# New culprit discovered in T-cell acute lymphoblastic leukemia

January 12 2012

A new study published in the journal *Nature Medicine* by NYU Cancer Institute researchers, shows how the cancer causing gene Notch, in combination with a mutated Polycomb Repressive Complex 2 (PRC2) protein complex, work together to cause T- cell acute lymphoblastic leukemia (T-ALL).

T-ALL is an aggressive blood cancer, predominately diagnosed in children. It occurs when one lymphoblast, an immature white blood cell, turns malignant, multiplying uncontrollably and spreading rapidly throughout the body. If left untreated, the disease can be fatal in a few weeks. Cancer-causing Notch mutations in T-ALL are well established, yet the detailed molecular mechanism mediating this Notch-induced cancer cell transformation was unknown until now.

"Our study presents new insight into how Notch acts in an antagonistic mode with PRC2 to promote T-ALL," said senior author, Iannis Aifantis, PhD, associate professor in the Department of Pathology and a member of the NYU Cancer Institute, an NCI-designated cancer center at NYU Langone Medical Center. "Moreover, our study shows frequent genetic inactivation on the genetic loci encoding for PRC2 components, inhibits its normal role as a gene expression regulator and further proves the tumor suppressor role of the complex in this disease."

The study shows a new dynamic interplay between Notch and PRC2 function. In the study, researchers analyzed Notch-driven epigenetic gene expression regulation changes in T-ALL. Findings show a clear loss

of PRC2 function from the sites of Notch1 binding. In addition, researchers found recurrent gene mutations and deletions of the components of PRC2 in T-ALL patient samples. In the study, loss of PRC2 function fueled the Notch mutation. This provides evidence for a central role of deregulation of PRC2 in Notch-induced T-ALL.

"The inactivation of PRC2 complex due to Notch in T-ALL constitutes an important pathogenetic event in the formation of this potentially deadly disease," said lead author of the study Panagiotis Ntziachristos, PhD, of the Department of Pathology at NYU Langone. "The PRC2 genetic alteration amplifies the Notch oncogene's communication signals leading to T-ALL. Our study experiments uncover a specific epigenetic switch during the progression of the disease that can be further exploited for the development of targeted epigenetic therapies."

The study shows T-ALL as an epigenetic disease, regulated by a subtle equilibrium between oncogenes and tumor suppressors. Oncogenes like Notch can infiltrate the normal function of PRC2 in specific gene loci leading to cancerous cell transformation. Mutations in PRC2 assist oncogenes like Notch by altering their DNA gene expression.

"Our studies offer new therapy avenues for the treatment of T-ALL," said Dr. Aifantis. "The detection of new genetic alterations in T-ALL provides a new platform for selecting potential treatment strategies for the disease. Drugs that can target histone demethylases, enzymes that catalyze the H3K27me3 modification, could be used alone or in combination with Notch1 inhibitors for the treatment of the disease."

Provided by NYU Langone Medical Center / New York University School of Medicine

Citation: New culprit discovered in T-cell acute lymphoblastic leukemia (2012, January 12)