
**The hematopoietic transcription factors RUNX1 and ERG prevent AML1-ETO oncogene overexpression and onset of the apoptosis program in t(8;21) AMLs**

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**Abstract**

The AML1-ETO (RUNX1-RUNX1T1) oncofusion protein present in 10% of all *de novo* acute myeloid leukemia (AML) cases, is a transcription factor that dis-regulates the pathways of myeloid differentiation. Here, we aimed to investigate the effects of AML1-ETO on gene expression and the epigenome in patient blast cells and cell line. Genome wide ChIP-seq analysis revealed two modes of AML1-ETO binding, one in which AML1-ETO binds promoter regions of active genes with high level of histone acetylation and one represented by distal element binding marked with low acetylation and low gene expression output. Using ChIP-seq and mass spectrometry interaction studies we identify ERG, FLI1, TAL1 and RUNX1 at all AML1-ETO occupied genomic regions, while LYL1 and LMO2 preferential bind in the context of distal regions. Reduced hi stone acetylation levels at distal regions seem HDAC dependent, as treatment with an HDACi increases acetylation and induces cell death. Both AML1-ETO modules are represented in most aberrantly regulated pathways, including many signaling pathways, self-renewal and apoptosis. We find that expression of the wild type transcription factors RUNX1 and ERG is required for a leukemic phenotype, as alterations in expression are associated with oncogenic overdose of AML1-ETO and the onset of an apoptosis program. Expression of AML1-ETO to the level of t(8;21) cells in myeloid differentiated iPS cells induces leukemic characteristics whereas overexpression increases cell death, validating this oncogene overdose concept. Together our results demonstrate that a balanced interplay of AML1-ETO, transcription factors and the epigenetic environment maintain the leukemic phenotype in t(8;21) AML cells.