Cell death protein could offer new anti-inflammatory drug target

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Scientists in Melbourne, Australia, have revealed the structure of a protein that is essential for triggering a form of programmed cell death, making possible the development of new drugs to treat chronic inflammatory diseases such as Crohn's disease and rheumatoid arthritis.

Dr James Murphy, Associate Professor John Silke, Dr Joanne Hildebrand, Dr Peter Czabotar, Professor Warren Alexander and colleagues from the Walter and Eliza Hall Institute have shown that the protein MLKL plays a crucial role in the signalling pathways that trigger a recently discovered cell death pathway called necroptosis. The results were published today in the journal *Immunity*.

Usually, when a cell detects that it is infected by a virus or bacteria or has other irreparable damage it self-destructs through a process called apoptosis. But Associate Professor Silke said some bacteria and viruses had developed ways of preventing this cell suicide, also allowing the invaders to survive. It is at this point that the 'back up' necroptosis pathway might be activated.

"During necroptosis the cell still self-destructs but in doing so it also sends an 'SOS' to the immune system to tell it that something has gone wrong with the cell's normal cell death process of apoptosis. So internally, the cell is still doing its best to self-destruct in an orderly and programmed way, but it is simultaneously sending signals to the immune system to mount a response to the invaders."

However there are times when the necroptosis pathway may be inappropriately activated, sending messages to the immune system that promote inflammation and the development of inflammatory diseases.

Dr Murphy said the discovery of MLKL's role in activating the necroptosis pathway was an important step in understanding this cell death pathway and its role in disease. "Necroptosis has only been defined in the past 10 years and the role MLKL plays was only discovered in 2012," Dr Murphy said.

"This study provides the first genetic proof that MLKL is required for necroptosis as well as the first full-length, atomic level, three-dimensional structure of a protein that regulates necroptosis. These discoveries are really exciting because they give us a new target to look at for developing treatments for people who suffer from an inflammatory disease."

The three-dimensional images of MLKL, which were obtained using the Australian Synchrotron, revealed an interesting detail about the protein, Dr Murphy said. "The structure revealed that MLKL is a 'dead enzyme', making it different from the other proteins in the signalling pathway," Dr Murphy said. "We discovered that MLKL needs to be 'switched on' before it can activate necroptosis. MLKL could therefore be a perfect target for treatments because it is different from almost every other cell-signalling protein, making it easier to develop highly specific drugs and limiting potential side effects."

Associate Professor Silke said the team was now trying to determine the 'on' and 'off' states of MLKL and how it could be modified to treat disease. "We are now trying to work out what MLKL looks like at the atomic level when it is switched 'on' so that we can begin to develop drugs that will block it," Associate Professor Silke said. "We are excited about this fundamental discovery and, with colleagues at the institute, we

are already using this knowledge to develop specific, drug-like molecules to test in disease models. This could directly lead to treatments that will help patients who have chronic inflammatory diseases including rheumatoid arthritis, inflammatory bowel syndrome, Crohn's disease and psoriasis."

Provided by Walter and Eliza Hall Institute