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Protein network signals found to drive myeloid leukemias

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Researchers have uncovered how mutations in a protein network drive several high-risk leukemias, offering new prospects for novel therapies. An existing drug might be repurposed to treat these leukemias, and the new understanding of the molecular mechanisms at work may offer clues to other drugs yet to be developed.

A team led by Wei Tong, PhD, a hematology researcher at hildren's Hospital of Philadelphia (CHOP), reveals how mutated proteins cause several types of leukemia, particularly chronic myelomonocytic leukemia (CMML) and juvenile myelomonocytic leukemia (JMML), both of which tend to have a poor prognosis as they progress to acute myeloid leukemia (AML). "These leukemias currently have few treatment options, so identifying the causative gene networks may lead to more effective targeted treatments," said Tong.

The study team investigated a well-known kinase, or signaling protein, called JAK2, which plays a key role in the development of blood-forming cells in bone marrow. If something disrupts the normal regulation of JAK2 activity, JAK2 triggers the uncontrolled growth of marrow cells that give rise to a myeloid leukemia. Until now, the molecular events that regulate JAK2 were poorly established.

Based on studies in animals and in primary human leukemia cells, Tong and colleagues now report that mutations in either of two proteins, CBL and LNK/SH2B3, form a complex with JAK2 to disrupt JAK2 regulation and cause leukemia.

"This research has major implications for leukemia patients," said Tong. "A drug called ruxolitinib inhibits JAK2 and is already approved by the Food and Drug Administration. Our studies in cells from leukemia patients strongly suggest that patients with mutations in any of the three proteins could benefit from ruxolitinib." She added that clinical research should test whether this drug can benefit patients with CMML and JMML, as well as AML patients who have CBL mutations.

In addition to the potential benefits of ruxolitinib, Tong said, the team's findings may lead researchers to develop novel leukemia drugs aimed at mutations in any of the three proteins in a precision medicine approach. "As we continue to discover that specific mutations may cause subtypes of cancer, learning the underlying molecular mechanisms provides opportunities to develop targeted treatments."

The research appeared online June 13 in *Genes and Development*.

More information: Kaosheng Lv et al, CBL family E3 ubiquitin ligases control JAK2 ubiquitination and stability in hematopoietic stem cells and myeloid malignancies, *Genes & Development* (2017). DOI: 10.1101/gad.297135.117

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