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Newly identified pathway in mitochondria fuels tumor progression across cancer types

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Scientists at The Wistar Institute have identified a novel protein pathway across several types of cancer that controls how tumor cells acquire the energy necessary for movement, invasion and metastasis. This protein pathway was previously only observed in neurons and represents a potential therapeutic target for several types of cancer. Study results were published in the journal *Nature Communications*.

Mitochondria serve as power generators of the cell, responsible for converting oxygen and nutrients into energy for cellular processes. Researchers have long observed that, instead of relying on mitochondria and oxygen, tumor cells switch to a different system of energy production to compensate for their increased energy needs and the low levels of oxygen typically found in tumor tissues. This process is known as the Warburg effect, and because it had been well-established in cancer cells, mitochondria were not regarded as major players in tumor biology until recently. This study confirms that mitochondria play an important role especially in disease progression, during which tumor cells break out of the primary mass and invade distant tissues in the body.

"The scientific community has been missing a fundamental aspect of cancer cell metabolism because we have overlooked the role of mitochondria and oxidative metabolic processes in cancer," said Dario C. Altieri, M.D., president and CEO of The Wistar Institute, director of The Wistar Institute Cancer Center, the Robert & Penny Fox Distinguished Professor, and lead author of this study. "Our findings,

along with those of others from the past few years, pave the way to a new research direction in the field, alluding to the need to further investigate the role of mitochondria in tumor metabolism."

The Altieri Laboratory found that mitochondria in tumor cells are repositioned close to the cell membrane to provide energy for movement. While this type of cellular behavior had been previously only observed in neurons, the group showed how a network of proteins, including SNPH and its partners, that control mitochondria trafficking in neurons are reprogrammed to perform the same function in tumor cells.

Using a genome-wide screening approach, Altieri and colleagues discovered that SNPH inhibits cell invasion by reducing cell movement in prostate cancer cells. They also found that when SNPH expression is inhibited, the mitochondria relocate from their typical position around the cell nucleus to the cell membrane. They evaluated the expression levels of SNPH and its partners in tissue samples from patients with epithelial and hematologic malignancies and found that reduced levels of SNPH correlate with disease progression and unfavorable prognosis across the tumor types.

"We were able to establish a correlation between this protein pathway and disease progression and survival in several cancer types besides prostate cancer. This indicates that we are dealing with a general mechanism of metastasis suppression, not specific to one single tumor type," said M. Cecilia Caino, Ph.D., a postdoctoral researcher in The Altieri Laboratory and first author of the paper. "Our observations have strong clinical implications, as some of the proteins in this network are druggable, opening new potential therapeutic opportunities for metastatic diseases."

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