Restoring 'chaperone' protein may prevent plaque build-up in Alzheimer's

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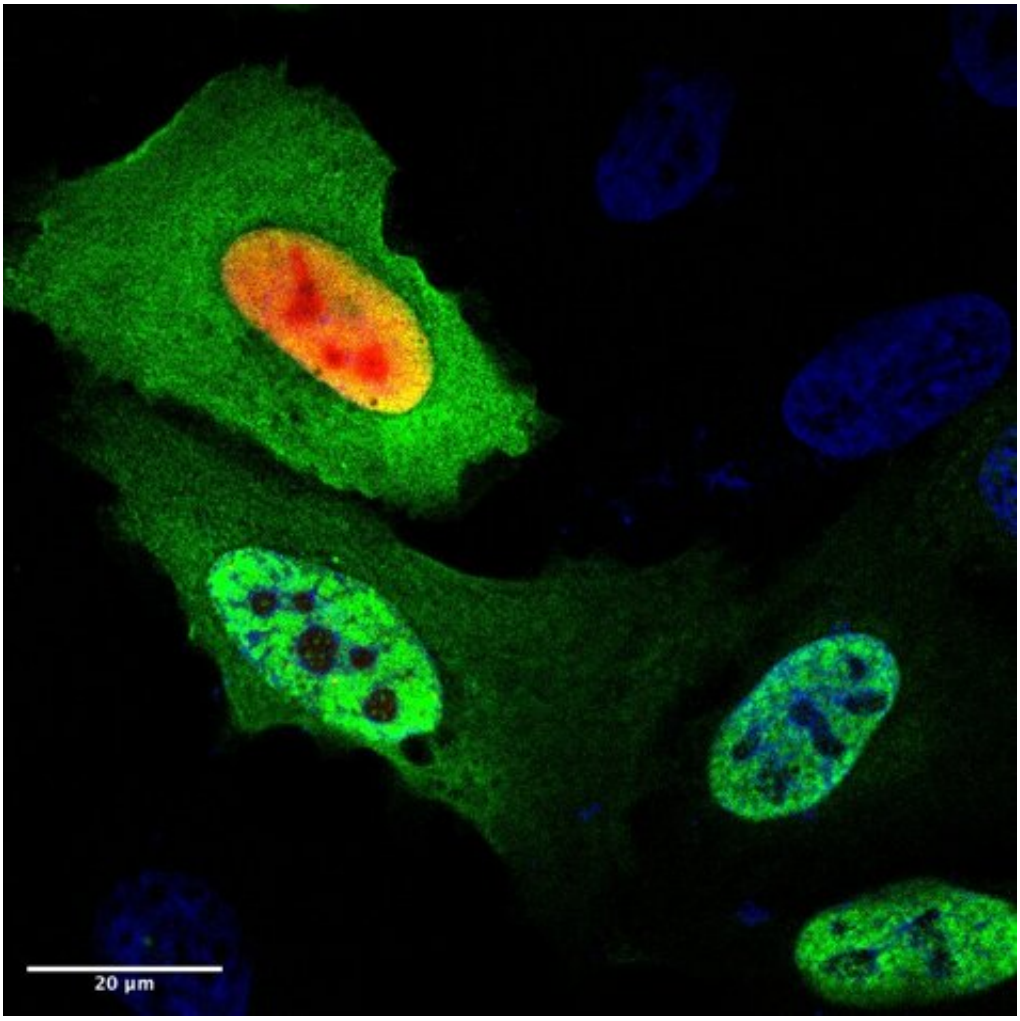

DAXX (red color at top) prevents the aggregation of mutant p53 protein associated with cancers (dark green color at bottom) in cells. Credit: Perelman School of Medicine at the University of Pennsylvania

For the first time, Penn Medicine researchers showed how restoring levels of the protein DAXX and a large group of similar proteins prevents the misfolding of the rogue proteins known to drive Alzheimer's and other neurodegenerative diseases, as well as certain mutations that contribute to cancers. The findings could lead to new targeted approaches that would restore a biological system designed to keep key proteins in check and prevent diseases.

The findings were published online in *Nature*.

The study focuses on DAXX, or death domain-associated protein, which is a member of a large family of human proteins, each with an unusually high content of two specific amino acid residues, aspartate and glutamate, referred to as polyD/E proteins. The various roles of DAXX and approximately 50 other polyD/E proteins in cell processes have emerged over time, but their role as a protein quality control system—a "chaperone" that directs protein folding, so to speak—was unanticipated.

"We solve a decades-long puzzle by showing this group of proteins actually constitute a major protein quality control system in cells and a never-before-seen enabler of proper folding of various proteins—including misfolding-prone proteins associated with various diseases," said senior author Xiaolu Yang, Ph.D., a professor of Cancer Biology in the Perelman School of Medicine at the University of Pennsylvania. "Keep that family of proteins functioning properly, and the tangling of rogue proteins may be diminished or stopped altogether."

Proteins are the workhorses of the cell. To ensure normal cellular function and protect against protein-misfolding associated with disease, organisms have evolved elaborate protein quality control systems to enable efficient protein folding. However, these systems, especially those in humans, are still not well understood, which limits the ability to develop effective therapies.

The researchers showed that DAXX and other polyD/E proteins facilitate the folding of proteins, reverse protein aggregates, and unfold misfolded proteins. They prevent neurodegeneration-associated proteins, such as beta-amyloid and alpha-synuclein from misfolding, tangling, and forming extracellular plaques and intracellular inclusions, they found. Beta-amyloid clumping between the nerve cells is observed in the brains of Alzheimer's disease patients and the target of many treatment approaches, while intracellular inclusions of alpha-synuclein are observed in the brains of patients with Parkinson's disease.

The team also showed DAXX's potential role in treating cancer.

DAXX restores native function to tumor-associated and aggregation-prone p53 proteins, reducing their cancer properties. That's important because p53 is the preeminent tumor suppressor and mutations in p53 are associated with a bevy of cancers, including lung, colon, pancreatic, ovarian, and breast cancer. Bolstering DAXX function, the authors said, might represent an alternative approach to therapeutically reestablish the tumor suppressive function of mutant p53 to treat patients.

"The findings give us a better understanding of a new biochemical activity that effectively contends with protein misfolding seen in Alzheimer's and other neurodegenerative diseases, as well as in cancer, and represent an opportunity to develop new approaches to treat these diseases," Yang said.

More information: Liangqian Huang et al, DAXX represents a new type of protein-folding enabler, *Nature* (2021). DOI: 10.1038/s41586-021-03824-5

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