Study: Protein helps prevent breast cancer metastasis

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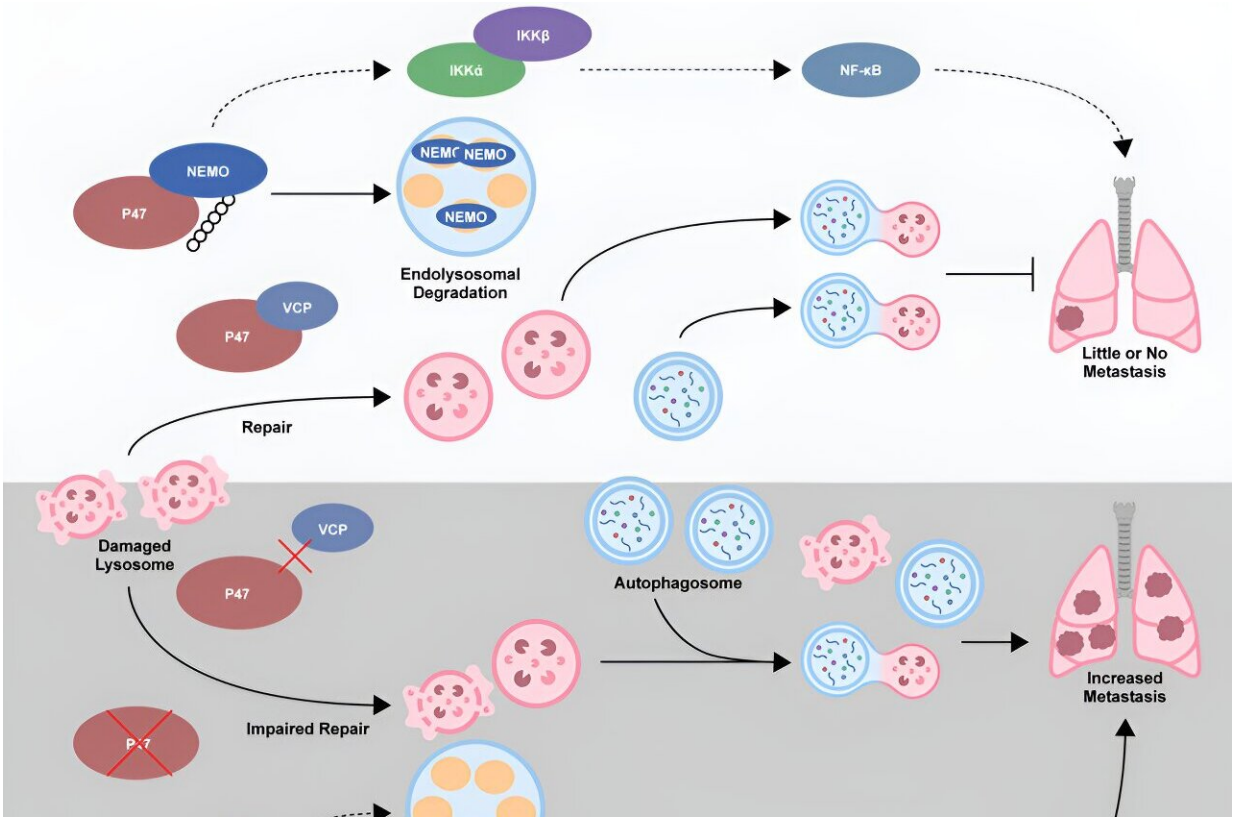

Graphical Abstract. Credit: *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.113780

While better screening and improved treatments are leading to better outcomes for patients with breast cancer, 90% of breast cancer deaths

are a result of metastasis, or the cancer growing and spreading to other parts of the body.

University of Cincinnati Cancer Center researchers in the lab of Jun-Lin Guan, Ph.D., have identified a new protein that helps prevent metastasis of a subset called HER2-positive breast cancer. About 20% of patients have HER2-positive breast cancer, and these cancers tend to be more aggressive than other types.

The study findings were published in the journal *Cell Reports.*

Autophagy background

Guan's lab has focused on how autophagy, or the cell's "recycling" function, affects cancer metastasis.

"Autophagy can be likened to a self-cleansing mechanism within cells," said Mingang Hao, Ph.D., first author of the study and research scientist in Guan's lab. "It allows them to eliminate undesirable or harmful components and emerge stronger and unharmed. In the context of cancer, dysfunctional autophagy has been linked to the development and progression of tumors."

Research published in 2021 led by Hao found that blocking autophagy in HER2-positive breast cancer cells helped eliminate cancer development in an animal model of the disease.

However, it was not clear whether the autophagy blockade also inhibited the process of cancer metastasis, as the lack of metastasis could be due to the elimination of the primary tumor growth in the model.

Very few studies in the field have directly examined the role of autophagy in metastasis, and most studies focused on genes thought to

only play a role in autophagy (so-called "core" autophagy genes).

"In addition to these primary autophagy genes, which have been a major focus of research on cancer development and progression, there are many other proteins that regulate autophagy within cells," Hao said.

A genetic library

Using CRISPR gene-editing technology, Hao and his colleagues created a specialized genetic library that targeted 171 different genes that are involved in autophagy regulation. By "turning off" each gene, the researchers aimed to identify specific genes that prevented the spread of breast cancer cells.

Using this technique, Hao said they identified a protein called p47 that prevents breast cancer metastasis.

"It does this by affecting different cellular pathways that are crucial for tumor cell movement," Hao said. "These findings help us better understand the mechanisms behind cancer metastasis and may eventually lead to new strategies for preventing or treating the spread of breast cancer."

In human breast cancer samples, lower p47 expression was correlated with higher breast cancer metastasis.

"This is one of the first few studies that links a particular autophagy regulatory gene with cancer metastasis with clear mechanisms that can potentially lead to the development of new therapies," said Guan, professor and former chair of the Department of Cancer Biology at UC's College of Medicine.

"I view this as one of the most important findings from my lab and a

culmination of a lot of research expertise as well as unique reagents we generated over the years."

Guan said cancer drugs are often developed to inhibit a gene that helps cancer cells grow, but in the case of p47, a potential therapy would seek to increase the functions of the protein so that it can prevent metastasis.

"I would argue it's more powerful than inhibiting something," he said, noting popular immunotherapy drug pembrolizumab similarly works by boosting a pathway the body uses to fight cancer.

Moving forward, the research team will seek to learn more about p47's mechanism of action and potential to be developed as a therapeutic. The researchers identified additional genes involved in autophagy that appear to affect metastasis and could become further targets for new treatments.

The gene library Hao custom-developed for this study is also available for other researchers at the Cancer Center and other institutions to use to identify potential targets in other cancers.

Hao began this particular line of research in 2018 and said patience, time, effort, and genuine interest in your work are essential for cancer researchers.

Guan said many researchers focus on one protein or gene at a time, but it takes specific expertise to conduct systematic, impactful research on many genes at one time.

"Mingang's previous work laid the foundation for this, so this is something very unique that not many labs would be able to perform," Guan said. "When I recruited him, this was the kind of thing I hoped he could do."

More information: Mingang Hao et al, In vivo CRISPR knockout screen identifies p47 as a suppressor of HER2+ breast cancer metastasis by regulating NEMO trafficking and autophagy flux, *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.113780