Achilles' heel identified in several neurodegenerative diseases

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Daria Mochly-Rosen is the senior author of a study that implicates two types of normally protective brain cells called glial cells in tripping off neuronal destruction. Credit: Steve Fisch

A Stanford research team has identified an oddball way brain cells spread inflammation in several neurodegenerative diseases—and an approach that could counter them all.

Many neurodegenerative diseases have a common feature that may make them amenable to the same treatment, investigators at the Stanford University School of Medicine have found.

"We've identified a potential new way to reduce nerve-cell death in a

number of diseases characterized by such losses," said Daria Mochly-Rosen, Ph.D., professor of chemical and systems biology at Stanford.

A paper describing the researchers' findings was published today in *Nature Neuroscience*. Mochly-Rosen is the senior author. The lead author is postdoctoral scholar Amit Joshi, Ph.D.

Alzheimer's disease, Huntington's disease and amyotrophic lateral sclerosis, or Lou Gehrig's disease, share a common mode of damaging brain cells, the scientists learned in studying both human cells in culture and mouse models of the diseases. This damage can be blocked by administering a substance that inhibits a critical step in that process.

The new study implicates two types of normally protective brain cells called glial cells in tripping off neuronal destruction: Microglia monitor the brain for potential trouble—say, signs of tissue injury or the presence of invading microbial pathogens—and scavenge debris left behind by dying cells or protein aggregates. Astrocytes, which outnumber the brain's neurons nearly 5 to 1, release growth factors, provide essential metabolites and determine the number and placement of the connections neurons make with one another.

Neuronal bits and fragments are perceived as foreign and targeted for clearance by microglia. But a vicious cycle of glial-cell activation and inflammation can occur in the absence of neuronal debris.

Mochly-Rosen, the George D. Smith Professor in Translational Medicine, and her colleagues discovered that mitochondria, essential components of cells, were conveying deleterious signals from microglia to astrocytes and from astrocytes to neurons. Mitochondria are tiny power packs: They furnish cells with energy. A typical nerve cell contains thousands of them. Their ability to communicate death signals from one cell to another was unexpected.

Convoluted tubular networks

Viewed close up, mitochondria are convoluted tubular networks that are perpetually being right-sized in a dynamic dance of fusion and fission, performed by opposing assemblies of enzymes. Mitochondria frequently get shuffled around from one part of a cell to another and must shift their shapes accordingly to accommodate their environments: Too much fusion, and they become too tubby to get around or work well. Too much fission, and they break up into dysfunctional fragments.

An enzyme called Drp1 that facilitates mitochondrial fission can be catapulted into hyperactivity by neurotoxic protein aggregates such as those linked to Alzheimer's, Parkinson's or Huntington's diseases or to amyotrophic lateral sclerosis. About seven years ago, Mochly-Rosen's team designed a tiny protein snippet, or peptide, called P110, that specifically blocks Drp1-induced mitochondrial fission when it's proceeding at an excessive pace, as happens when a cell is damaged.

The study showed that sustained P110 treatment via a subcutaneous pump over periods of several months lowered the microglial and astrocytic activation and inflammation in the brains of mice.

Then, experimenting with microglia in culture, the researchers introduced toxic proteins that cause different neurodegenerative diseases. Each of these manipulations kicked the microglia into an inflamed state, and they released, into the broth they were bathed in, something that could trip off inflammatory responses in astrocytes. But adding P110 to the microglial culture dishes substantially dialed down this subsequent transfer of microglial inflammation to the astrocytes. Something the microglia had expelled was providing the signal.

Likewise, something in the culture broth in which inflamed astrocytes had been immersed killed neurons. But P110 blunted that destruction, as

well. Additional experiments showed that both types of glial cells were expelling damaged mitochondria into the broth.

'Lethal for nearby neurons'

"Most people have thought that mitochondria situated outside of cells must be ghosts of dead or dying cells," Mochly-Rosen said. "But we found plenty of high-functioning mitochondria in the culture broth, along with damaged ones. And the glial cells releasing them appear very much alive."

As has been recently reported, even healthy cells routinely release mitochondria into their surrounding environment. This can be beneficial if those mitochondria are healthy, too. However, the mitochondria released by inflamed microglia and astrocytes were more apt to be damaged. When expelled mitochondria are in bad shape, it's lethal for nearby neurons.

Blocking this mitochondrial fragmentation with P110 in the microglia or in the astrocytes was enough to significantly reduce neuronal death.

How do expelled mitochondria that are damaged produce inflammation and neuronal cell death? "We're working hard to find that out," she said.

Joshi and Mochly-Rosen have filed for a patent on P110 and its utility in Huntington's disease, ALS and other neurodegenerative diseases.

Mochly-Rosen is a member of Stanford Bio-X, the Stanford Cardiovascular Institute, the Stanford Maternal & Child Health Research Institute, the Stanford Cancer Institute and the Wu Tsai Neurosciences Institute at Stanford, a faculty fellow of Stanford ChEM-H, and founder and co-director of SPARK At Stanford and the founder and president of SPARK Global.

Other Stanford co-authors of the study are medical student Paras Minhas; former postdoctoral scholar Shane Liddelow, Ph.D.; Bereketeab Haileselassie, MD, instructor in pediatric clinical care medicine; and Katrin Andreasson, MD, professor of neurology and neurological sciences. Researchers from the Washington University School of Medicine also contributed to the study.

The study is dedicated to the memory of the late Stanford neuroscientist Ben Barres, MD, Ph.D., who first identified many of the crucial roles of glial cells.

More information: Fragmented mitochondria released from microglia trigger A1 astrocytic response and propagate inflammatory neurodegeneration, *Nature Neuroscience* (2019). DOI: 10.1038/s41593-019-0486-0 , nature.com/articles/s41593-019-0486-0

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