When cells 'eat' their own power plants: Scientists solve mystery of cellular process

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A mix of serendipity and dogged laboratory work allowed a diverse team of University of Pittsburgh scientists to report in the Oct. 1 issue of *Nature Cell Biology* that they had solved the mystery of a basic biological function essential to cellular health.

By discovering a mechanism by which mitochondria – tiny structures inside cells often described as "power plants" – signal that they are damaged and need to be eliminated, the Pitt team has opened the door to potential research into cures for disorders such as Parkinson's disease that are believed to be caused by dysfunctional mitochondria in neurons.

"It's a survival process. Cells activate to get rid of bad mitochondria and consolidate good mitochondria. If this process succeeds, then the good ones can proliferate and the cells thrive," said Valerian Kagan, Ph.D., D.Sc., a senior author on the paper and professor and vice chair of the Pitt Graduate School of Public Health's Department of Environmental and Occupational Health. "It's a beautiful, efficient mechanism that we will seek to target and model in developing new drugs and treatments."

Dr. Kagan, who, as a recipient of a Fulbright Scholar grant, currently is serving as visiting research chair in science and the environment at McMaster University in Ontario, Canada, likened the process to cooking a Thanksgiving turkey.

"You put the turkey in the oven and the outside becomes golden, but you can't just look at it to know it's ready. So you put a thermometer in, and

when it pops up, you know you can eat it," he said. "Mitochondria give out a similar 'eat me' signal to cells when they are done functioning properly."

Cardiolipins, named because they were first found in heart tissue, are a component on the inner membrane of mitochondria. When a mitochondrion is damaged, the cardiolipins move from its inner membrane to its outer membrane, where they encourage the cell to destroy the entire mitochondrion.

However, that is only part of the process, says Charleen T. Chu, M.D., Ph.D., professor and the A. Julio Martinez Chair in Neuropathology in the Pitt School of Medicine's Department of Pathology, another senior author of the study. "It's not just the turkey timer going off; it's a question of who's holding the hot mitt to bring it to the dining room?" That turns out to be a protein called LC3. One part of LC3 binds to cardiolipin, and LC3 causes a specialized structure to form around the mitochondrion to carry it to the digestive centers of the cell.

The research arose nearly a decade ago when Dr. Kagan had a conversation with Dr. Chu at a research conference. Dr. Chu, who studies autophagy, or "self-eating," in Parkinson's disease, was seeking a change on the mitochondrial surface that could signal to LC3 to bring in the damaged organelle for recycling. It turned out they were working on different sides of the same puzzle.

Together with Hülya Bay?r, M.D., research director of pediatric critical care medicine, Children's Hospital of Pittsburgh of UPMC and professor, Pitt's Department of Critical Care Medicine, and a team of nearly two dozen scientists, the three senior authors worked out how the pieces of the mitochondria signaling problem fit together.

Now that they've worked out the basic mechanism, many more research

directions will likely follow, said Dr. Chu.

"There are so many follow-up questions," she said. "What is the process that triggers the cardiolipin to move outside the mitochondria? How does this pathway fit in with other pathways that affect onset of diseases like Parkinson's? Interestingly, two familial Parkinson's disease genes also are linked to mitochondrial removal."

Dr. Bayir explained that while this process may happen in all cells with mitochondria, it is particularly important that it functions correctly in neuronal cells because these cells do not divide and regenerate as readily as cells in other parts of the body.

"I think these findings have huge implications for brain injury patients," she said. "The mitochondrial 'eat me' signaling process could be a therapeutic target in the sense that you need a certain level of clearance of damaged mitochondria. But, on the other hand, you don't want the clearing process to go on unchecked. You must have a level of balance, which is something we could seek to achieve with medications or therapy if the body is not able to find that balance itself."

More information: www.nature.com/ncb/journal/vao … nt/full/ncb2837.html

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