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POSTER ABSTRACTS

602.MYELOID ONCOGENESIS: BASIC

Novel Fusion Gene Aven-NUTM1 Induces Mice Myeloid Leukemia Vulnerable to HDAC Inhibitors

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Chromosomal rearrangements involving the NUTM1 gene produce fusion genes commonly found in NUT carcinoma. While recurring NUTM1 fusions have been reported in other neoplasms, including AML, their roles in leukemogenesis remain unclear.

We identified the AVEN-NUTM1 (AN) fusion gene in an AML patient resistant to standard chemotherapy, and went to assess AN's leukemogenicity via bone marrow transduction and transplantation. Mice transplanted with AN-transduced hematopoietic stem/progenitor cells (HSPCs) developed transplantable myeloid leukemia with a median survival of 342 days. RNA sequencing revealed downregulation of genes related to hematopoietic cell lineage commitment and upregulation of genes related to early hematopoietic progenitors and MYC-targeted genes in AN-transformed leukemic cells.

Co-immunoprecipitation confirmed that AVEN-NUTM1 can interact with and activate EP300 as previously reported. To determine whether AN's interaction with EP300 is related to its ability to induce malignant transformation, we mutated the interaction site and constructed mutants of other structural domains. Colony-forming and replating assays showed that HSPCs expressing AN with mutations in the EP300 binding site lost their ability to self-renew and form colonies.

A CUT&RUN assay followed by sequencing showed that the most enriched motif in overlapping peaks between AN and EP300 were ETS motifs, suggesting the involvement of an ETS transcription factor family member in AN-activated EP300-induced leukemia.

We further found that both the patient's primary cells and bone marrow cells from leukemic mice were especially vulnerable to HDAC inhibitors.

These results demonstrate that the AVEN-NUTM1 fusion gene can drive the development of myeloid leukemia in mice, AN's ability to bind and activate P300 is closely linked to its leukemogenicity, and that HDAC inhibitors are effective in targeting AN leukemia cells. The study provids valuable insights for the targeted treatment of NUTM1-related leukemia patients.

Disclosures No relevant conflicts of interest to declare.

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