Cell survival protein research reveals surprise structure

October 14 2011

Dr Doug Fairlie (right) and Dr Erinna Lee, from the institute's Structural Biology division, have shown that a pro-survival protein called Bcl-w can adopt a surprising structure.

Researchers from the Walter and Eliza Hall Institute have found a structural surprise in a type of protein that encourages cell survival, raising interesting questions about how the proteins function to influence programmed cell death.

Programmed cell death, or apoptosis, is a natural process in which cells are instructed to die by members of the Bcl-2 family of proteins. It is important for controlling cell numbers and destroying defective or unwanted cells, but is also involved in the development of some cancers such as leukaemia and breast cancer in which the cells have an oversupply of pro-survival proteins, resisting signals that tell them to die.

Dr Doug Fairlie, Dr Erinna Lee, and Professor Peter Colman from the institute's Structural Biology division have shown that a pro-survival protein called Bcl-w can adopt a surprising structure unlike that seen in any other Bcl-2 family protein to date. The results were published today in the journal *Structure*.

"We determined the structure of an unusual form of Bcl-w, a pro-survival protein discovered here at the institute," Dr Fairlie said. "Unexpectedly, we found that, structurally, Bcl-w was able to change its shape significantly. Such a change had not previously been reported for the pro-survival proteins."

Researchers at the institute have spent many years studying the proteins involved in programmed cell death. Programmed cell death is controlled by pro-survival molecules, which stop cells from dying, and pro-death molecules, which instruct cells to die.

"It is well known, from biochemical analyses, that these proteins have to change shape in order to function, but we don't know how that shape change occurs or what it looks like," Dr Fairlie said. "A number of our structural biologists are working on solving this particular problem."

Dr Lee said the research team was able to show that, with respect to Bcl-w at least, some of these shape changes can affect the protein's function, perhaps in a negative way.

"It could be a way of regulating what these proteins do within a cell, or it could be an inherent structural difference particular to the Bcl-w protein that makes it behave slightly differently to other pro-survival proteins," she said. "We're still trying to understand exactly what that means for the field."

Dr Fairlie said the research gave some idea of the types of changes these

proteins can undergo, something that is not well understood. “Bcl-w is an interesting case because it does not seem to be associated with tumour growth and resilience to chemotherapy agents to the same extent as other pro-survival proteins. It may be that Bcl-w, unlike other Bcl-2 proteins and demonstrated in our structure, has evolved an inherent structural flexibility that restricts its pro-survival activity, which could explain why it is not often implicated in tumour development,” he said.

“It will be particularly interesting to see whether the types of structural changes we see in Bcl-w also happen with the pro-death proteins, which would tell us a lot more about how these proteins work to kill a cell,” he said.

More information: www.cell.com/structure/abstract/S0969-2126%2811%2900257-7

Provided by Walter and Eliza Hall Institute