C-096

THE AML1/ETO TARGET GENE WBSCR5 (NTAL/LAB) IS REGULATED DURING THE MYEOLID DIFFERENTIATION

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The AML1/ETO target gene WBSCR5 codes for a 28 KDa protein also named NTAL (non-T Cell activation linker) or LAB (linker activator for B Cell) that is phosphorylated and activated by two different signalling pathways, FCeRI aggregation and c-Kit activation. NTAL/LAB transgene is able to rescue thymocyte development in LAT (linker activator for T Cell) deficient mice, and mast cells of NTAL/LAB deficient mice are hyperresponsive to stimulation via FCeRI. Our group has demonstrated that WBSCR5 mRNA is strongly downregulated after induction of the AML1/ETO protein in the U937/AE 9/14/18 cell line and repressed both in t(8;21) positive cell lines and primary AML blasts (Fliegauf et al., Oncogene 2004, 23: 9070-9081). Little is known about the function of the WBSCR5 protein in normal and leukemic myeloid cells. We therefore performed myeloid differentation assays to investigate the function of this gene in myelopoiesis. By Northern blot analysis, WBSCR5 mRNA was expressed at highest levels in NB4 and U937 cells, less in HL60 cell line and not expressed in Kasumi-1 cell line (AML1/ETO positive cell line). We could also detect at the protein level that WBSCR5 protein, which was repressed after the induction of AML1/ETO in U937/ AE 9/14/18 cell line, was expressed at high levels (comparable to LCL-GK B cells) in NB4, somewhere less in U937 and HL60 myeloid cells and absent in Kasumi-1 cells. When HL60 cells were treated with 1.3% DMSO (inducing the granulocytic differentation pathway) or 10^{-7}M PMA (inducing a monocytic differentiation pathway), WBSCR5 mRNA was markedly upregulated after three days. In contrast, WBSCR5 mRNA was strongly downregulated during the ATRA induced differentation of NB4 and U937 cells. We conclude that WBSCR5 mRNA and protein are repressed by the AML1/ETO protein and its RNA expression is regulated during granulocytic and monocytic differentation. Further experimentation is directed at the mode of repression of WBSCR5 by AML1/ETO.