

COOPERATION OF AML1-ETO AND ONCOGENIC KIT IN ACUTE MYELOGENOUS LEUKEMIA

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A significant portion of AML patients have the cytogenetic abnormality t(8;21) which generates the fusion protein AML1-ETO, leading to a disruption of the core binding factor complex that regulates transcription of hematological genes. Patients harboring the translocation alone usually have a good prognosis; however, a substantial portion of patients bearing an additional oncogenic receptor tyrosine kinase, KIT, mutation have significantly worse prognosis. A mutation of aspartic acid to valine (KITD814V) in the activation loop results in altered substrate recognition and utilization, constitutive tyrosine autophosphorylation, and promiscuous signaling. Little is known concerning possible mechanisms of cooperation between AML1-ETO and KITD814V. Using an IL-3 dependent murine myeloid cell line, we show that growth of AML1-ETO bearing cells remain ligand dependent, while cells that express both AML1-ETO and KITD814V demonstrate ligand independent proliferation. Furthermore, functional assays show that expression of AML1-ETO and KITD814V leads to an increase in cell cycling and decrease in apoptosis that may contribute to the observed ligand independent proliferation. Using a syngenic murine transplantation model we demonstrate that mice transplanted with AML1-ETO and KITD814V bearing cells succumb to a fatal myeloproliferative disease (MPD)-like phenotype, while AML1-ETO expressing mice remain disease free. This suggests that AML1-ETO alone is not sufficient to induce ligand independent growth, nor MPD, but may cooperate with KITD814V to enhance proliferation. Continuing research aims to investigate mechanisms of cooperation between KITD814V and AML1-ETO that contribute to ligand independent growth *in vitro*, transformation *in vivo*, and poor overall prognosis in AML patients bearing the two mutations.