‘Exploring the role of ERK5 in Triple Negative Breast Cancer’
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Abstract

Breast cancer is the most commonly diagnosed cancer among women and is classified by the presence of hormone receptors and human epidermal receptor 2 (HER2). Receptor positive breast cancers have available targeted therapies for treatment; however, the triple-negative breast cancer (TNBC) subtype lacks these receptors and to date has no targeted therapy. TNBC is a particularly aggressive, challenging to treat breast cancer, and is most prevalent in younger Black and Hispanic women, making this an underserved cancer. Due to the nature of the disease and its prevalence in minority populations, it is imperative to find effective novel targeted therapies.

One avenue researchers are interrogating for novel drug targets is through the exploration of protein kinases. Here, we focused on the extracellular signal-regulated kinase 5 (ERK5) a member of the MEK/ERK5 pathway which regulates cellular proliferation, survival, differentiation, and apoptosis. The ERK5 pathway is known to have effects on TNBC, however the impact of this kinase on the tumor microenvironment (TME) is not currently evaluated.

ERK5 kinase evaluation was performed through the knock out (KO) of ERK5 in TNBC. Following validation of stable repression, conditioned media (CM) experiments were performed to understand the effects of ERK5 on the TNBC TME. Results demonstrated that MDA-MB-231-ERK5KO CM altered adipose derived stromal/stem cell (ASC) cytokine gene expression and cell death. Results from this study will be used to better understand the role of ERK5 in TNBC microenvironment and better inform novel drug targets.

Methodology

The MEK/ERK5 pathway is a part of the mitogen activated protein kinase (MAPK) family, which has a well-defined role in oncogenesis. In TNBC specifically, ERK5 has been linked with drug resistance, metastatic progression, and more recently inflammation in tumors. TNBC is associated with markers for inflammation (IL8, IL6). Prior studies show that TNBC increases inflammation in ASCs. However, the role of ERK5 in ASC mediated inflammation is not known. The methods used here will use an ERK5 KO cell line (Figure 1A) in combination with CM experiments (Figure 1B) and qRT-PCR to determine if ERK5 is required for processes which drive inflammation in ASC through conditioned media experiments.

Conclusion & Future Directions

Conclusion
- ERK5KO suppressers TME associated genes in TNBC
- Secretome of ERK5KO in TNBC does not regulate ASC cell number
- ERK5 and the MEK pathway may alter ASC cytokine expression in specific donors
- ERK5 KO inhibits ASC inflammation in donors with young patient age
- ASC cytokine expression unaltered in ASC donors with increased age

Future Directions
- Due to the heterozygous nature of our donor population, the possibility of donor specific effects is likely. Widening the donor population would combat this.
- Additional studies on ASC donor age and ERK5 are necessary

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