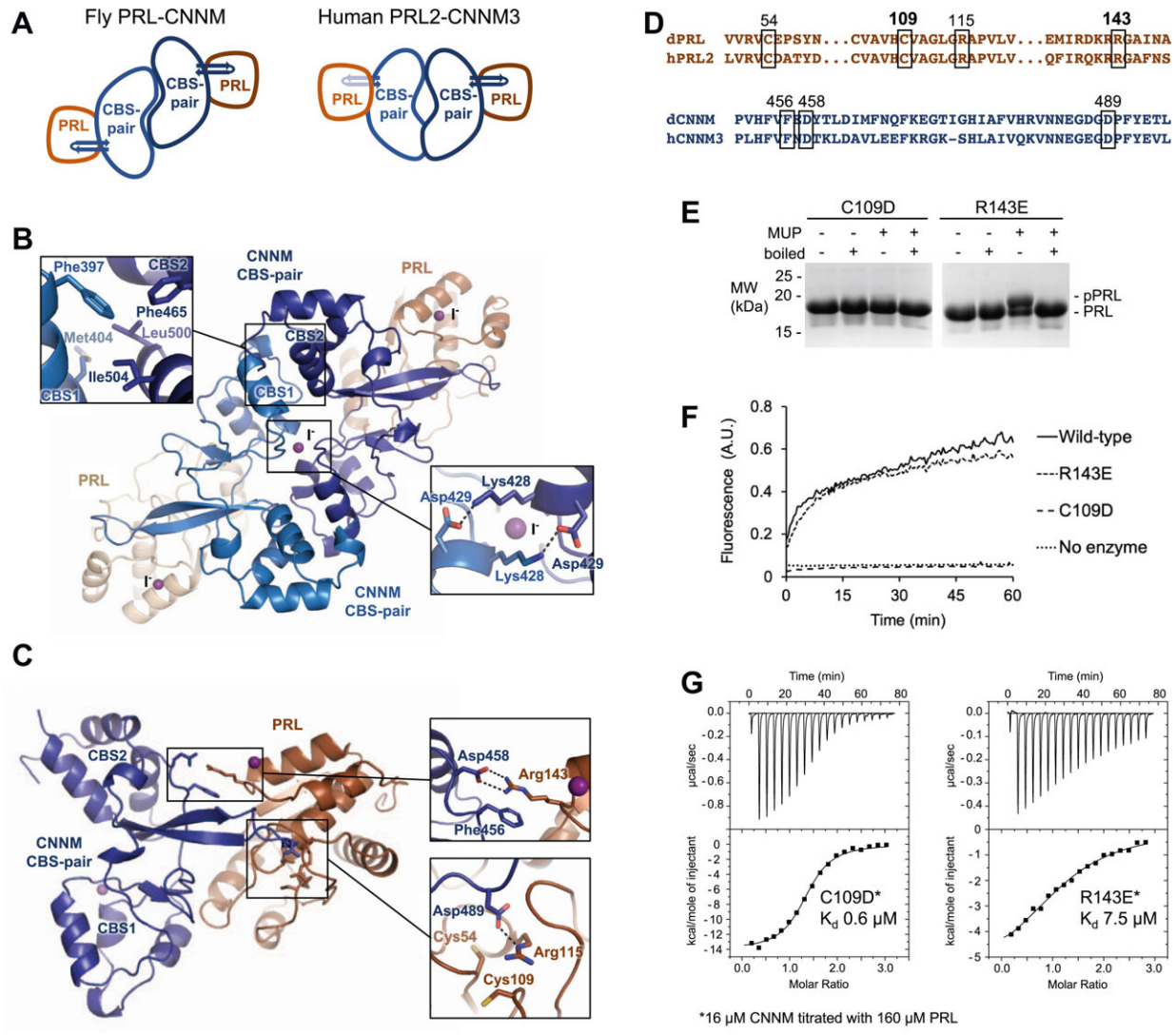
Tiny proteins found across the animal kingdom may play a key role in cancer spread

May 15 2023



Structure of Drosophila PRL bound to the CBS-pair domain of Drosophila CNNM. A, comparison of CBS-pair dimerization. The fly CBS-pair domains form an antiparallel dimer, unlike the parallel arrangement of CBS-pair dimers

from mammalian CNNM proteins. An extended β-sheet from each CBS-pair monomer binds one PRL protein. B, protein-protein contacts between the fly CBS-pair domains. The inset show hydrophobic interface and polar contacts around one of the three iodide ions (I^-) in the crystal. C, contacts between the CBS-pair domain and PRL. Binding is mediated by an extended β-sheet that inserts CNNM aspartic acid residue 458 into the PRL active site formed by cysteine 109 and arginine 115. The catalytic cysteine 109 and the regulatory cysteine 54 are both reduced. An intermolecular salt bridge between a CNNM aspartic acid 458 and PRL arginine 143 is conserved between the human and fly complexes. The interaction is stabilized by the stacking of phenylalanine 456 with the arginine side-chain. D, conservation of key residues between the Drosophila (dPRL, dCNNM) and human (hPRL2, hCNNM3) proteins. E, Phos-tag SDS-PAGE analysis showing the formation of phosphocysteine intermediate by the R143E mutant but not C109D in the presence of the substrate MUP. F, phosphatase assays with DiFMUP showing WT activity by the Drosophila PRL R143E mutant but no activity for C109D. G, ITC analysis of complex formation shows the C109D mutation diminishes binding affinity less than two-fold, while the R143E mutation weakens it 20-fold. CBS, cystathionine-β-synthase; DiFMUP, 6,8-difluoro-4-methylumbelliferyl phosphate; MUP, 4-methylumbelliferyl phosphate; PRL, phosphatases of regenerating liver. Credit: *Journal of Biological Chemistry* (2023). DOI: 10.1016/j.jbc.2023.103055

Phosphatases of regenerating liver (PRLs) are a family of enigmatic proteins involved in cell growth and metabolism present in various species. From humans to fruit flies, they play a unique role in the growth of cancerous tumors and the spread of cancer throughout the body. New research emerging from McGill University is contributing to what is known about PRLs, which could potentially become an important tool in the development of cancer-fighting treatments.

Led by Kalle Gehring, a professor in the Department of Biochemistry and founding director of the McGill Centre for Structural Biology, the researchers focused on unraveling the mystery around PRLs. "It's

important for us to study PRLs because they are so important in cancer," said Gehring, "In some cancers such as metastatic colorectal cancer, the proteins are overexpressed up to 300-fold."

Published in the *Journal of Biological Chemistry*, Prof. Gehring and his colleagues (with data collected at the Canadian Light Source (CLS) at the University of Saskatchewan) confirmed that not only PRLs exist in all kinds of single- and multi-cell animals, but that the role of PRLs in binding magnesium transporters is common among all studied species.

This overexpression of PRLs makes cancer cells more metastatic and drives the spread to other organs. This data could help to further the understanding of how these proteins influence human disease.

"What we learned is that they all bind the magnesium transporters in the same way," says Gehring. "We're excited because it helps us understand this pathway, and that will reveal new targets for drugs to prevent cancer progression."

More information: Rayan Fakih et al, Burst kinetics and CNNM binding are evolutionarily conserved properties of phosphatases of regenerating liver, *Journal of Biological Chemistry* (2023). DOI: 10.1016/j.jbc.2023.103055

Provided by McGill University