

Tracing cell death pathway points to drug targets for brain damage, kidney injury, asthma

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University of Pittsburgh scientists are unlocking the complexities of a recently discovered cell death process that plays a key role in health and



disease, and new findings link their discovery to asthma, kidney injury and brain trauma.

The results, reported today in the journal *Cell*, are the early steps toward drug development that could transform emergency and critical care treatment.

Damaged or malfunctioning <u>cells</u> can wreak havoc on the body, so it's essential to destroy and recycle them safely and efficiently. One way this is accomplished is through ferroptosis, a highly regulated cell death program that uses iron ("ferro" means iron), and was first discovered in 2012, explained senior author Valerian Kagan, Ph.D., D.Sc., professor in the Pitt Graduate School of Public Health's Department of Environmental and Occupational Health. The work also was led by Sally Wenzel, M.D., director of the University of Pittsburgh Asthma Institute at UPMC, and Hülya Bay?r, M.D., research director of Pediatric Critical Care Medicine at Children's Hospital of Pittsburgh of UPMC.

To function harmoniously, the billions of cells in the body use a sophisticated and coordinated language to communicate. Last year, the team published two papers that uncovered the signaling language that cells use to initiate ferroptosis. The communication process they found requires a group of naturally occurring oxidized phospholipids called OOH-phosphatidylethanolamines (OOH-PEs). Phospholipids are the basic building blocks that make up cell membranes, which separate what's inside a cell from everything else outside.

However, if too many of these phospholipid signals are generated and too many cells die, the organs and tissues of the body cannot function normally.

"Discovering ferroptosis was just the tip of the iceberg - it's essential that we learn how to keep it under control. If we want to do that, we



must understand how it works," said Kagan. "And, by discovering how several key proteins interact with the phospholipid molecules to cause ferroptosis, that is what we did. Now we can move forward with the translational work of finding ways to limit ferroptosis and prevent the massive cell death that leads to catastrophic organ and tissue failure."

In the new work, the team used a variety of methods, including a new technique called lipodomics, to discover that the production of OOH-PE is a major crossroads at which a cell decides whether to initiate ferroptosis.

Previous research had shown that OOH-PEs were made by a group of enzymes known as 15-lipoxygenases (15LOs). In the course of its study, the team discovered that a protein called PEBP1 was acting as a "warden" controlling whether the 15LO enzymes made either OOH-PEs or another type of membrane building block. When the cell made increasing amounts of OOH-PEs, it initiated ferroptosis.

The researchers also used several cell culture experiments to demonstrate that PEBP1 and other key players in this pathway play a role in driving ferroptosis in several diseases, such as in kidney cells during renal failure, neurons in <u>brain trauma</u> and airway cells in asthma. Preventing PEBP1 from binding to 15LOs might be a way to prevent ferroptosis, says Kagan.

"Better treatments for traumatic brain injury and acute kidney injuries are desperately needed," said Bay?r, co-senior author of the new work. "Gaining insight into these conditions at the molecular level is extremely crucial to developing new therapies."

In traumatic brain and acute kidney injuries, there is typically an everwidening area of <u>cell death</u>, indicating that ferroptosis is continuing unabated, even after cells involved in the initial injury have been cleared,



said Bay?r, also a professor in Pitt's departments of Critical Care Medicine and Environmental and Occupational Health. This points to a longer therapeutic window of opportunity during which the ferroptotic pathway could be targeted with drugs to halt these devastating injuries.

A future therapy targeting ferroptosis could work differently for asthma, noted Wenzel, the lead author.

"Asthma is not just about stopping an attack, it's also about prevention and both are a major unmet need among patients," said Wenzel, also a professor of medicine in Pitt's School of Medicine. "Our study identified how ferroptotic death signals can damage the cells lining the airway. Targeting these pathways could lead to both preventative and treatment options for asthma exacerbations."

Provided by University of Pittsburgh Schools of the Health Sciences

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