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# Researchers identify a novel player in acute myeloid leukemia

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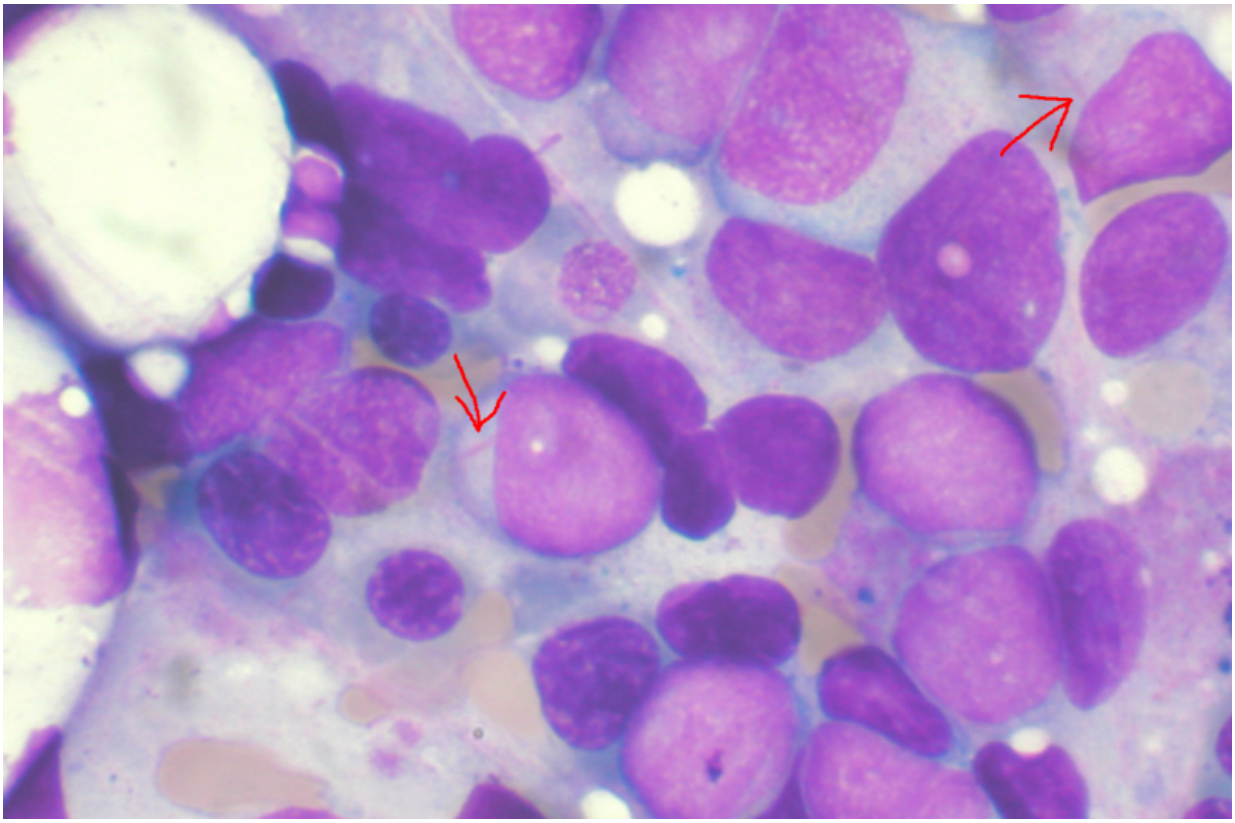

Bone marrow aspirate showing acute myeloid leukemia. Several blasts have Auer rods. Credit: Wikipedia

A new study led by scientists at Sanford Burnham Prebys has shown that the protein RNF5 plays an unusual role in acute myeloid leukemia

(AML). Unlike its expected role, marking aberrant proteins for destruction, RNF5 binds with a second cell protein called RBBP4 to control expression of genes implicated in AML. These findings, published in *Nature Communications*, have important implications for improving AML patient outcomes.

"AML cells are highly dependent on the RNF5 protein," says Ze'ev Ronai Ph.D., director of the NCI-designated Cancer Center at Sanford Burnham Prebys and senior author of the paper. "If we inhibit it, AML cells don't survive. We can also use RNF5 levels to stratify patients for specific treatments. For example, if AML patients have low levels of RNF5 or RBBP4, they respond better to HDAC inhibitors, which are targeted treatments already used in the clinic."

The Ronai lab has been studying RNF5 for about ten years, mostly in breast and skin cancers, and became curious about its role in AML because AML patients with high RNF5 levels often have poor outcomes. In this study, the Ronai lab worked closely with clinicians at Scripps MD Anderson in La Jolla, the Rambam Health Care Campus in Israel and other leading scientists to generate the findings.

Normally, as a ubiquitin ligase, RNF5 helps mark other proteins for destruction. But this research found that RNF5 picks up a different skill in AML cells, partnering with the epigenetic regulator RBBP4. Rather than degrading it, RNF5 modifies RBBP4 such that it impacts its recruitment to control expression of genes associated with AML growth.

"It was quite surprising for us to find this ubiquitin ligase is actually regulating gene transcription in AML," says Ali Khateb, Ph.D., a postdoctoral researcher in the Ronai lab and first author on the paper. "Ubiquitination improves recruitment of this epigenetic regulator to target genes. When you don't have RNF5 in the cells, there is less recruitment of RBBP4 to the target genes, leading to their increased

expression—and this inhibits AML growth."

The team continued to accumulate evidence that RNF5 and RBBP4 work together to drive AML. By analyzing patients' samples from the U.S. and Israel, they confirmed that patients with high RNF5 levels have poor prognosis. They also showed that animals injected with cells that are inhibited for RNF5 have a delay in leukemia development and longer survival. Further work showed that inhibiting RBBP4 produced the same results.

These findings could have several therapeutic ramifications. Inhibiting RNF5 could make existing targeted therapies more effective. "We found that when RNF5 or RBBP4 are inhibited, AML cells become super sensitive to HDAC inhibitors," says Khateb.

"Patients with lower levels of either RNF5 or RBBP4 will probably respond better to HDAC inhibitors," says Ronai. "We may be able to identify which AML patients will respond to these treatments based on their RNF5 or RBBP4 expression."

**More information:** RNF5 Regulation of RBBP4 Determines Acute Myeloid Leukemia Growth and Susceptibility to Histone Deacetylase Inhibitors, *Nature Communications* (2021). DOI: 10.1038/s41467-021-25664-7

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