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The Emerging Genetics of T-cell Acute Lymphoblastic Leukemia: a Fish Tale

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Subsets of childhood T-cell leukemias arise from oncogenes activated by antigen receptor gene translocations. Otherwise, little is known about the molecular pathogenesis of these leukemias of thymocytes. Here we show that three different T-cell oncogenes (LYL1, HOX11 and TAL1) are often expressed in the absence of chromosomal abnormalities, and that HOX11 activation is significantly associated with a favorable prognosis. Using oligonucleotide microarrays, we identified three distinct gene expression signatures that were indicative of leukemic arrest at specific stages of normal thymocyte development: LYL1+ (pre-T), HOX11+ (early cortical thymocyte) and TAL1+ (late cortical thymocyte). Hierarchical clustering analysis of the microarray findings allowed us to devise a prognostically relevant classification system that accommodated all T-cell cases in this series and integrated oncogene activation and specific chromosomal deletions into emerging multistep molecular pathways of thymocyte leukemogenesis. These results demonstrate a previously undetected molecular heterogeneity among childhood T-cell leukemias, and suggest the ability of gene expression profiling to stratify patients into clinically relevant subgroups.

We have used the zebrafish animal model system to help clarify developmental pathways subverted in human T cell leukemia, which act downstream of the dysregulated expression of master transcriptional regulatory proteins in developing thymocytes. We have generated a model of clonally derived T-cell acute lymphoblastic leukemia in transgenic zebrafish expressing mouse *c-myc* under control of the zebrafish *Rag2* promoter. Visualization of leukemia cells expressing a chimeric transgene encoding Myc fused to green fluorescent protein (GFP) revealed that leukemias arose in

the thymus, spread locally into gill arches and retro-orbital soft tissue, and then disseminated into skeletal muscle and abdominal organs. Leukemia cells homed back to the thymus in irradiated fish transplanted with GFP-labeled lymphoblasts. The T-cell leukemias that arise in *Rag2-myc* transgenic fish aberrantly overexpress both *Tal1* and *Lmo2*, indicating that these leukemias faithfully recapitulate the pattern of oncogene expression found in 60% of human T-cell leukemias. This transgenic model provides a platform for small molecule and genetic screens aimed at identifying chemicals or mutations that suppress or enhance *c-myc*-induced carcinogenesis. Forward genetic screens in the zebrafish hold promise for the discovery of genetic modifiers, such as tumor suppressor genes, whose mutational inactivation will enhance the rate of tumorigenesis, and genes that encode novel candidate drug targets, whose inactivation should delay or prevent the onset of malignancy.

References:

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