Pores finding reveals targets for cancer and degenerative disease

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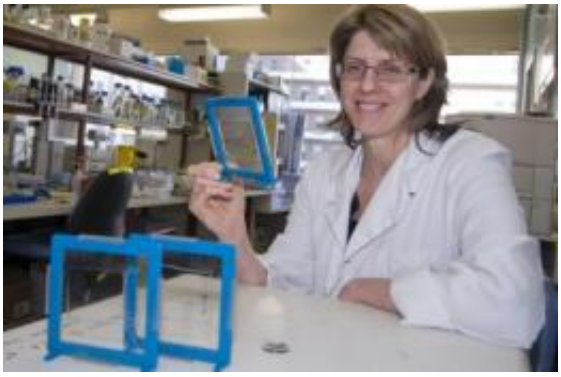

Dr. Ruth Kluck has been investigating the role in apoptosis of two proteins, Bak and Bax. Her studies have revealed how Bak forms a pore in the mitochondria. Pore formation is the point of no return in apoptotic cell death as it allows cytochrome c, which is the protein that initiates cell death, to escape from the mitochondria. Credit: Walter and Eliza Hall Institute of Medical Research

Walter and Eliza Hall Institute scientists have identified a key step in the biological process of programmed cell death, also called apoptosis.

Apoptosis is important in human biology as it removes unwanted and sometimes dangerous cells from our bodies, protecting us against cancer development. It can also, however, lead to the development of degenerative diseases when healthy cells are errantly destroyed.

The research, led by Dr Ruth Kluck from the institute's Molecular

Genetics of Cancer Division, is crucial to the development of drugs that can turn on apoptosis, thereby more effectively killing cancer cells. It could also be used in developing compounds that turn off the apoptosis that leads to degenerative disorders.

Dr Kluck has been investigating the role in apoptosis of two proteins, Bak and Bax. It is thought that understanding their role will identify targets against which drugs to regulate cell death could be designed.

"The pivotal step towards cell death is the formation of a pore in the mitochondria; mitochondria make and supply energy to the cells," Dr Kluck said. "Pore formation is the point of no return in apoptotic cell death as it allows cytochrome c, which is the protein that initiates cell death, to escape from the mitochondria. Only two proteins are known to form the pore, Bak and Bax."

In 2008 Dr Kluck and her colleagues published their finding that, in order to form the pore, Bak first changes shape and then combines with another Bak protein to form a doublet.

"We have now identified the second step in how Bak forms that pore," Dr Kluck said. "Once the doublet is formed it can combine with other Bak doublets by what's called a second interface. This second interface seems to allow doublets to assemble into the larger complexes that form the pore."

The team of Dr Kluck, Dr Grant Dewson, Mr Tobias Kratina, Dr Peter Czabotar and Professor Jerry Adams from the institute and Dr Catherine Day from the University of Otago published their finding in the 25 November issue of *Molecular Cell*.

Dr Kluck said the team would continue to study how the large complexes of Bak and Bax force a hole in the mitochondrial membrane, how to

start this process more effectively in cancer cells, and how to prevent it in brain and other healthy cells.

"A major black box in understanding apoptosis is how Bak and Bax work. Because these proteins change shape and lodge in a membrane they are hard to study. Any understanding we gain about how Bak and Bax form a pore, how they change shape and how they bind to each other, will help us understand how cancer cells can be targeted to die."

Provided by Walter and Eliza Hall Institute

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