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Novel role of RNA editing by ADAR2 in core binding factor acute myelogenous leukemia

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A team of researchers from the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS), co-led by Professor Daniel G. Tenen and Associate Professor Polly Chen

Leilei, made an unprecedented discovery of a hitherto unappreciated mechanism leading to ADAR2 (adenosine deaminases acting on RNA) dysregulation in core binding factor acute myelogenous leukemias (CBF-AML), and highlighted the functional relevance of the role of ADAR2 role in leukemogenesis. The research was published in the journal *Blood* on Feb. 16, 2023.

Adenosine to inosine (A-to-I) RNA editing, catalyzed by the ADAR family of enzymes ADAR1 and ADAR2, has been shown to contribute to multiple cancers. However, little is known about their roles in hematological malignancies. Here, the team comprehensively profiled the ADAR expression (ADAR1–3) in different subtypes of AML and found that ADAR2, but not ADAR1 and ADAR3, was differentially expressed in CBF-AML patients. CBF-AML is characterized by the presence of either t(8;21) or inv(16) translocations, which affect the RUNX transcription factor heterodimer.

The team also discovered a previously undescribed regulatory mechanism leading to ADAR2 downregulation in AMLs, in which the formation of the AML1-ETO fusion gene and its truncated form AE9a halts the transcription of the ADAR2 gene. To further support their hypothesis that the loss of ADAR2 and RNA editing may specifically contribute to the development of CBF-AML, they re-expressed ADAR2 in CBF-AML and non-CBF-AML and found that leukemogenesis was suppressed in the CBF-AML cells. In addition, the team also discovered for the first time that the RNA editing capability of ADAR2 was essential for suppressing leukemogenesis in an AE9a-driven AML mouse model.

"Understanding the role of ADAR2 and ADAR2-mediated RNA editing in cancer has long been neglected, with researchers in this field being more focused on the role of ADAR1 and RNA editing in cancers, including hematological malignancies. Our motivation is to

systematically investigate the potential role of ADAR-mediated RNA editing in AML," said Assoc. Prof. Chen, the co-lead author of this paper and an internationally-known expert in the role of RNA editing in cancer.

This work propels the team to delve deeper into the causes and functional consequences of ADAR2 dysregulation in multiple diseases, including cancer, as well as the underlying mechanisms (editing-dependent or independent) leading to pathogenesis. CBF-AML accounts for up to 20% of AML cases.

While it has a relatively good prognosis, approximately half of AML patients will eventually relapse with subsequent poor survival rates. Therefore, the ability to modulate the level of ADAR2 and editing frequency of its RNA substrates may hold great potential for developing RNA therapeutics against CBF-AMLs, leading to improved treatment outcomes.

More information: Mingrui Guo et al, Core binding factor fusion downregulation of ADAR2 RNA editing contributes to AML leukemogenesis, *Blood* (2023). DOI: 10.1182/blood.2022015830

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