Important signalling pathway for leukaemia cells discovered—enables development of new treatments

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A research group led by Professor Daoguang Yan from Jinan University in Guangdong has cooperated with Professor Vesa Olkkonen from the Minerva Foundation Institute for Medical Research on the Meilahti Campus to uncover a new mechanism which enhances the viability of cancerous T-cells and promotes their reproduction.

The researchers discovered that the T-ALL leukaemia cells use a specific signalling pathway to maintain their intense, oxygen-dependent energy metabolism and ability to divide. The pathway is largely based on the ORP4L protein, which is expressed only in cancerous T-cells but not in healthy ones.

"The new results establish that ORP4L binds the protein group that transmits signals on the membranes of the cancerous cells, which accelerates the release of calcium ions from the endoplasmic reticulum. This way the 'power plants' of the cell which run on oxygen, the mitochondria, are free to produce energy to their full capacity," explains Professor Olkkonen.

Severing the newly discovered signalling pathway could prevent cancerous cells from growing and reproducing. This means that identifying the pathway will enable the development of new leukaemia treatments which target different sections of the pathway.

The study was published in the esteemed *Nature Communications* journal.

Interest in ORP proteins brings researchers together

Professor Yan has been in charge of his research group at Jinan University in Guangzhou, Guangdong, since 2009. While working in Helsinki at the National Public Health Institute of Finland between 2005 and 2007, Yan became interested in ORPs, a family of proteins which bind oxysterols (oxidised cholesterol derivatives) in humans, and their role in cell signalling. Oxysterol-binding proteins are found in the areas where cell organelles come into contact: they transmit lipids and signals between them.

An abnormally intense expression of the ORP4 protein had previously been observed in certain cancer cells, and Yan and Olkkonen suspected that it transmitted signals which maintained the malignancy of the cells. In 2009, Professor Yan discovered that ORP4L was being excessively expressed in T-ALL leukaemia cells, and ever since, he has been studying the function of this protein and its significance in leukaemia.

Professor Olkkonen's research group identified the ORP protein family between 1999 and 2001, and is still studying the functions of these proteins, including ORP4L. Olkkonen has made regular visits to Yan's laboratory, and together with Yan has supervised the ORP4L research, the top project at the laboratory.

ORP inhibitors to become new cancer drugs?

The now-published study used both cultured cancerous T-cell lines and leukaemia cells isolated directly form the blood of patients. The expression of the ORP4L protein was blocked or excessively boosted in

experiments on the cultured cells. The significance of the protein in the reproduction of leukaemia cells was also studied in vivo by transferring ORP4L-manipulated human leukaemia cells to immune-deficient mice.

"What makes our findings particularly interesting is that small-molecule inhibitors for the ORP proteins have been discovered, and we may be able to use them to develop new drugs to treat T-ALL leukaemia and perhaps other types of cancer as well," Olkkonen states.

More information: Wenbin Zhong et al. ORP4L is essential for T-cell acute lymphoblastic leukemia cell survival, *Nature Communications* (2016). DOI: 10.1038/NCOMMS12702

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