Review of Methodology in Biomechanical Breast Cancer Research

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ABSTRACT

While the tumor microenvironment is an important topic in oncology, only recently has mechanotransduction been a focus due to its better-understood role in cell signaling. However, study of these mechanisms is difficult *in vivo* as it is hard to accurately measure force within organisms. To this end, we elucidated a specific mechanosensitive PIEZO pathway in triple-negative breast cancer and researched *in vivo* methodology in study. We complement this research by touching on bioinformatic techniques that complement *in vivo* and *in vitro* research as well as discuss *in silico* models. Overall, while *in vivo* and *in silico* study improve, increased integration will hasten development and lead to fully computational experimental models. This may allow ease of research as well as expedite simpler personalized medicine.

AUTHOR CONTRIBUTIONS

Keo Chhun researched and wrote the introduction. Taman Kanchanapalli researched and wrote *in vivo* methodology. Lalith Roopesh researched and wrote the bioinformatic work, conclusions, abstract, and put together the references.

All authors reviewed and put together the poster together.

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INTRODUCTION

The tumor microenvironment (TME) is the cellular environment in which cancer cells reside. Within this environment, the body's immune cells struggle to perform their duties and the non immune cells function to nourish the tumor. For example, CD8+ T cells become unable to function properly due to over stimulus from the antigen-rich environment present in TMEs[7]. They also contain cancer stem cells, which are thought to be responsible for relapses as they go into a dormant state after treatment and reemerge later[10].

Mechanotransduction is the process of converting mechanical stimuli into electrochemical responses that affect the TME. For example, when osteocytes undergo mechanical stimulation, they release more prostaglandins, a hormone with various functions ranging from smooth muscle contraction to pain mediation[3].

Some general mechanotransduction pathways are the p38 MAPK/HSP27 pathway and the JNK/c-Jun pathway. In the p38 MAPK/HSP27 pathway, the application of compression upon the cancer cells activated the relevant p38 mitogen-activated protein kinase and heat shock protein 27. The activation of these proteins, along with the JNK/c-Jun pathway, leads to actin cytoskeleton remodeling and cancer cell migration[4].

The main focus of this literary review is on the breast cancer PIEZO pathway. In this pathway, the PIEZO family of mechanical-gated ion channels plays a role in the development of cancer. For example, the PIEZO1 gate assists in the migration of breast cancer cells. Another example is the PIEZO2 gate, which causes various effects ranging from increased invasiveness of TNBC (triple negative breast cancer) cells to worse prognosis (prediction of disease progress) of TNBC[5].

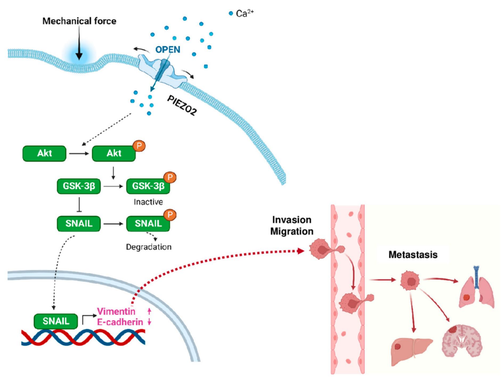

Figure 1. Model of PIEZO2's role in breast cancer. Adapted from Katsuta et al.[5]

IN VIVO METHODOLOGY

In vivo experimentation is generally harder due to higher difficulty in controlling every variable, stress indication variability, applicability to wider populations, and expensiveness. Despite these setbacks, there are three specific methods of In-Vivo experiment we can do to measure the effects of stress on tumor cells.

Elastography is the usage of ultrasound-based elasticity imaging which combines early methods of palpation and US methods of tissue stiffness imaging. This method is used *In vivo* to assess heterogeneity which is the quality of a tissue space being diverse[8]. This is indicative of cancer because it identifies the genotype of cancer cells, their micro-environment, blood and lymphatic microvasculature, and spatial distribution of desmoplastic reaction. Elastography creates *in vivo* elastic modulus images on cancerous tumors and found that they were more heterogeneous when compared with benign tumors[8]. This innovative method would be able to identify cells that are experiencing stress and the levels of stress that causes them to undergo carcinogenesis.

Cancerous cells that are inadequately detected using elastography can undergo compression optical coherence elastography (OCE) to map tissue strain with microscale spatial resolution[6]. This puts a tissue's properties into delineated microstructural features. Strain is relative to mechanical properties, so OCE combines quantitative images with a compliant stress sensor that consists of a layer of translucent silicone that correlates stress-strain behavior with rigidities[6]. With these images, elasticity is determined and validated by mapping freshly excised malignant and benign breast tissues.

A major issue in stress detection is the volatility of cancers' response to therapeutic drugs. 3D-engineered anisotropic collagen scaffolds are tools used to understand tumor invasiveness and treatment response. Collagen scaffolds are generated to analyze the stromal environment of breast cancers[2]. Once tumor cell invasion occurs, immunofluorescence microscopy, coupled with the optical coherence method, finds that both the rate and capacity of tumor cells are determined for quantification[2].

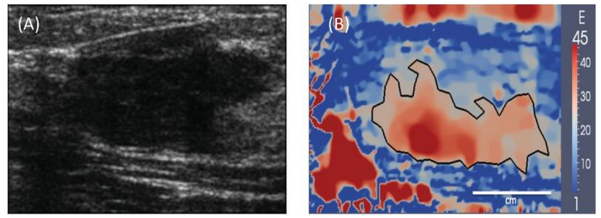

Figure 2. Ultrasound imaging of two heterogeneous fibroadenomas. Adapted from Liu et al.[8]

BIOINFORMATIC WORK

Bioinformatic tools are applicable in assisting *in vivo* or *in vitro* studies as well as basic modeling. Gene expression level can be used to classify patients, and further analysis with Gene Set Enrichment Analysis (GSEA) allows comparison of transcriptomic profiles to sort patients with high and low levels of PIEZO1 expression[5]. This is possible due to faster sequencing and novel platforms of data (such as cBioportal) that allow comparisons at a global scale[1].

Potentially more powerful than *in vivo* models in the future, mathematical and computational modeling of the environment is already making strides. Focus is now given to modeling cells as individuals rather than tumors as a whole, using lattice-based, force-based, or repulsion/adhesion forces. More complex biochemical interactions with the extracellular matrix or fibers are also considered[9]. As more advanced models develop, bioinformatic work may move from predictive to experimental research.

CONCLUSIONS

In vivo study of the biomechanical pathways in breast cancer proves difficult, but recent imaging techniques combined with bioinformatic analysis shows strides. More focus should be given to developing more accurate bioinformatic models through greater integration with *in vivo* model study.

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