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Scientists create 3D image of key protein involved in blood and other cancer development

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Scientists at the Walter and Eliza Hall Institute have created the first three-dimensional image of a key protein known to be involved in the development of blood and other cancers.

The discovery showed the protein, called Trib1, plays a vital role in controlling how and when other proteins are degraded, which is essential for managing protein levels in the cell. The finding could be used to develop new drugs to treat cancers such as leukaemia, caused by malfunctioning of the Trib1 protein.

Trib1 is part of the protein family Tribbles, which play diverse roles in cell signalling and development. Tribbles are named after the small, furry creatures from Star Trek that reproduce uncontrollably. Excess Tribbles drive the abnormal production of immune cells, causing a type of blood cancer called acute myeloid leukemia (AML).

Institute researchers Dr James Murphy and Dr Isabelle Lucet, in collaboration with Dr Peter Mace from the University of Otago, New Zealand, characterised the human Tribbles protein Trib1.

Dr Murphy said the research showed how Trib1 played an important role in controlling protein levels within the cell. "The amount of protein in a cell depends on the balance between production and degradation," Dr Murphy said. "Defects in protein degradation, or in the controllers of protein degradation, disrupt this balance and can lead to diseases such as cancer."

Using the Australian Synchrotron, Dr Mace, Dr Murphy and colleagues were able to obtain detailed three-dimensional images of Trib1. "The structure of Trib1 is really exciting," Dr Murphy said. "We can now see how Trib1 is able to trigger protein destruction, which will provide critical clues for developing drugs that target Trib1 to treat cancers."

Lead investigator Dr Mace said Trib1 acted as a scaffold to bring many proteins together, forming a large complex that caused specific proteins to be degraded. "As well as explaining how Trib1 functions, our research could help us design novel therapeutic agents for the treatment of AML," Dr Mace said. "For example, some AML patients have too much Trib1, which causes a loss of proteins that would normally inhibit cancer. Understanding the structure of Trib1 provides critical clues about how we could block Tribbles for the treatment of AML."

Dr Murphy said that Trib1 was an unusual type of protein called a pseudokinase. "Pseudokinases were once thought to be evolutionary dead ends, but we now know that they play critical roles in cells," he said. "Precisely how Trib1 lost its old activity and gained other functions has been a real mystery."

Visualising Trib1 finally allowed the team to answer this question. "The powerful X-ray beams created by the synchrotron enabled us to see that Trib1 has undergone huge contortions compared to its ancestors. These structural changes prevent Trib1 from driving chemical reactions, and instead allow it to act as a scaffold to bring proteins together," Dr Murphy said.

Source:
Walter and Eliza Hall Institute
