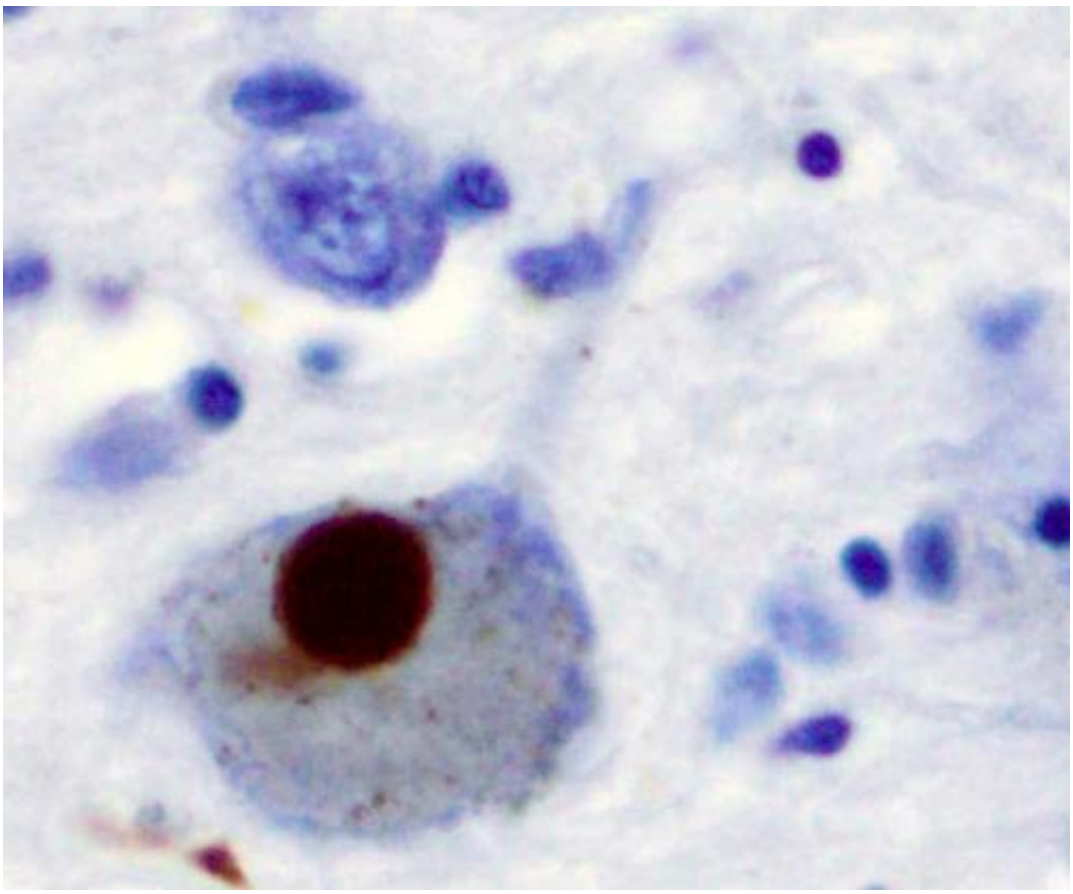
Medical Xpress

'STING' protein's efforts to clean up brain cell damage may speed Parkinson's disease progress

May 19 2022



Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

In studies with mouse and human tissue, as well as live mice, Johns Hopkins Medicine researchers report that a snag in the normal process of cleaning up broken DNA in brain cells may hasten the progression of Parkinson's disease. Specifically, the researchers found that a protein dubbed "STING" responds to cleanup signals in brain cells damaged by Parkinson's disease by creating a cycle of inflammation that may accelerate the disease's progression.

The findings, published April 4 in the *Proceedings of the National Academy of Sciences*, could advance the search for drugs and new drug targets to stop or slow the progression of Parkinson's disease.

Parkinson's disease is a neurodegenerative disorder marked by the buildup of a misfolded protein, called alpha-synuclein, in brain cells. As more misshapen proteins clump together, they kill off brain cells called dopamine neurons, leaving behind large swaths of dead brain matter. As these brain cells die, they impair a person's ability to move, think or regulate emotions. Previous studies showed that as brain cells are damaged by alpha-synuclein clumps, they release pieces of damaged DNA into the nerve cell's body.

"Freely floating DNA is not good for neurons, so the immune system has evolved ways to clear it out," says Ted Dawson, M.D., Ph.D., director of the Johns Hopkins Institute for Cell Engineering and professor of neurology at the Johns Hopkins University School of Medicine.

As part of this immune response, the STING protein—STING stands for stimulator of interferon genes—initiates a cascade of inflammatory chemical signals that bring immune cells to the site to clean up the damaged DNA. While this response may be beneficial to destroying viruses and bacteria in the rest of the body, the researchers suspect such an inflammatory response in the brain may disrupt the delicate balance of brain cell signals, leading to a worsening of Parkinson's disease.

To investigate that possibility, the researchers began scanning lab-grown mouse brain cells exposed to misfolded alpha-synuclein aggregation for the presence of the STING protein. The Johns Hopkins team found that the highest STING levels were present among supportive cells in the brain called microglia, which act as trash collectors within the brain. The presence of STING protein in microglia suggests that the microglia themselves are susceptible to DNA damage in Parkinson's disease. "When the cleanup crew members themselves may be malfunctioning, it poses a problem for the immune response in the brain," says Dawson.

The researchers suspected that the inflammatory response initiated by STING might send the microglia's immune response into overdrive because of internal DNA damage. The response, the researchers suggest, may trigger microglia to unnecessarily destroy more dopamine neurons.

Upon examining the brain tissue of mice injected with misfolded alpha-synuclein, the researchers found that mice with deactivated STING proteins had less microglial activity and brain cell death. These mice also performed better in physical tasks of strength and movement used to examine Parkinson's disease progression in mice.

"By deactivating STING, we could turn off the inflammatory response in mice, suggesting that this pathway is involved in the inflammation that occurs with pathological alpha-synuclein," says Dawson.

The Johns Hopkins team also examined the brain tissue of people who died with Parkinson's disease, and found elevated levels of STING in their brain tissues.

Dawson's research team plans to examine the STING cell signaling pathway for potential drug targets that could stop the inflammatory response.

Other researchers involved in this study include Jared Hinkle, Jaimin Patel, Nikhil Panicker, Senthilkumar Karuppagounder, Devanik Biswas, Bonn Belingon, Rong Chen, Saurav Brahmachari, Olga Pletnikova, Juan Troncoso and Valina Dawson of Johns Hopkins.

More information: Jared T. Hinkle et al, STING mediates neurodegeneration and neuroinflammation in nigrostriatal α-synucleinopathy, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2118819119

Provided by Johns Hopkins University School of Medicine