New leukemia study results from Switzerland, the United States and the Netherlands described

Investigators in Switzerland, the United States and the Netherlands have published new leukemia data.

Study 1: Data detailed in "Lentiviral PU.1 overexpression restores differentiation in myeloid leukemic blasts" have been presented. "PU.1, a transcription factor of the ETS family, plays a pivotal role in normal hematopoiesis, and particularly in myeloid differentiation. Altered PU.1 function is possibly implicated in leukemogenesis, as PU.1 gene mutations were identified in some patients with acute myeloid leukemia (AML) and as several oncogenic products (AML1-ETO, promyelocytic leukemia-retinoic acid receptor alpha, FMS-like receptor tyrosine kinase 3 internal tandem duplication) are associated with PU.1 downregulation," investigators in Geneva, Switzerland report.

"To demonstrate directly a role of PU.1 in the blocked differentiation of leukemic blasts, we transduced cells from myeloid cell lines and primary blasts from AML patients with a lentivector encoding PU.1. In NB4 cells we obtained increases in PU.1 mRNA and protein, comparable to increases obtained with all-trans retinoic acid-stimulation. Transduced showed increased myelomonocytic surface antigen expression, decreased proliferation rates and increased apoptosis. Similar results were obtained in primary AML blasts from 12 patients. These phenotypic changes are characteristic of restored blast differentiation," wrote S. Durual and colleagues, University Hospital.

The researchers concluded: "PU.1 should therefore constitute an interesting target for therapeutic intervention in AML."

Durual and colleagues published their study in Leukemia (Lentiviral PU.1 overexpression restores differentiation in myeloid leukemic blasts. Leukemia, 2007;21(5):1050-9).

For additional information, contact S. Durual, University Hospital Geneva, 1Division of Hematology, Geneva, Switzerland.

Study 2: Apoptosis of leukemic CEM cells was linked to calcium (Ca²⁺)-dependent upregulation of E4BP4 expression.

According to recent research from the United States, "Glucocorticoid (GC)-evoked apoptosis of T-lymphoid cells is preceded by increases in the intracellular Ca²⁺ concentration ([Ca²⁺](i)), which may contribute to apoptosis. This report demonstrates that GC-mediated upregulation of the bZIP transcriptional repressor gene, E4BP4, is dependent on [Ca²⁺](i) levels, and correlates with GC-evoked apoptosis of GC-sensitive CEM-C7-14 cells."

"Calcium chelators EGTA and BAPTA reduced [Ca²⁺](i) levels and protected CEM-C7-14 cells from Dex-evoked E4BP4 upregulation as well as apoptosis. In the GC-resistant sister clone, CEM-Ci-15, Dex treatment did not induce [Ca²⁺](i) levels, E4BP4 expression or apoptosis, however, the calcium ionophore A23187 restored Dex-evoked E4BP4 upregulation and apoptosis," explained S.J. Priceman and colleagues, California State University of Northridge.

The researchers concluded, "CEM-C7-14 cells were more sensitive to GC-independent increases in [Ca²⁺](i) levels by thapsigargin, and a corresponding increase in E4BP4 expression and cell death, compared to CEM-Ci-15 cells, suggesting a direct correlation between [Ca²⁺](i) levels, E4BP4 expression, and apoptosis."

Priceman and colleagues published their study in Biochemical and Biophysical Research Communications (Calcium-dependent upregulation of E4BP4 expression correlates with glucocorticoid-evoked apoptosis of human leukemic CEM cells. Biochem Biophys Res Commun, 2008;344(2):491-499).

For additional information, contact R.D. Medh, California State University of Northridge, Dept. Biology, Northridge, CA 91330, USA.

Study 3: Infants with acute myeloid leukemia (AML) have a high incidence of t(7;12)(q36;p13).

According to a study from Netherlands, "The t(7; 12)(q36;p13) is a recurrent translocation involving the ETV6/TEL gene (12p13) and a heterogeneous breakpoint at 7q36. A fusion transcript between HLXB9 and ETV6 in AML with t(7; 12) is occasionally found."

"To study the incidence of t(7; 12) in infant and childhood acute leukemia, we screened 320 cases <36 months using FISH. Additionally, 28 pediatric cases >36 months with cytogenetic breakpoints at 12p and 7q were investigated. We studied the presence of an HXLB9-ETV6 fusion transcript and quantified the expression of various genes located in the 7q36 breakpoint region," explained A.R.M. Vonbergh and colleagues, Erasmus Medical Center.

"In total, 6 AML patients carried the t(7; 12) of which 5 were infants and 1 child of 18 months. Only 1 out of 99 infant ALL patients harbored the t(7; 12). No t(7;12) was found in older children with AML or ALL. AML patients carrying a t(7; 12) had a poor outcome with a 3-year EFS of 0%. A fusion of HLXB9 to ETV6 was found in 4 AML cases with t(7;12)."

"The 7q36 genes NOM 1, LMBR1, RNF32, and SHH were equally expressed among t(7;12)-positive AML versus t(7;12)-negative AML, t(7;12)-negative ALL, or normal bone marrow. However, the HLXB9 expression was highly increased in t(7;12)-positive cases, including those with an HLXB9-ETV6 fusion," found the investigators.

The researchers concluded that "the t(7;12) is almost exclusively present in infant AML and covers 30% of infant AML, while it is extremely rare in infant ALL and older children. The t(7; 12) is associated with a poor outcome and an ectopic expression of HLXB9 is commonly involved in this genetic subtype of
leukemia.*

Vonbergh and colleagues published the results of their research in Genes Chromosomes & Cancer (High incidence of t(7;12)(q36;p13) in infant AML but not in infant ALL, with a dismal outcome and ectopic expression of HLXB9. Genes Chromosomes Cancer, 2006;45(8):731-739).

For additional information, contact A.R.M. Vonbergh, Erasmus Medical Center, Dept. of Clinic Genetics, Dr. Molewaterpl 50, NL-3015 GE Rotterdam, Netherlands.

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