Mitochondria-driven cancer pathways in triple negative breast cancer


Department of Molecular and Human Genetics and Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX-77030; Agilent Technologies, Inc. Wilmington DE, 19808

Abstract: Divergent pathways of triple negative breast cancer (TNBC) are still poorly understood. Thus, it is important to identify the underlying mechanisms of TNBC progression. Mitochondrial correlates are known to affect tumor properties and patient outcomes. Here we have generated transcellular mitochondrial models to understand mitochondria-regulated cancer pathways and performed different experiments to compare the tumor properties of the cybrids. All OMICs approach was used to identify the differences between parental and hybrid cell lines.

Mitochondria maintain oncogenic properties

Technical and biological triplicate analysis of Cybrid models with breast cancer mitochondrial cell (brain-digest (plug) omics) analysis is analyzed on An Agilent Advantage RBC Mapping 2×40 μm slides with in-run quality controls. Bar graph showing the number of unique proteins and peptides identified (1% FDR) in each triplicate analysis of breast cancer mitochondrial cell is shown. (A) Total protein for (B) ELisa for (C) Cytb. Cybrid lysate from 6060 interface coupled to an eluted QIP using a 1:10 gradient. The data was processed by Spectrum Mill software (Agilent Technologies, Santa Clara, CA). A1N4-159B-2, MCF10A-1, SUM159, and MDA-MB231-1 were analyzed with this RBC map.

Mitochondria is critical in Src autophosphorylation

Pathway analysis from microarray gene expression data of 1564 cybrid suggested Src as one of the top downregulated pathways in breast cancer mitochondrial cell. Analysis of ToT data using our Src assay and our pathway analysis showed that Src is significantly upregulated in basal subsets of tumors compared to hormone regulated breast cancers. Wnt/β-Catenin pathway is regulated by breast cancer mitochondrial cell, which is likely regulated by Src and is regulated by breast cancer mitochondrial cell. Pathway analysis of breast cancer mitochondrial cell and its regulatory pathways of breast cancer mitochondrial cell were observed in our research.

Mitochondrial ATP regulate Src activity

Conclusions

- Mitochondria-nuclear crosstalk in cancer cells can regulate several oncogenic pathways and tumor progression.
- Mitochondrial tumor characteristics is critical in the regulation of Src (Y416) autophosphorylation, ERK1/2 oncogene expression and metastatic potential of TN breast cancer.
- Mitochondrial ATP is responsible for the phosphorylation of Src (Y416) and the regulation of its downstream oncogenic pathways.

Three novel findings will have significant impact on the treatment of breast cancer and the development of new drug targets for currently non-targetable TNBC.

- Our findings on mitochondrial targets as promising combination therapy for the management of TN breast cancer.
- Further study is in progress to explore the clinical and therapeutic application of this finding.