criteria and account for intratumoral and intertumoral heterogeneity, as well as patient specific heterogeneity of the associated adipose stromal environment. Figure created using Biorender.com.

models may not recapitulate the microenvironment observed in vivo. Frazier et al. highlighted the ideal breast cancer MPS model design criteria previously described by Bissell, Griffith, Prestwich, and their colleagues as having attributes including: materials of human origin, extracellular matrix, heterogenous cell population, validated pharmacodynamic/pharmacokinetic features, human-relevant absorption/distribution/metabolism/excretion (ADME) properties, adaptability, economy, and user-friendly set up [8]. Mimicking the tumor microenvironment is of particular interest due to its pivotal role in tumor progression and treatment response [9]. The tumor microenvironment (TME) is a heterogeneous network consisting of a diverse population of cells and ECM components that create a unique signaling network with the tumor itself [10, 11]. Given the proximity of breast tumors to mammary adipose tissue, more efforts have been made to enhance the complexity of current models and capture the entirety of the TME with the inclusion of adipose tissue and adipose-derived stromal/stem cells (ASCs) [12-16]. Current models include traditional 2D co-cultures [17-22], 3D co-cultures [23-31], spheroids and organoids [32-37], bioprinted and engineered microenvironments [38-43], microfluidic systems [44], and xenograft models [12, 36, 45-48]. In particular, Obatala Sciences' ObaCell® Fat-On-A-

Chip technology has supported the investigation of methionine aminopeptidase 2 (MetAP2) inhibitors as a targeted treatment for adipose-associated breast tumors. As emphasized in **Figure 1**, the engineering of preclinical breast cancer adipose tissue models is multifactorial in nature. Models require not only the attributes described by Bissell, Griffith, and Prestwich, but also need to incorporate patient-derived tissues, cell, and their derivatives to grasp intertumoral heterogeneity [9, 12, 49]. More importantly, the heterogeneity of adipose tissue and ASCs and donor specific differences must be taken into careful consideration with the generation of breast cancer adipose tissue preclinical models [50].

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