Team decodes cellular death signals

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A multidisciplinary international team of scientists solved the mystery of a recently discovered type of controlled cell death, mapping the path to potential therapies for conditions ranging from radiation injury to cancer. The study, led in part by the University of Pittsburgh, is reported today in two papers in *Nature Chemical Biology*.

Ferroptosis is a way the body uses iron (which is "ferro" in Latin) to catalyze a reaction that safely destroys and recycles a malfunctioning or damaged cell. Until this study, scientists didn't know how the body signaled - within the damaged cell and to other cells - that this well-regulated death needed to occur.

"Our team successfully decoded the signaling language that cells use to trigger ferroptosis," said Valerian E. Kagan, Ph.D., D.Sc., professor in the Pitt Graduate School of Public Health's Department of Environmental and Occupational Health, and lead author of one of the papers. "You can think of it like the scanners and radios that policemen use to find and arrest a criminal.

"The goal is to communicate enough information to neutralize the problem and remove the criminal, or damaged cell, but without creating such a commotion that you disrupt the society, which, in this example, would be other, well-functioning cells."

Through two years of experiments bridging fields ranging from public health and critical care medicine to basic biology and chemistry, the team analyzed hundreds of molecular combinations generated in the

ferroptotic process to discover that only four molecules actually signal for the cell to die. All four are phospholipids - naturally occurring molecules that make up cell membranes.

"Scientists have long known that these lipids were important for encasing the cell and giving it structure," said Kagan. "What they didn't know - what we've only learned in recent scientific history - is that they do so much more, including communicating and signaling messages like 'danger' inside the cell itself, to other cells and to the cellular community as a whole, so that organisms can function in a coordinated way."

Kagan and Hülya Bayır, M.D., professor in Pitt's Department of Critical Care Medicine and senior author of one of the papers, had previously worked together to decode another type of more well-known cell death, called apoptosis. They then decided to pursue the more esoteric ferroptosis, which had first been discovered in 2012.

"Ferro means iron, and we live in Pittsburgh, the Iron City - it would be a shame for us not to understand this process," said Kagan, whose team looked for therapeutic value as they decoded the signaling process.

Kagan and Bayır also study ways to protect people against radiation, such as what would be given off in a terrorist attack. The findings gave them reason to think that ferroptosis may underlie radiation induced cellular damage as well.

"More and more, we're appreciating that the damage from acute radiation is happening to the lining of the intestine, and that damage triggers a cascade of health complications that lead to sepsis, a very deadly syndrome," said Bay?r. "We believe that the radiation is triggering ferroptosis in the cells that line the intestine. If we can stop that process and get the body to repair, rather than systematically destroy, those cells, we might save the victims of devastating dirty bomb

attacks."

Conversely, in cancer, the body is failing to destroy dysfunctional cancer cells, allowing tumors to grow unchecked. By understanding the ferroptotic pathway, the researchers hope to find medications that can prompt it to recognize and kill cancer cells.

The researchers have already partnered with several UPMC clinicians to explore ways to translate their scientific findings into therapies that could help patients.

More information: Oxidized arachidonic and adrenic PE s navigate cells to ferroptosis, *Nature Chemical Biology*, nature.com/articles/doi:10.1038/nchembio.2238

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