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Mitochondrial metastasis suppressor pathway controls tumor cell metabolic reprogramming

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A novel mitochondrial variant of the protein Syntaphilin, or SNPH, which orchestrates the choice between cancer cell proliferation and metastasis in response to oxygen and nutrient shortage in the tumor microenvironment, has been identified by researchers at The Wistar Institute. This study describes a novel metastasis suppressor pathway and was published in the *Journal of Clinical Investigation*.

"Metastatic disease is the primary cause of death for cancer patients. We've made tremendous strides in targeted cancer therapies, but we still face the challenge of drug resistance, and our knowledge of the mechanisms of metastatic dissemination is not quite as deep," said lead author of the study Dario C. Altieri, M.D., president and CEO of The Wistar Institute, director of The Wistar Institute Cancer Center, and the Robert & Penny Fox Distinguished Professor. "Our findings contribute much-needed information on tumor plasticity leading to metastatic dissemination, and may lead to new therapeutic aproaches."

Tumor cells must be able to adapt to unfavorable environmental conditions, including low oxygen, scarcity of nutrients and high levels of toxins. This process, referred to as tumor plasticity, requires them to reprogram their metabolism to serve their energy needs. Under stressful condition, tumor cells are often forced to operate a switch between proliferation and motility, both of which pose high energy requirements, shifting the balance between local tumor growth and metastatic

dissemination. Previous Wistar research has identified a key role for mitochondria, the power generators within the cell, in cell invasion and metastasis, whereby mitochondria are relocated to the periphery of tumor cells to fuel their movement.

In this study, Altieri and colleagues described a novel metastasis suppressor pathway orchestrated by SNPH, a protein that was originally only found in neurons. They discovered a novel, shorter variant of the protein, which is present in many normal and tumor tissues and localizes in mitochondria, acting as a "rheostat," or a molecular switch, between tumor cell proliferation and metastasis.

The Altieri laboratory studied the function of the short SNPH variant in vitro in prostate cancer and glioblastoma cells. They depleted SNPH expression and observed energetic defects, including oxidative stress, or the accumulation of free oxygen radicals, and arrest of proliferation. Conversely, forced expression of SNPH resulted in suppression of mitochondrial re-localization to the cell membrane and consequently reduced cell motility. These observations suggest that SNPH promotes tumor cell proliferation and local tumor growth at the expense of invasion and metastatic dissemination. In vivo studies in mouse models of melanoma confirmed the role of SNPH in controlling metastasis and showed that the mitochondrial localization is required for SNPH functions.

Furthermore, Altieri and colleagues observed that stressful conditions in the surrounding environment, such as low oxygen availability, repressed SNPH expression. This finding reaffirms that turning off SNPH is a key mechanism in tumor plasticity, which halts proliferation and favors cell motility when the local environment is unfavorable, to allow tumor cells to colonize alternative sites.

"Decrease in SNPH expression is a hallmark of tumor progression,

correlating with metastatic disease and poor outcome," said Jae Ho Seo, Ph.D., associate staff scientist in the Altieri lab and co-first author of the study. "Because this novel stress-regulated pathway is selectively exploited in cancer cells as opposed to normal tissues, it may offer novel therapeutic opportunities to specifically disrupt the metabolic requirements of metastatic cells."

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