Link found between cell death and inflammatory disease

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Mr James Rickard, Mr Joseph Evans and Ms Joanne O'Donnell (L-R) were part of an institute team that showed cell death by necroptosis could be the underlying cause of inflammatory disease.

(Medical Xpress)—A team of Melbourne researchers has shown a recently discovered type of cell death called necroptosis could be the underlying cause of inflammatory disease.

The research team discovered that a previously identified molecule involved in necroptosis, called RIPK1, was essential for survival by preventing uncontrolled inflammation. This finding could lead to future treatments for inflammatory diseases including Crohn's disease, rheumatoid arthritis and psoriasis.

The researchers, from the Walter and Eliza Hall Institute, also discovered that the 'survival' molecule RIPK1 acts as the 'gatekeeper' between cell life and death. In a paper published in the journal *Cell*, they reveal RIPK1 is essential for a cell's decision to live or die, and in choosing how to die.

Institute researchers Associate Professor John Silke from the Cell Signalling and Cell Death division, Dr Motti Gerlic from the Inflammation division and Dr Ben Croker led the project, working with PhD students Mr James Richard, Ms Joanne O'Donnell and Mr Joseph Evans. Associate Professor Silke said the team had shown for the first time that RIPK1 (receptor interacting protein kinase 1) was a master controller of cell life and death.

"We showed that, in the body, RIPK1 is not only essential for initiating necroptosis, but also for inhibiting necroptosis and the runaway inflammation that can cause severe tissue damage," Associate Professor Silke said. "We also found that it played a role in another type of programmed cell death called apoptosis. Our research highlighted that RIPK1 is the gatekeeper that controls whether a cell lives or dies, and the decision it makes on how to die."

Necroptosis is a type of 'controlled' death that instructs a cell to die while stimulating an inflammatory reaction to let the immune system know something has gone wrong. However when this cell death pathway begins to spiral out of control, it can lead to inflammatory disease. Necroptosis has also been implicated in neurodegenerative disease, brain injuries caused by blood loss, and some viral infections.

Dr Gerlic said their study provided the first evidence that RIPK1 was essential for inhibiting necroptosis. "This research puts a new dogma on the table about RIPK1 and its role in controlling or inhibiting necroptosis," Dr Gerlic said. "It is also the first time that we have shown

necroptosis and the molecules involved actually induce inflammatory disease, suggesting that targeting this pathway could be useful for treating human conditions such as psoriasis, rheumatoid arthritis and Crohn's disease."

Associate Professor Silke said necroptosis was a newly discovered type of cell death that had only really been studied in the past five years. "When our time comes to die, we don't have a choice," he said. "However cells make this choice all the time – not only whether they die, but also how they die. They can choose to die quietly, or they can make a fuss. Necroptosis is their way of letting everyone else know that they are dying and help is needed usually when something has gone wrong such as a viral infection."

Dr Gerlic said the research team had also shown RIPK1 played other important roles in the body. "As part of the research we found that RIPK1 was essential for keeping blood stem cells alive after bone marrow transplant," he said. "This finding is particularly important when considering treatments that target RIPK1, as it could have unwanted side-effects for other cells in the body. Therefore it is important to ensure any potential drugs are properly investigated for any off-target effects."

Associate Professor Silke said the institute was already capitalising on its expertise in necroptotic cell death with a drug discovery program to identify small molecules that could target molecules downstream of RIPK1 in the necroptotic pathway, such as MLKL (mixed lineage kinase domain-like).

Provided by Walter and Eliza Hall Institute of Medical Research

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