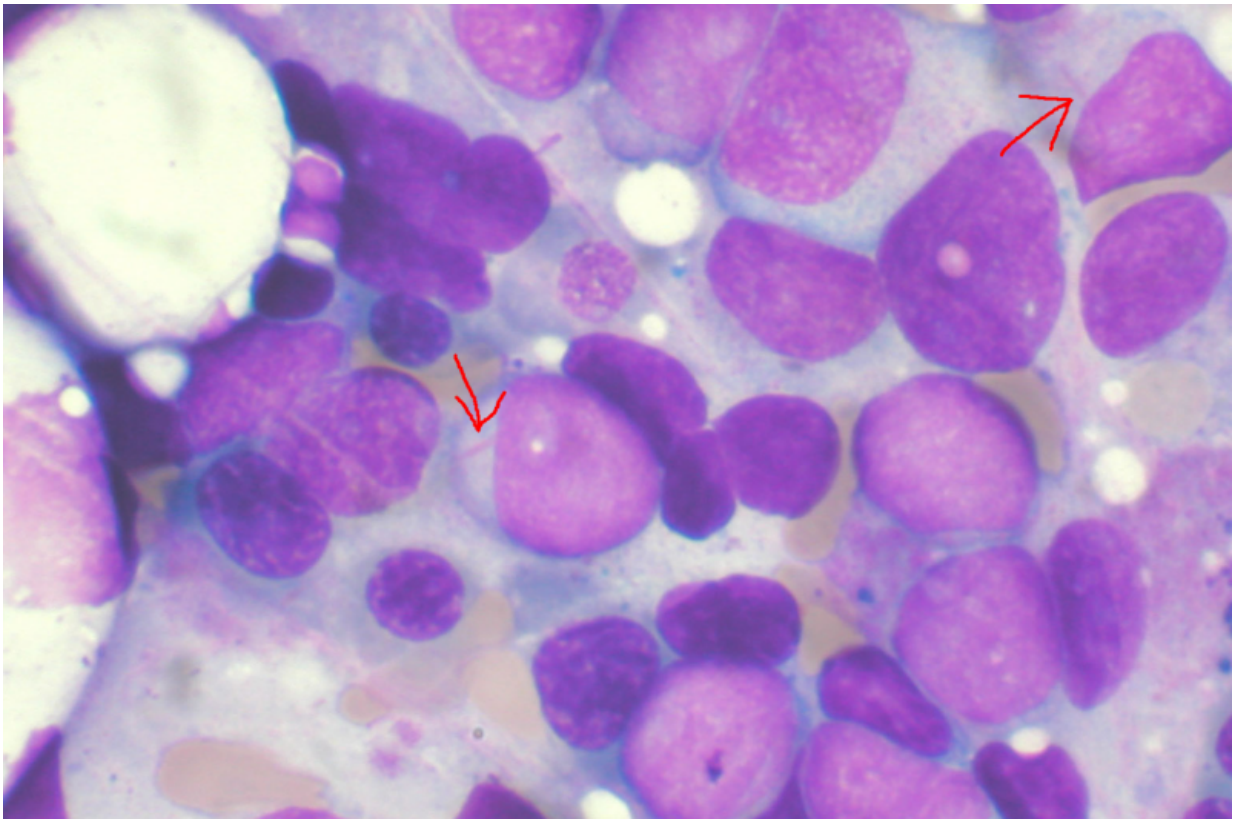
Medical Xpress

Covalently closed circular RNA regulates BAP1 deubiquitinase activity in leukemia

August 13 2020



Bone marrow aspirate showing acute myeloid leukemia. Several blasts have Auer rods. Credit: Wikipedia

Every year, 1.1 million new cases of blood cancers are diagnosed worldwide. Presently, chemotherapy remains the most common and

effective course of treatment. However, the emergence of more aggressive forms of leukemia in adults prompts a need for early detection and new therapeutic approaches to achieve better clinical outcomes.

In a novel step forward, researchers from the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS) have identified covalently closed circular RNAs (circRNAs) from key genes involved in leukemia development and provided greater understanding of their roles in hematological malignancies.

Mutations in additional sex combs-like 1 (ASXL1) gene, an epigenetics remodeler, have been found in acute myeloid leukemia (AML), chronic myelomonocytic leukemia (CMML) and myelodysplastic syndrome (MDS), and are associated with poor overall survival. Recently, the ASXL1 gene locus was shown to undergo alternative splicing to produce circRNAs. While previous studies on circRNAs have primarily been focused on understanding the origins of these non-coding RNAs, the CSI Singapore research group led by Assistant Professor Sudhakar Jha investigated the role of circRNAs in modulating the epigenetics landscape and the effects on differentiation in hematopoietic development and leukemogenesis.

The findings of the study were published in the prestigious scientific journal *Haematologica* in July 2020.

New mechanism responsible for leukemia development

CircRNAs have been shown to have higher stability, are abundant, and highly conserved compared to linear RNAs. In addition, they can be detected in extracellular vesicles, exosomes and blood plasma thereby

highlighting their potential as non-invasive biomarkers. Through RNA sequencing, the research team uncovered circRNA isoforms from the ASXL1 gene locus.

The team's analysis made inroads into understanding the role of circASXL1-1 in leukemia. Their data show that depletion of circASXL1-1 led to decreased H2AK119 ubiquitination (H2AK119ub) and this was through BRCA-1 associated protein 1 (BAP1) activity, a deubiquitinating enzyme and an important epigenetic regulator in leukemia. Furthermore, Asst Prof Jha and Dr. Shweta Pradip Jadhav, a Research Fellow in his team, found that circASXL1-1 binds to BAP1 to regulate its catalytic activity.

"This work has provided insights into a new mechanism for the regulation of H2AK119ub levels in hematopoietic progenitors—via interaction of circASXL1-1 and BAP1," explained Asst Prof Jha.

Tapping on the newly established understanding, the research team aims to identify genes involved in myeloid differentiation program of haematopoietic stem cells (HSCs). These genes can in turn be targeted to restore the normal course of differentiation in leukemia or to help induce apoptosis of immature and abnormally differentiated cells. The epigenetic signature identified could thus pave the way for future therapeutic developments of "epi-drugs."

Moving forward, the research team intends to generate data supporting the use of circASXL1-1 in antisense therapy for malignant and non-malignant blood disorders using the newly acquired knowledge. More importantly, findings from this study will lay the foundation for the development of new RNA-based therapeutics for leukemia.

More information: Shweta Pradip Jadhav et al. circASXL1-1 regulates BAP1 deubiquitinase activity in leukemia, *Haematologica*

(2019). DOI: 10.3324/haematol.2019.225961