

Team unveils widespread tumor suppression mechanism that stops cancer progression by interfering with cell metabolism

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Wistar's Dr. Dario Altieri. Credit: The Wistar Institute

According to a study by The Wistar Institute, the tumor suppressor Parkin, whose levels are reduced in different cancer types, causes acute metabolic and oxidative stress, suppresses mitochondrial trafficking, and blocks tumor cell movement, reducing primary and metastatic tumor growth. These findings, published today in *Science Advances*, demonstrate that metabolic and mitochondrial reprogramming, which are well-established hallmarks of tumor progression, act as potent drivers of disease.

"We've known for a century that progression from a small, premalignant lesion to an aggressive tumor and then metastasis is accompanied by changes in metabolism that allow [cancer cells](#) to support increased energy demands due to continuous growth and adapt to unfavorable microenvironment conditions," said study lead author Dario C. Altieri, M.D., Wistar president and CEO, director of the

Institute's Cancer Center and the Robert & Penny Fox Distinguished Professor. "Our study provides evidence that reprogramming the metabolic and [mitochondrial function](#) is a cancer-promoting factor opposed by tumor suppression mechanisms, and we identified one that is relevant to halting several different types of cancer."

Altieri and colleagues studied a gene called Parkin that is altered in Parkinson's disease. Through a degradation mechanism called mitophagy, Parkin was known to protect [brain cells](#) by facilitating selective removal of damaged mitochondria, the organelles that produce energy. Previous evidence indicated that Parkin might have a role in regulating cancer cell metabolism and suppressing tumor growth, but the mechanisms remained elusive.

Researchers re-introduced Parkin in prostate cancer [cells](#) and other cancer cell types that did not express the protein and observed reduced cell movement and a blocking of invasion. Concordantly, deletion of Parkin in [normal cells](#) increased cell motility.

In vivo, Parkin-expressing prostate cancer cells formed smaller tumors and had lower metastatic potential. The team found that Parkin expression was low or undetectable in patient-derived tissue samples and cancer cell lines and decreased in all the tumor types contained in The Cancer Genome Atlas database compared with their respective normal counterpart.

A global proteomic study of cancer cells modified to express Parkin revealed alterations in the protein networks that control cell movement and metastasis and decreased oncogenic signaling.

Importantly, these effects were independent of Parkin's role in mitophagy in response to mitochondrial damage. Researchers then asked whether other pathological conditions could activate Parkin. They found that exposing Parkin-expressing cancer cells to stress conditions such as nutrient deprivation and DNA-damaging agents resulted in a strong increase in Parkin levels.

Parkin functions as an enzyme that promotes ubiquitination, a process that modifies proteins to flag them for degradation. Researchers observed that this function is required for Parkin's tumor suppressive activity. Forced Parkin expression in cancer cells alters ubiquitination in protein networks that control cell death, mitochondrial function and glucose metabolism. As a consequence, Parkin interferes with movement of mitochondria within the cells, which affects their function in tumor progression.

"Our lab has described the role these organelles play in cancer, showing that changes in mitochondrial size, shape and distribution within the cells allow for increased cell motility, metastatic dissemination and other aggressive disease traits," said Ekta Agarwal, Ph.D., first author of the study and a postdoctoral fellow in the Altieri lab. "This new study shows how a tumor suppressor pathway opposes mitochondrial dynamics to counteract cancer progression."

Researchers further dissected the mechanism of Parkin tumor suppression and its role in controlling metabolism, and demonstrated that Parkin expression blocks an enzyme called transketolase (TKT) that is involved in glycolysis, a [metabolic pathway](#) specifically used by cancer cells to generate energy. This block results in reduced energy production.

TKT also plays a key role in counteracting oxidative stress in the cell. Therefore, another consequence of its inhibition is buildup of reactive oxygen species and [oxidative stress](#) in the mitochondria, which inhibit mitochondrial function and, in turn, tumor [cell motility](#).

From this study, Parkin emerges as a critical, stress-activated effector of a [tumor](#) suppression pathway

that antagonizes malignant cell proliferation and metastatic competence by interfering with the ability of [cancer](#) cells to reprogram their metabolism.

More information: A cancer ubiquitome landscape identifies metabolic reprogramming as target of parkin tumor suppression, *Science Advances* (2021). [DOI: 10.1126/sciadv.abg7287](https://doi.org/10.1126/sciadv.abg7287)

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