Cell death proteins key to fighting disease

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Mr Jason Brouwer and colleagues showed how key proteins change shape to initiate cell death.

Melbourne researchers have uncovered key steps involved in programmed cell death, offering new targets for the treatment of diseases including lupus, cancers and neurodegenerative diseases.

The research teams from the Walter and Eliza Hall Institute worked together to discover the three-dimensional structure of a key cell death protein called Bak and reveal the first steps in how it causes cell death. Their studies were published in *Molecular Cell* and *Proceedings of the National Academy of Sciences*.

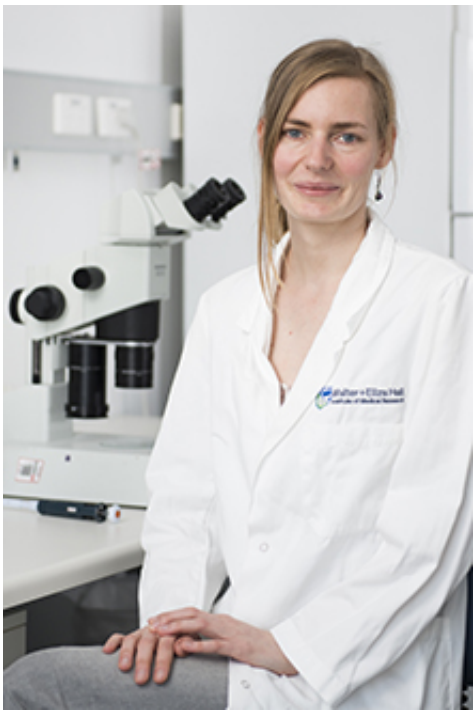
Programmed cell death, known as apoptosis, occurs naturally when the

body has to remove unwanted cells. Chemical signals tell the cell to die by activating the apoptosis proteins Bak and Bax, which break down the 'energy factory' of the cell, known as the mitochondria. When this process goes awry, defective cells such as cancer cells can continue to live, or healthy cells can die unnecessarily, such as occurs in Alzheimer's disease.

Visualising death proteins

Using the Australian Synchrotron, Mr Jason Brouwer, Dr Peter Czabotar, Dr Ruth Kluck and colleagues from the institute's Structural Biology division investigated how the structure of Bak changes in order to initiate cell death. The research was published in *Molecular Cell*.

"Understanding the way cell death proteins work and what they look like is crucial to finding new ways to treat disease," Dr Czabotar said. "Our research showed how Bak morphs from one shape to another to trigger apoptosis. Once Bak becomes 'activated' within the cell, it couples with another Bak molecule to form a 'dimer', which then goes on to initiate apoptosis."



Dr Dana Westphal and colleagues found key cell death proteins don't pierce through the mitochondrial membrane as previously thought.

Dr Czabotar said understanding apoptosis would allow researchers to develop new ways to treat disease. "Knowing the structure of these proteins and how they work in the cell is essential in designing new treatments to fight disease."

Seeking the hole story

Dr Dana Westphal, Dr Kluck, Dr Grant Dewson, Professor Jerry Adams and colleagues from the Molecular Genetics of Cancer and Cell Signalling and Cell Death divisions examined how the Bak and Bax dimers attach to mitochondria and perforate them. The research was published in *Proceedings of the National Academy of Sciences.*

Dr Kluck said dimers of Bak and Bax break open the mitochondrial surface, but the mechanism remains poorly understood. "A crucial stage of apoptosis is the release of key proteins from within the mitochondria," she said. "Scientists thought this happened by Bak and Bax poking through the mitochondrial membrane to form a hole, but our work has shown this doesn't happen. Instead, these proteins collapse onto the oily surface of the mitochondria and crowd the surface until holes form."

"We and others are now working to discover exactly how these proteins come together to destroy the mitochondria and trigger apoptosis. A deeper understanding of this pivotal event is likely to suggest new ways to regulate apoptosis to combat disease."

More information: Jason M. Brouwer, Dana Westphal, Grant Dewson, Adeline Y. Robin, Rachel T. Uren, Ray Bartolo, Geoff V. Thompson, Peter M. Colman, Ruth M. Kluck, Peter E. Czabotar, Bak Core and Latch Domains Separate during Activation, and Freed Core Domains Form Symmetric Homodimers, *Molecular Cell*, Volume 55, Issue 6, 18 September 2014, Pages 938-946, ISSN 1097-2765, dx.doi.org/10.1016/j.molcel.2014.07.016.

"Apoptotic pore formation is associated with in-plane insertion of Bak or Bax central helices into the mitochondrial outer membrane." *PNAS* 2014 111 (39) E4076-E4085; published ahead of print September 16, 2014, DOI: 10.1073/pnas.1415142111

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