New insights into T-cell acute lymphoblastic leukaemia development

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A research team from the National University of Singapore (NUS) led by Assistant Professor Takaomi Sanda, Principal Investigator from the Cancer Science Institute of Singapore and Department of Medicine at NUS Yong Loo Lin School of Medicine, has provided new insights into the molecular mechanism affecting how genes are produced during normal T-cell development, and contributing to leukaemia formation. Results of the study have been published in the journal *Leukemia*.

T-cells are a type of white blood cell which develops in the thymus (hence the name T-cell), a primary lymphoid organ. These cells play an indispensable role in the body's cellular defence system. In T-cell acute lymphoblastic leukaemia (T-ALL), which is a cancer of the white blood cells, T-cells carry genetic mutations which cause them to multiply uncontrollably. Production of genes during T-cell development is strictly controlled by the body. Different genes are turned 'on' and 'off' at various stages of T-cell development, in order to ensure T-cells become fully functional in the immune system.

TAL1 triggers the super-enhancer 'switch'

Specifically, the research team studied the protein TAL1, which is encoded by a cancer causing gene previously found to contribute to the development of T-ALL, and discovered that TAL1 activates a 'molecular switch' called a super-enhancer, which subsequently leads to a cluster of genes called GIMAP being activated. This may result in T-cell

precursors growing abnormally and not developing into functional T-cells in the body, leading to the development of T-ALL.

Super-enhancers are regions of DNA that increase production of genes linked to important cellular decisions. They can be sensitive to disturbances and occur frequently at cancer genes. The activation of the super-enhancer induces genes to be abnormally activated, instead of being strictly controlled.

Asst Prof Sanda said, "Currently, most of the patients with T-ALL are young children. While recent improvements in chemotherapy have significantly boosted cure rates for T-ALL, the introduction of intensive chemotherapy causes both short- and long-term adverse effects. Moreover, there are only a limited number of new drugs with specific activity against malignant T-cells. Moving forward, we are looking into identifying potential therapeutic compounds that inhibits the activation of this super-enhancer. We hope to be able to translate it into meaningful therapies for patients afflicted by T-ALL."

More information: W S Liau et al. Aberrant activation of the GIMAP enhancer by oncogenic transcription factors in T-cell acute lymphoblastic leukemia, *Leukemia* (2016). DOI: 10.1038/leu.2016.392

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