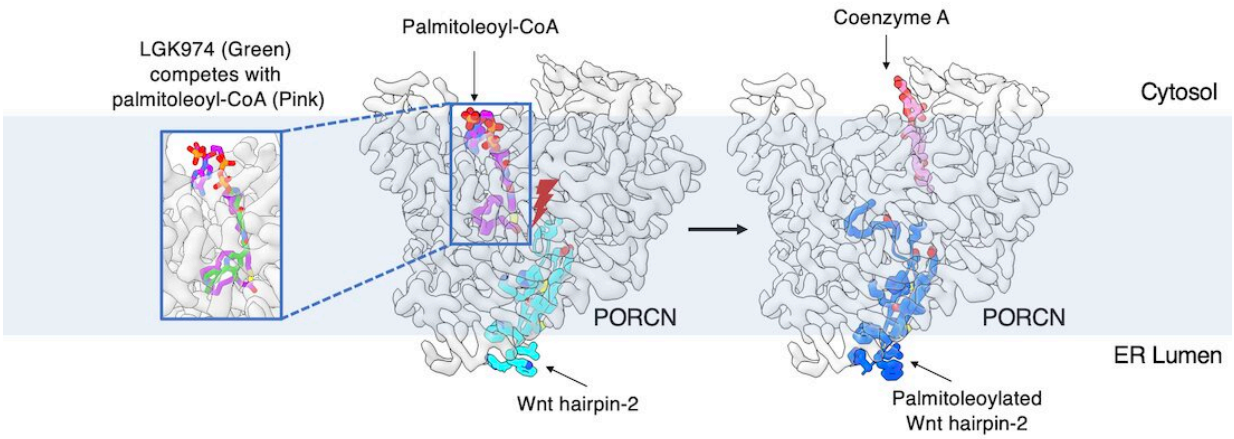
New cryo-EM images shed light on Wnt signaling

August 16 2022



Cryo-EM reveals how Wnt, a key signal molecule for human development and cancer, is modified by an enzyme named PORCN. Credit: UT Southwestern Medical Center

Using UT Southwestern's Cryo-Electron Microscopy Facility, researchers have captured images of an enzyme for Wnt lipidation, which is pivotal to human development and crucial for Wnt signaling activation. The findings, reported in *Nature*, shed light on the mechanisms behind this activity and could eventually lead to new drugs to treat various malignancies.

"We are able to push the research envelope further into the key area of cancer-related signaling pathways thanks to UT Southwestern's state-of-the-art cryo-electron microscopy (cryo-EM) facility," said Xiaochun Li, Ph.D., Associate Professor of Molecular Genetics and Biophysics, who co-led the study with Yang Liu, a fourth-year graduate student, and Xiaofeng Qi, Ph.D., a postdoctoral researcher. Both Mr. Liu and Dr. Qi work in the Li lab. "The revealed scientific mechanism could accelerate the development of novel cancer-fighting drugs toward advanced solid tumors."

Scientists have long known that members of the Wnt family of proteins are pivotal for embryonic development, kicking off signaling pathways necessary for functions such as axis formation, cell fate specification, and cell proliferation and migration. When Wnt proteins were first discovered in the early 1980s, they were immediately associated with cancer; aberrant Wnt signaling is known to contribute to pancreatic cancer, melanoma, triple-negative breast cancer, and other types of malignancies.

To perform their signaling functions, Dr. Li explained, Wnt proteins must first be activated by the addition of a lipid molecule, a job performed by an enzyme called Porcupine (PORCN). How this occurs structurally and the mechanism by which investigational drugs inhibit this activity have been unknown.

To investigate, Dr. Li and his colleagues gathered cryo-EM images of four structures: PORCN bound to a co-enzyme called palmitoleoyl-CoA, which contributes the lipid molecule to activate Wnt; PORCN bound to LGK974, an investigational drug known to inhibit Wnt signaling; PORCN bound to LGK974 and WNT3A, a Wnt family member; and PORCN bound to an activated, lipid-modified WNT3A protein. Cryo-EM, a technique recognized by a 2017 Nobel Prize, freezes proteins in place to get atomic-resolution microscopic images.

These images showed that WNT3A, PORCN, and palmitoleoyl-CoA come together in a sandwich-type configuration, with PORCN in the middle flanked by the two other precursors. When WNT3A and PORCN were incubated with LGK974 instead of palmitoleoyl-CoA, the investigational drug took the place of the palmitoleoyl-CoA, blocking its ability to bind and contribute the lipid molecule; without this lipid modification, Dr. Li said, WNT3A can't set off a signaling cascade.

Additionally, the images solved a decades-old mystery as to why the lipid chain that modifies Wnt proteins differs structurally from that on a related protein called Hedgehog, which is also involved in human development and cancer and activated by lipid modification. While the lipid chain on Hedgehog is made of a saturated fatty acid, causing it to extend into a straight line, the one on PORCN is unsaturated, causing it to kink into a C-shape. The researchers found that this kink is necessary for the lipid chain to fit into a cavity on PORCN, a critical step before transferring it onto Wnt.

Dr. Li noted that LGK974 is one of several drugs that affect Wnt signaling that is currently in clinical trials against various cancers. Knowing the atomic structures of Wnt, PORCN, palmitoleoyl-CoA, and their complexes could lead to drugs better designed to block these interactions.

More information: Yang Liu et al, Mechanisms and inhibition of Porcupine-mediated Wnt acylation, *Nature* (2022). DOI: 10.1038/s41586-022-04952-2

Provided by UT Southwestern Medical Center

2024 from https://phys.org/news/2022-08-cryo-em-images-wnt.html