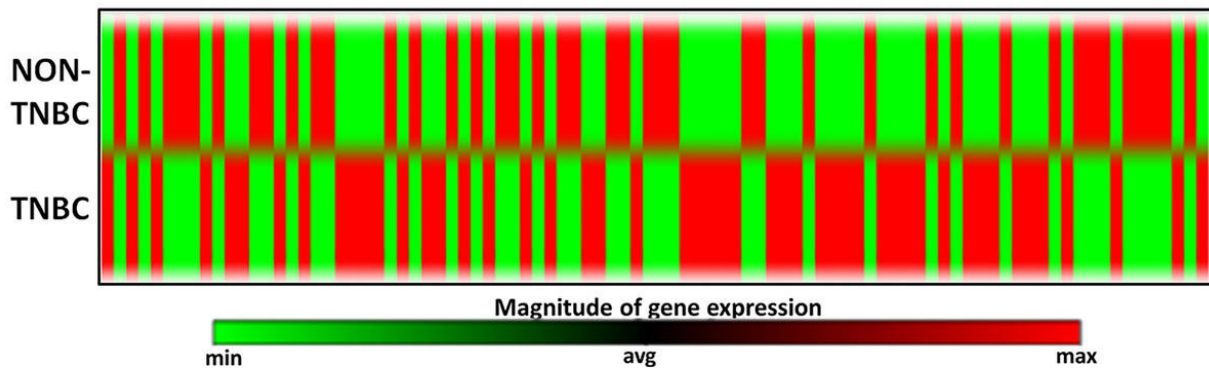


Study uncovers therapeutic targets for aggressive triple-negative breast cancers

February 3 2018, by Katherine Unger Baillie



Heat Map showing differences in the expression of mitochondrial and metabolism genes between TNBC and non-TNBC tumors.

A "heat map" shows that triple-negative breast cancer has a signature all its own when it comes to mitochondrial gene expression. Credit: University of Pennsylvania

As part of a breast-cancer diagnosis, doctors analyze the tumor to determine which therapies might best attack the malignancy. But for patients whose cancer is triple-negative—that is, lacking receptors for estrogen, progesterone and Her2—the options for treatment dwindle. Triple-negative cancers, or TNBC, also tend to be more aggressive than

other cancer subtypes.

While it is known that defects in mitochondria, the cells' energy generators, are associated with the initiation of breast cancers, it is currently unclear whether alterations in mitochondrial DNA or [mitochondrial function](#) contributes to TNBC metastasis or to their notorious resistance to chemotherapy.

New findings from a study led by researchers at the University of Pennsylvania have made inroads into a strategy to identify TNBC tumors at risk for metastasis, and eventually target these cancers with drugs. The work, which compared the metabolic profiles of different [cancer](#) subtypes, identified patterns associated with aggressive triple-negative breast cancers that point to the possibility for more accurate risk assessment and personalized treatment.

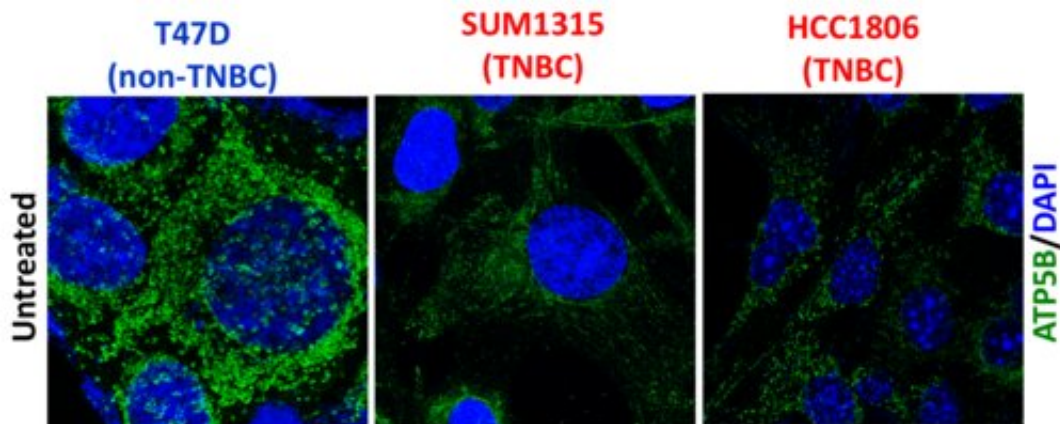
"Currently there is no molecular diagnostic to identify which TNBC patients might be poor responders to available chemotherapies," said Manti Guha, a research assistant professor in Penn's School of Veterinary Medicine. "By identifying unique mitochondrial defects and alterations in metabolic gene expression in the most aggressive subset of tumors, this study provides new molecular biomarkers that could identify the aggressive subset of TNBCs and more importantly offer these patients promising options for treatment."

"The role of mitochondria in disease has been largely overlooked in western medicine," added Douglas Wallace, director of the Center for Mitochondrial and Epigenomic Medicine at Children's Hospital of Philadelphia and a mentor and collaborator of Guha's who was not an author on the paper. "Manti's work is transformative for this particular cancer because by identifying what is different about the mitochondrial energy system in triple-negative [breast cancer](#) compared to other, less dangerous forms of breast cancer gives us a real window into how we

might intervene."

Guha's coauthors on the study, which appears in the journal *BBA: Molecular Basis of Disease*, were Penn Vet's Satish Srinivasan, Dawei Dong, Rumela Chakrabarti and Narayan G. Avadhani; Mike Feldman and Russ P. Carstens of Penn's Perelman School of Medicine; the Children's Hospital of Philadelphia's Pichai Raman and Deanne Taylor; the University of Pittsburgh's Yuefu Jiang and Brett A. Kaufman; Kagohsima University's Yuko Kijima; and Columbia University's Martin Picard.

In an earlier report, Guha and colleagues had shown that, by experimentally inducing mitochondrial dysfunction, breast cancer cells can be reprogrammed towards metastasis.



Confocal images showing mitochondrial protein(ATP5B, green) is reduced in TNBCs SUM1315 and HCC1806 compared to non-TNBC T47D.

The research implicated mitochondrial function in the aggressive nature of triple-negative breast cancers. Above, fluorescent green dye lights up a mitochondrial protein in tumor tissue. Triple-negative cancer samples contain noticeably reduced expression of this protein. Credit: University of Pennsylvania

"We have known for almost a century that, compared to normal cells, tumors have impaired mitochondrial functions and metabolic reprogramming," Guha said. "I was interested in identifying if there were differences in mitochondrial signatures among breast-tumor subtypes and if this variability in mitochondrial genome and functions among patient tumors can help identify cancer patients who are at an increased risk for metastasis."

The researchers made use of tissue samples from patients with different breast-cancer subtypes, defined cancer lines and previously collected genomic data representing 825 [breast cancer patients](#). Screening for mitochondrial DNA copy numbers, they found that patients who had more advanced disease were more likely to have the lowest mtDNA copy numbers. They also found clear patterns in mtDNA copy numbers between breast-cancer subtypes, with triple-negative cancers having the most reduced copy numbers. Additional screening revealed an imbalance in a particular sequence of mtDNA that was prevalent in triple-negative tumors but not in other breast tumor subtypes.

"This particular mtDNA sequence imbalance is fairly unique and has not been reported in cancers," Guha said. "This could potentially be used to stratify patients into different risk categories."

Examining breast-cancer cell lines, they found differences in oxygen consumption between triple-negative and other cancer subtypes, indicating impaired cellular respiration and thus mitochondrial function in those cells.

In a broad screen of 84 genes related to metabolism, a process that mitochondria regulate, the researchers found clear patterns that characterized triple-negative tumors from other breast-tumor subtypes. These genes could serve as potential therapeutic targets for intervention, or as biomarkers to identify breast tumors that are more likely to

metastasize, the researchers noted.

"We observed unique mitochondrial aberrations in TNBCs which can serve as a diagnostic marker of TNBC metastasis and be utilized to improved combined chemotherapeutic or individualized approaches," Guha said.

To build on these findings, Guha and colleagues are investigating whether FDA-approved therapies, or those currently in clinical trials, that target metabolic pathways could prove particularly effective against [triple-negative breast cancer](#).

More information: Manti Guha et al, Aggressive triple negative breast cancers have unique molecular signature on the basis of mitochondrial genetic and functional defects, *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* (2018). [DOI: 10.1016/j.bbadis.2018.01.002](https://doi.org/10.1016/j.bbadis.2018.01.002)

Provided by University of Pennsylvania

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