A signal to spread: Scientists identify potent driver of metastasis

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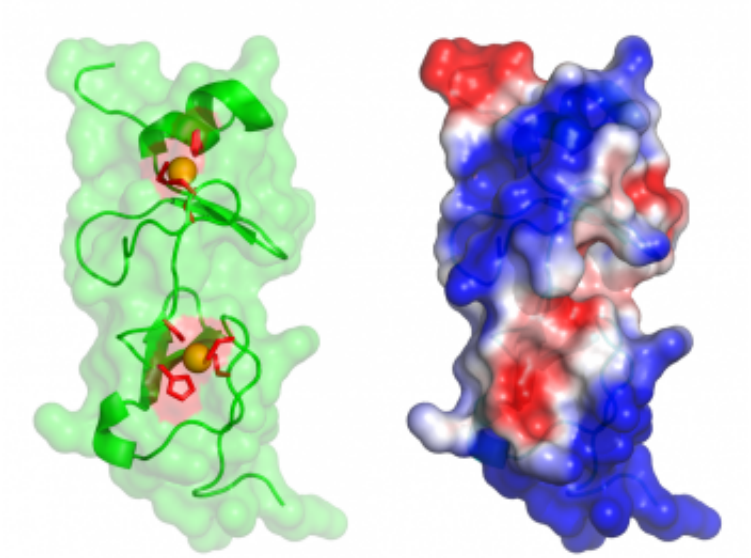

An international team of researchers led by scientists at The Wistar Institute have discovered and defined LIMD2, a protein that can drive metastasis, the process where tumors spread throughout the body.

Their study, published in the March issue of the journal *Cancer Research*, defines the structure of LIMD2 and correlates the protein in metastatic bladder, melanoma, breast, and thyroid tumors. Wistar scientists have also developed and patented a monoclonal antibody that may one day be used as a prognostic test to see if tumors have LIMD2,

and plans are underway to create inhibitors—potential drugs that may target cells that produce LIMD2.

"This is the result of a five year effort to characterize LIMD2, which is a new protein that we found to be expressed only in metastatic lesions, and not in the primary tumor or in normal tissues or organs," said Frank Rauscher, III, Ph.D., a professor in The Wistar Institute Cancer Center. "LIMD2 is a great candidate for targeting with a drug, which would inhibit the ability of these cells to leave a primary tumor and to colonize other organs."

According to Rauscher, LIMD2 is part of a family of proteins that communicate signals to the cell nucleus from the cytoskeleton of the cell—the structural scaffolding that supports the cell. Scientists have looked to these proteins as potential drivers of metastasis since they control signals that regulate how the cell interacts with nearby cells, including how cells may migrate and adhere to other tissues, which are traits tumors use to metastasize. LIMD2, in particular, is a key component to a chain of chemical events that control cell motility, or movement, which is a defining characteristic of metastasis, Rauscher says.

"Cancer metastasis is really the final frontier in cancer medicine, because metastasis kills," Rauscher said. "We can treat a primary tumor, usually successfully, with surgery, drugs, chemotherapy or radiation, but once the cancer spreads to organs throughout the body it frequently becomes unstoppable."

"We contend that LIMD2 is a marker that could help physicians profile tumors, and a potential drug target that could yield a potent therapy for a variety of advanced cancers, perhaps in combination with existing or emerging therapies," Rauscher said.

LIMD2 had earlier been identified as a biomarker for papillary thyroid cancer metastasis and, as a member of the a family of proteins known to be active in both the cell's nucleus and cytoplasm, piqued the interest of the Rauscher laboratory. Their studies demonstrated that LIMD2 appeared in abundance in samples of metastatic tumors, but were rarely expressed by primary tumors or healthy cells.

To further characterize the structure and function of LIMD2, the Rauscher laboratory collaborated with scientists across The Wistar Institute Cancer Center and scientists from around the world. They developed a structural model of the LIMD2 protein and demonstrated that the protein interacted with integrin-linked kinase (ILK), an enzyme with critical importance to the process of cellular movement, proliferation, and metastasis. Computer modeling analysis revealed that LIMD2 binds to ILK, and further studies demonstrated that LIMD2 promotes ILK activity. The "pocket" where LIMD2 binds to ILK, the researchers say, could be a promising target for a small molecule-based drug inhibitor.

Provided by The Wistar Institute

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