MedicalXpress

Researchers identify key genetic trigger of acute myeloid leukemia

November 28 2007

A gene called N-Myc leads a double life in certain white blood cells when it is overexpressed, helping to trigger a cancer called acute myeloid leukemia (AML) under some conditions while triggering apoptosis, or cell suicide, under other conditions, according to results of a mouse study done by investigators at St. Jude Children's Research Hospital.

“This discovery gives researchers an important insight into N-Myc’s role in human AML and might contribute to new strategies for treating this leukemia or disrupting this gene’s ability to cause it,” said Gerard Grosveld, Ph.D., chair of the St. Jude Department of Genetics and Tumor Cell Biology. Grosveld is senior author of a report on this work that appears in the Nov. 15 issue of *Cancer Research.*

AML is a cancer of immune cells called myeloid cells, which accumulate in bone marrow and replace normal cells, then spread to other parts of the body. This cancer is diagnosed in about 20 percent of children with leukemia. About half of children with AML achieve long-term survival following chemotherapy.

Artificially forcing overexpression of N-Myc in bone marrow cells of mice strongly promotes this type of leukemia; that finding is significant since N-Myc overexpression frequently occurs in human AML.

Previously, researchers had reported that overexpression of N-Myc as a result of amplification of the N-Myc gene occurs in a variety of cancers such as neuroblastoma, a common solid tumor of childhood that arises

from nervous system cells; retinoblastoma, a cancer of the eye; and Wilms tumor, a cancer of the kidney. Amplification means that extra copies of the gene are present. Results of research elsewhere suggested but did not prove that N-Myc also plays a role in AML.

In the present study, Grosveld's team examined the RNA in cancerous white blood cells from 137 St. Jude patients who had favorable, intermediate or unfavorable prognosis and compared those RNA samples to ones obtained from four healthy bone marrow donors. RNA is the decoded form of a gene that cells use as a blueprint to produce the protein coded for by that gene.

The researchers reported that, depending on the type of AML, the level of N-Myc RNA in AML bone marrow was between two- and 33-fold higher than in normal bone marrow cells.

The team also showed that myeloid cells that were genetically engineered to overexpress N-Myc became immortalized, or had an unlimited life span. Thus, unlike normal myeloid cells with a limited life span, these immortalized cells continued to produce daughter cells in a culture dish and grew much faster than did normal cells. In addition, the St. Jude researchers showed that immortalization of these cells was associated with a decrease in the level of a protein called transforming growth factor beta and an increase in the level of a protein called JNK.

"Decreased levels of transforming growth factor beta and increased levels of JNK are known to be associated with the transformation of myeloid cells into leukemic cells in humans," Grosveld said. "So those findings in our lab suggest once again that N-Myc is linked to AML."

The St. Jude team then investigated the other side of N-Myc's double life—its ability to trigger apoptosis and kill the cell instead of making it reproduce uncontrollably. The researchers showed that when myeloid

cells overexpressing N-Myc were placed in culture dishes that lacked an anti-apotosis, growth-promoting protein called IL-3, about 75 percent of the cells died within 24 hours. IL-3 is a type of protein called a cytokine, which stimulates blood progenitor cells in the bone marrow to grow, develop and reproduce. In addition, the cells overexpressing N-Myc significantly reduced the activity of several other proteins that normally work together to prevent apoptosis—a known effect of the protein made by the N-Myc gene as well as those made by other Myc genes.

“By eliminating IL-3 from the culture, we were able to unmask the apoptotic effect of N-Myc, which greatly increased cell death,” Grosveld said.

Mice that received bone marrow cells genetically engineered to overexpress N-Myc developed AML and died within 50 days. When leukemic cells were transplanted from those mice into genetically identical mice, the newly transplanted mice died within 28 days.

Grosveld’s team believes that the AML does not result from N-Myc overexpression alone. Instead, the investigators showed that AML requires an additional change in the affected cells because they all overexpressed another gene, called Twist. Twist normally inhibits apoptosis by disrupting an important tumor-suppressing biochemical pathway. When N-Myc is overexpressed, this pathway is activated and triggers cell death, preventing the onset of AML. But when upregulation of Twist suppresses this pro-apoptosis mechanism, the cell continues to multiply. Upregulation is the increased activity of a gene caused by a specific signal.

“This work not only demonstrates the critical role N-Myc plays in AML, but also maps out the cooperation with other genes that blunt N-Myc’s apoptotic effects, thereby tipping the delicate balance between cell death and cancer,” Grosveld said. Other authors of this report include Hiroyuki

Kawagoe, Ayten Kandilci and Tanya Kranenburg (St. Jude).

Source: St. Jude Children's Research Hospital