

Leukemia

Data from Greece and the United States provide new insights into leukemia

2007 JUN 11 -- Researchers in Greece and the United States have published new leukemia data.

Study 1: Investigators publish new data in the report "Activation of Prn-p gene and stable transfection of Prn-p cDNA in leukemia MEL and neuroblastoma N2a cells increased production of PrP(C) but not prevented DNA fragmentation initiated by serum deprivation. Prion protein (PrP(C)) via its isoform PrP(SC) is involved in the pathogenesis of transmissible spongiform encephalopathies (TSEs). We observed that murine erythroleukemia (MEL) cells arrested in phase G(1) undergo transcriptional activation of Prn-p gene," investigators in Thessaloniki, Greece report.

"Here, we explored the potential role of activation of Prn-p gene and cytosolic accumulation of PrP(C) in growth arrest, differentiation, and apoptotic DNA fragmentation by stably transfecting MEL and N2a cells with Prn-p cDNA. Stably transfected MEL cells (clones # 6, 12, 20, 38, and 42) were assessed for growth and differentiation, while clones N2a13 and N2a8 of N2a cells for growth and apoptosis by flow cytometry using Annexin V and propidium iodide (PI). Our results indicate that (a) Induction of terminal differentiation of stably transfected MEL cells led to growth arrest, activation of Prn-p gene, concomitant expression of transfected Prn-p cDNA, suppression of bax gene, cytosolic accumulation of PrP(C), and DNA fragmentation. The latter was also induced in non-differentiated MEL cells growing under serum-free conditions; (b) similarly, serum deprivation promoted growth arrest, apoptosis/necrosis associated with DNA fragmentation in parental N2a and N2a13 cells that produced relative high level of PrP(C) and not PrP(SC). These data indicate that activation of Prn-p gene and expression of transfected Prn-p cDNA in cells of both hematopoietic and neuronal origin occurred concomitantly, and led to cytosolic accumulation of PrP(C) and DNA damage induced by serum deprivation. PrP(C) production failed to protect DNA fragmentation induced by serum deprivation," wrote D.D. Gougoumas and colleagues, University of Thessaloniki, Department of Pharmaceutical Sciences.

The researchers concluded: "The question how does PrP(C) contribute to growth arrest and DNA fragmentation is discussed."

Gougoumas and colleagues published their study in the *Journal of Cellular Physiology* (Activation of Prn-p gene and stable transfection of Prn-p cDNA in leukemia MEL and neuroblastoma N2a cells increased production of PrP(C) but not prevented DNA fragmentation initiated by serum deprivation. *Journal of Cellular Physiology*, 2007;211(2):551-9).

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Study 2: Apoptosis of leukemic CEM cells was linked to calcium (Ca^{2+})-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 Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$), which may contribute to apoptosis. This report demonstrates that GC-mediated upregulation of the bZIP transcriptional repressor gene, E4BP4, is dependent on $[\text{Ca}^{2+}]_i$ levels, and correlates with GC-evoked apoptosis of GC-sensitive CEM-C7-14 cells."

"Calcium chelators EGTA and BAPTA reduced $[\text{Ca}^{2+}]_i$ 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 $[\text{Ca}^{2+}]_i$ 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.

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The researchers concluded, "CEM-C7-14 cells were more sensitive to GC-independent increases in $[Ca^{2+}]_i$ levels by thapsigargin, and a corresponding increase in E4BP4 expression and cell death, compared to CEM-C1-15 cells, suggesting a direct correlation between $[Ca^{2+}]_i$ 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*, 2006;344(2):491-499).

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Study 3: FHIT gene replacement therapy using a chimeric adenovirus shows promise for leukemia.

"Expression of the FHIT protein is lost or reduced in most solid tumors and a significant fraction of hematopoietic malignancies. Adenovirus 5 (Ad5) virus or adeno-associated viral vectors have been used to study the tumor suppressor function of FHIT in solid tumors, but these tools have not been effective in leukemias. We have generated a chimeric FHIT-containing adenovirus composed of Ad5 and the group B adenovirus called F35 with which we have been able to efficiently infect hematopoietic cells," scientists in the United States report.

"Infection efficiency of Ad5/F35-FHIT and Ad5/F35-GFP viruses was tested in leukemia cell lines that lacked FHIT expression, and biological effects of successful infection were assessed," said Flavia Pichiorri and colleagues at Ohio State University. "An acute myelogenous leukemia, a chronic myelogenous leukemia, and four acute lymphoblastic leukemia human cell lines were examined as well as two EBV-transformed B lymphoblastoid cell lines that expressed endogenous FHIT."

The researchers reported, "Two of four acute lymphoblastic leukemia cell lines, Jurkat and MV4;11, which were efficiently infected with Ad5/F35-FHIT, underwent growth suppression and massive induction of apoptosis without apparent activation of caspase-8 or caspase-2 and late activation of caspase-3. Treatment of infected cells with caspase-9 and caspase-3 inhibitors partially blocked FHIT-induced apoptosis. The two remaining infected acute lymphoblastic leukemia cell lines, Molt-3 and RS4;11, were apparently unaffected."

"Restoration of FHIT expression in the chronic myelogenous leukemia K562 cell line and the acute myelogenous leukemia KG1a cell line also induced apoptosis but at later time points than seen in the acute lymphoblastic leukemia Jurkat and MV4;11 cell lines," stated the investigators. "IV injection of Ad5/F35-FHIT-infected Jurkat cells resulted in abrogation of tumorigenicity in the NOD/SCID xenogeneic engraftment model. FHIT restoration in some FHIT-deficient leukemia cells induces both antiproliferative and pro-apoptotic effects involving the intrinsic caspase apoptotic pathway."

Pichiorri and coauthors published their study in *Clinical Cancer Research* (Preclinical assessment of FHIT gene replacement therapy in human leukemia using a chimeric adenovirus, Ad5/F35. *Clin Cancer Res*, 2006;12(11 Part 1):3494-3501).

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