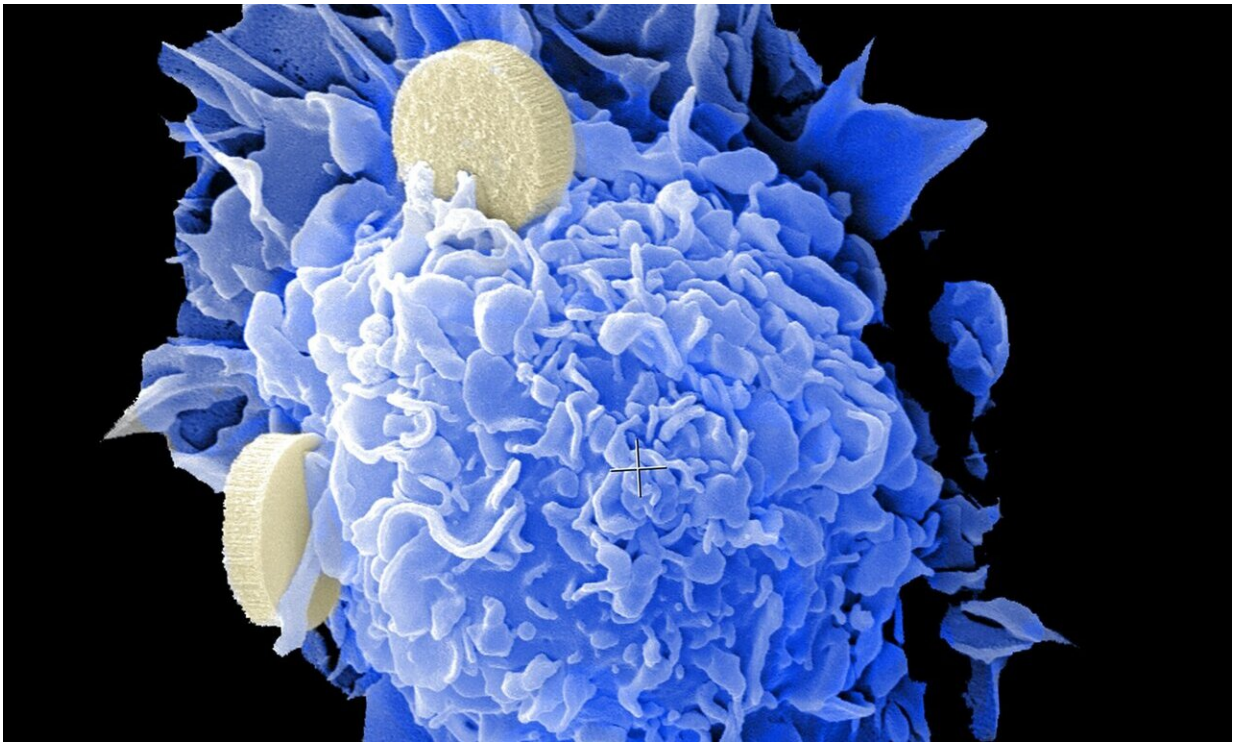
MedicalXpress

Study provides new insight into how cellular proteins control cancer spread

August 12 2020



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A new insight into cell signals that control cancer growth and migration could help in the search for effective anti-cancer drugs. A McGill-led study reveals key biochemical processes that advance our understanding of colorectal cancer, the third most common cancer among Canadians.

Using the CMCF beamline at the Canadian Light Source (CLS) at the University of Saskatchewan, scientists from McGill University and Osaka University in Japan were able to unlock the behavior of an enzyme involved in the spread of cancer cells. In a study published in the *Journal of Biological Chemistry*, the team found that there is a delicate interaction between the enzyme, PRL3, and another protein that moves magnesium in and out of cells. This interaction is crucial to colorectal cancer growth.

"These enzymes were first seen in liver cells that were activated to start growing, so somehow they act as a growth signal," said McGill biochemistry professor and corresponding author Dr. Kalle Gehring.

It was generally believed that PRL3 proteins acted as enzymes to control cancer cells. Therefore, it came as a surprise when Gehring and his team found that a mutation that leads to a loss of the enzyme activity still maintained the same influence over cancer growth and migration. "What our new paper showed is that a second activity of PRL3, control of a magnesium transporter, is the signal that instructs the cancer to travel to other parts of the body. It was very exciting that the mutant protein that has no catalytic activity, but still binds very tightly to magnesium transport proteins, turned out to be as oncogenic as the wild-type protein," said Gehring.

The team's findings call into question long-standing hypotheses about the role PRL3 plays in the spread of cancer and indicate that the binding mechanism is somehow key.

Understanding that binding the magnesium transporters and not the enzyme's catalytic activity influences cancer growth and migration signaling is key information for identifying novel compounds to prevent cancer spread. Current drug screening against PRL3 has focused on identifying compounds that block phosphatase activity. By testing the

wrong function, the screens may have missed other compounds of therapeutic interest. Shifting the focus to the enzyme's ability to bind to magnesium transporters is one way to help companies identify better therapeutics for cancer through drug screening methods.

Future work will include more detailed studies on the role of the magnesium transporter and its interactions with PRL3.

More information: Guennadi Kozlov et al, PRL3 pseudophosphatase activity is necessary and sufficient to promote metastatic growth, *Journal of Biological Chemistry* (2020). DOI: 10.1074/jbc.RA120.014464

Provided by McGill University