

Molecular Pathogenesis of AML (Mouse Models of Acute Myeloid Leukemia with AML1-ETO Fusion Proteins)

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Abstract

Acute myeloid leukemia (AML) is a common hematopoietic malignancy characterized by the abnormal proliferation and differentiation of myeloid progenitor cells. The fusion gene *AML1-ETO* is a product of t(8;21)(q22;q22) chromosomal translocation, one of the most common chromosomal translocations associated with acute myeloid leukemia. Therefore, analyzing the molecular mechanism of AML1-ETO in the process of AML development will provide valuable information to normal hematopoiesis and leukemogenesis. In order to investigate the role of AML1-ETO in leukemogenesis and to mimic the progression of t(8;21) leukemia, we have generated three AML1-ETO expressing mouse models using approaches of fusion gene knock-in, tetracycline inducible expression, and tissue specific MRP8 promoter directed expression. The analyses of these mice indicate that (1) AML1-ETO dominantly blocks AML1 function during early hematopoiesis, (2) AML1-ETO has a very restricted capacity to transform hematopoietic cells although certain abnormal maturation and proliferation of progenitor cells from these animals can be detected, (3) Additional mutations are required for the development of acute myeloid leukemia in AML1-ETO expressing mice, which is demonstrated by administration of mutagenesis reagent N-nitroso-N-ethylurea (ENU) to MRP8-AML1-ETO mice. The MRP8-AML1-ETO transgenic mice provide an excellent model that can be used to isolate additional genetic events and to further understand the molecular pathogenesis of AML1-ETO related leukemia.
