

Investigators discover a 'double life' for a key Parkinson's disease protein

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A graphic depicts the “two faces of alpha-synuclein” and the transition from normal states (upper, organized molecular machines on a well-defined grid) to pathologic states in which there is membrane disruption, altered protein interactions and localization (lower, chaotic, disrupted machines, darker tone). Credit: Gergana Petrova.

One of the hallmarks of Parkinson's disease (PD) is the accumulation in the brain of a protein known as alpha-synuclein. For more than two decades, alpha-synuclein has been a focal point of attention for researchers, clinicians and drug makers interested in PD. But alpha-synuclein's function is not well understood. A new study led by investigators at Brigham and Women's Hospital, Harvard Stem Cell Institute and the Broad Institute of Harvard and MIT shines new light on the role of alpha-synuclein, uncovering a new function for the protein with relevance for PD and related conditions. Findings are published in *Cell*.

"Our study offers new insights into a [protein](#) that is known to be at the center of the development of Parkinson's [disease](#) and related disorders," said corresponding author Vikram Khurana, MD, Ph.D., chief of the Division of Movement Disorders within the Department of Neurology at the Brigham and Harvard Medical School, and a principal investigator within the Ann Romney Center for Neurologic Diseases at the Brigham. "This is a protein that is being targeted by current therapeutics, but its function has been elusive. Traditionally, alpha-synuclein has been thought to play a role in binding to the [cell membrane](#) and transporting structures known as vesicles. But our study suggests alpha-synuclein is leading a double life."

Khurana and colleagues' initial leads came from yeast and fruit fly models of alpha-synuclein toxicity and were substantiated through studies of human cells, patient-derived neurons and [human genetics](#). The team found that the very same part of the alpha-synuclein protein that interacts with vesicles also binds to "P-body" structures, machinery in the cell that regulates the expression of genes through messenger RNAs (mRNAs). In induced pluripotent stem cell-derived neurons generated from PD patients with alpha-synuclein gene mutations, the physiologic

structure and function of the P-body was lost, and mRNAs were abnormally regulated. The same occurred in [tissue samples](#) from postmortem brains from patients. Human genetic analyses supported the disease-relevance of these findings: patients who accumulate mutations in P-body genes appeared to be at higher risk for PD.

The authors describe alpha-synuclein as a "toggle switch" that regulates two very distinct functions: transport of vesicles and gene expression. In disease states, the balance is broken. The findings have potential implications for development of treatments for PD. The authors note that more clarity is needed on which of the P-body machinery components might be the best targets for a therapeutic intervention. Ongoing genetic studies aim to identify which patients might be best suited for such an intervention, and how much this newly discovered pathway contributes to risk of the disease and [disease progression](#) in PD patients at large.

"If we want to be able to develop treatments that target [alpha-synuclein](#), we need to understand what this protein does and the potential consequences of reducing its level or activity," said lead author Eric Hallacli, Ph.D., of the Department of Neurology and the Ann Romney Center for Neurologic Diseases at the Brigham. "This paper provides important information to fill our knowledge gaps about this protein, which may be beneficial for clinical translation."

More information: Vikram Khurana, The Parkinson's disease protein alpha-synuclein is a modulator of Processing-bodies and mRNA stability, *Cell* (2022). [DOI: 10.1016/j.cell.2022.05.008](https://doi.org/10.1016/j.cell.2022.05.008).
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