

RaDAR guides proteins into the nucleus

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A Ludwig Cancer Research study has identified a novel pathway by which proteins are actively and specifically shuttled into the nucleus of a cell. Published online today in *Cell*, the finding captures a precise molecular barcode that flags proteins for such import and describes the biochemical interaction that drives this critically important process. The discovery could help illuminate the molecular dysfunction that underpins a broad array of ailments, ranging from autoimmune diseases to cancers.

Although small proteins can diffuse passively through pores built into the nuclear membrane, most nuclear proteins have to be actively driven into the nucleus through specialized pores to ensure that the cell functions normally. Proteins targeted to specific compartments in cells often carry a sequence of amino acids that, like a barcode, tells components of the cell's transport machinery where they should be located in order to perform their biochemical duties.

"Until now, only one nuclear import pathway for active transport has been extensively characterized," says Xin Lu, Ludwig director at the University of Oxford whose laboratory led the study. "It targets proteins that encode what's known as the nuclear localization signal (NLS). Yet about half of the proteins that get into the nucleus do not bear an NLS, and how they get there has long puzzled researchers. Now we have discovered an alternative signal by which proteins devoid of NLS are tagged for nuclear import." The finding will help scientists better understand the roles many hitherto poorly characterized proteins play in cellular life, and identify many others that work within the nucleus on such tasks as gene regulation and expression.

The researchers were led to their discovery while investigating how an important tumor suppressor [protein](#) known as ASPP, which Lu's laboratory has been studying for many years, gets into the nucleus. Their experiments revealed that a widely shared element of protein structure found in ASPP, known as the ankyrin repeat (AR), plays a central role in the protein's [nuclear localization](#).

Lu's team shows in the study that the import signal that flags proteins for the new pathway consists of two consecutive ARs that share one feature: each has a hydrophobic amino acid (one with chemical properties that repel water) that is located 13 amino acids into the repeat. This structural signature, they find, is bound by a small protein named RanGDP. Lu and her colleagues have named this new pathway the RaDAR (RanGDP-Ankyrin Repeat) nuclear import pathway. They have so far identified more than 46 proteins encoded by the human genome that carry this barcode for nuclear delivery.

In decoding this new nuclear import signal, Lu and her team also uncover a possible molecular mechanism underlying human familial melanomas, which are often linked to mutations in a protein known as p16. "We show that the p16 mutation most frequently associated with such cancers," Lu explains, "confers the RaDAR barcode to the protein, resulting in its aberrant accumulation in the nucleus." The RaDAR signature is also associated with a number of regulators of cell proliferation and gene regulation, including the NF- κ B family of proteins, which shuttle between the cytoplasm and nucleus, and have been implicated in several human cancers, and autoimmune and inflammatory diseases.

Lu's team is now investigating the spectrum of proteins that use the RaDAR pathway and exploring methods by which the ankyrin repeat that bears that barcode might be exploited to develop entirely novel diagnostics and therapies. That includes incorporating the new nuclear

import barcode into synthetic molecules named DARPins to target biologics and other kinds of drugs specifically to the [nucleus](#).

Provided by Ludwig Institute for Cancer Research

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