Medical Xpress

Scientists uncover potential trigger to kill cancer

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Dr Ruth Kluck of the Walter and Eliza Hall Institute of Medical Research. Credit: Walter and Eliza Hall Institute of Medical Research

Melbourne researchers have discovered a new way of triggering cell death, in a finding that could lead to drugs to treat cancer and autoimmune disease.

Programmed cell death, also called apoptosis, is a natural process that removes unwanted cells from the body. Failure of apoptosis can allow cancer cells to grow unchecked or immune cells to inappropriately attack the body.

The protein known as Bak is central to apoptosis. In healthy cells Bak sits in an inert state but when a cell receives a signal to die, Bak transforms into a killer protein that destroys the cell.

Institute researchers Dr Sweta Iyer, Dr Ruth Kluck and colleagues have discovered a novel way of directly activating Bak to trigger cell death. Their findings have just been published in the journal *Nature Communications*.

The researchers discovered that an antibody they had produced to study Bak actually bound to the Bak protein and triggered its activation.

Dr Kluck said the findings were completely unexpected.

"We were excited when we realised we had found an entirely new way of activating Bak," Dr Kluck said. She hopes to use this discovery to develop drugs that promote cell death.

"There is great interest in developing drugs that trigger Bak activation to treat diseases such as cancer where apoptosis has gone awry," she said. "This discovery gives us a new starting point for developing therapies that directly activate Bak and cause cell death."

The researchers used information about Bak's three-dimensional

structure to find out precisely how the antibody activated Bak.

"It is well known that Bak can be activated by a class of proteins called 'BH3-only proteins' that bind to a groove on Bak. We were surprised to find that despite our antibody binding to a completely different site on Bak, it could still trigger activation," Dr Kluck said.

Drugs that target this new activation site could be useful in combination with other therapies that promote cell death by mimicking the BH3-only proteins.

"The advantage of our antibody is that it can't be 'mopped up' and neutralised by pro-survival proteins in the cell, potentially reducing the chance of drug resistance occurring," Dr Kluck said.

The researchers are now working with collaborators to develop their antibody into a drug that can access Bak inside cells.

More information: Sweta Iyer et al. Identification of an activation site in Bak and mitochondrial Bax triggered by antibodies, *Nature Communications* (2016). DOI: 10.1038/ncomms11734

Provided by Walter and Eliza Hall Institute