Precision prevention for prostate cancer

June 7 2021

Aditya Dutta and research collaborators found that, under conditions of stress, the NKX3.1 gene, which is critical in prostate biology, moves to the mitochondria — the powerhouse of the cell — in order to protect against prostate cancer. Credit: University of Delaware

The University of Delaware's Aditya Dutta and collaborators are investigating the NKX3.1 gene and its role in prostate cancer—the most common cancer and the second-leading cause of cancer-related death among men in the United States.

In prostate biology, NKX3.1 is big. The gene regulates everything—development, maintenance, disease initiation and progression.

In a new research article published in *Cancer Discovery*, the researchers found that, under conditions of stress, NKX3.1 moves to the mitochondria—the powerhouse of the cell—in order to protect against prostate cancer. Mitochondria play a pivotal role in stress responses.

"Mitochondria are like the canary in the coal mine," said Dutta, a UD assistant professor with appointments in both the Department of Animal and Food Sciences as well as the Department of Biological Sciences. "They act as stress sensors and lead the cell's response to stress."

Most patients diagnosed with prostate cancer are put on active surveillance. Close monitoring determines exactly when their cancer will become aggressive. This study's results are promising for these patients. Microscopic histological analysis for NKX3.1 will allow for a precision prevention approach, helping patients determine their risk for progression to aggressive disease.

"The role of NKX3.1 in prostate cancer has been known for over two decades; however, its role was limited to its function in the nucleus of the cell," Dutta said. "Our analysis of NKX3.1 in animal models and human prostate specimens indicated the gene's presence outside the nucleus, specifically in the mitochondria."

NKX3.1 and prostate cancer risk

NKX3.1 is a master regulator that undergoes functional loss in up to 80% of early-stage prostate cancers. Analyses show that loss of NKX3.1 is the initiating event in the evolution of prostate cancer. Additionally, prostate cancer aggressiveness in African-American men is linked to

reduced levels of NKX3.1. The researchers identified the lack of NKX3.1 mitochondrial function in two mutations associated with increased risk of aggressive prostate cancer, highlighting the potential use of NKX3.1 non-nuclear localization as a tool for risk assessment in prostate cancer.

"This means that we can look for NKX3.1 outside the nucleus, and, if it's indeed found outside, your odds of developing aggressive disease go up significantly," Dutta said. "You need treatment right away."

Mitochondria—tumor friend or foe?

Mitochondria take on a unique role in tumors. In normal cells, mitochondrial energy production is typically related to nutrient uptake. However, in cancer cells, this is not the case; they redirect nutrients to make more DNA to rapidly multiply. Cancer cells need to grow rapidly. Growth needs energy. So, cancer cells partake in a fine balancing act, getting just the right amount of energy for growth.

"It reminds you of a juggler who ensures that the pins never fall, and the show goes on," said Dutta. "NKX3.1 moves into the mitochondria to ensure optimal energy production and brings the show—oxidative stress causing prostate cancer initiation and progression in this case—to an end."

More information: Alexandros Papachristodoulou et al, NKX3.1 localization to mitochondria suppresses prostate cancer initiation, *Cancer Discovery* (2021). DOI: 10.1158/2159-8290.CD-20-1765

Provided by University of Delaware