Small molecule 'jams the switch' to prevent inflammatory cell death

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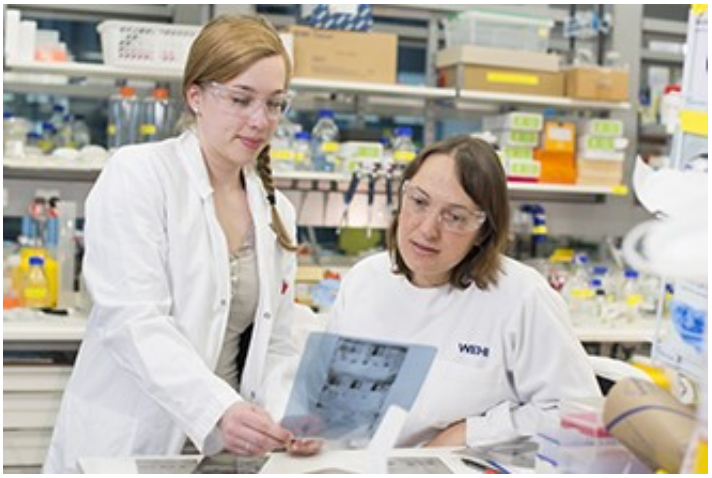

Ms Maria Tanzer, Dr Joanne Hildebrand (L-R) and colleagues have discovered a small molecule can prevent a key protein from triggering a form of cell death than causes inflammatory disease.

(Medical Xpress)—Walter and Eliza Hall Institute scientists have discovered a small molecule that blocks a form of cell death that triggers inflammation, opening the door for potential new treatments for inflammatory disease such as rheumatoid arthritis, Crohn's disease and psoriasis.

The researchers made the discovery while investigating how a protein called MLKL kills cells in a process known as necroptosis. Their findings were published today in the journal *Proceedings of the National*

Academy of Sciences.

Necroptosis is a recently discovered cell death pathway linked to immune disorders. It is a vital process in which cells undergo programmed death while warning the immune system that something has gone wrong, such as during viral infection. However when necroptosis is inappropriately activated, it can promote inflammation and the development of inflammatory disease.

Dr Joanne Hildebrand, Ms Maria Tanzer, Dr James Murphy, Associate Professor John Silke and colleagues studied how MLKL changes shape to trigger cell death. "MLKL is the final protein in the cell death pathway but it needs to be activated before it can kill the cell," Dr Hildebrand said. "Understanding how it becomes active can help uncover new ways to treat disease."

Dr Hildebrand said the research team found that a particular part of the protein became 'unlatched' when activated, allowing it to attach to the cell membrane and trigger cell death. "It's like flicking a molecular switch," she said. "We showed that when the switch can't be 'turned on', MLKL doesn't become active and necroptosis is prevented."

Ms Tanzer said the team tested a range of small molecules to see if any could stop the switching on of MLKL and had identified one that prevented MLKL from becoming active. "This small molecule binds to MLKL in such a way that it 'jams the switch' that makes it active," she said. "We are really excited by this discovery because not only have we shown this particular part of the protein is essential for necroptosis, we also have a starting point in a drug discovery program."

Dr Murphy said institute scientists would now embark on a collaborative project with Catalyst Therapeutics to develop a potent new drug based on the small molecule identified in the study. "MLKL is an appealing

target because research suggests it does only one thing, which is kill the cell," he said. "Blocking this protein doesn't impact other functions of the cell, reducing the chance of unwanted side-effects."

"If we can create a compound that better targets this particular part of MLKL, we can prevent necroptosis and improve treatments for inflammatory disease."

More information: The complete paper is available online: www.pnas.org/content/early/201 … 987111.full.pdf+html

Provided by Walter and Eliza Hall Institute of Medical Research