Hot Papers in Pediatric Hematology/Oncology

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Investigators from St. Jude Children’s Research Hospital performed a genome-wide association study on 321 children, ages 0.1-23.8 years, treated for acute lymphoblastic leukemia to identify germline variants correlating with the occurrence and severity of vincristine-induced neurotoxicity. Genome-wide single-nucleotide polymorphism (SNP) analyses were completed on blood DNA samples of 222 patients enrolled in St Jude’s protocol Total XIIIB from 1994-1998, and 99 patients enrolled in the Children’s Oncology Group (COG) protocol AALL0433 from 2007-2010. Vincristine-induced peripheral neuropathy was assessed clinically according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) through January 2001 for the St. Jude cohort and May 2011 for the COG cohort.

Moderate to life-threatening vincristine-induced neuropathy developed in 28.8% and 22.2% of patients in the St. Jude and COG cohorts, respectively. A SNP, rs924697, in the promoter region of CEP72 gene on chromosome 5, encoding a centrosomal protein for microtubule formation had a significant association with vincristine neuropathy. Among the 50 children (16% of patients) with the homozygous high risk CEP72 genotype, 56% had at least 1 episode of moderate to life-threatening neuropathy, compared to 21.4% with the heterozygous or low risk alleles. Patients homozygous for the high risk allele also had 2.4 fold greater neuropathy severities compared to these other genotypes. Human leukemia cells and induced pluripotent stem cell neurons in vitro, revealed that reducing CEP72 expression increased cellular vincristine sensitivity. The authors conclude that future clinic trials with a larger study population may be helpful to establish dosing guidelines in vincristine sensitive patients with an inherited polymorphism in the promoter region of CEP72.


Investigators from multiple institutions led by University of California San Francisco researchers, studied the effects of postnatal mutations in immunomodulatory genes and their immunoglobulin-diversifying enzymes, AID and RAG1-RAG2, in a mouse model to determine the mechanisms of how childhood vaccines reduce the incidence of leukemia. The enzymes, AID and RAG introduce DNA mutations that allow early B and mature B lymphocytes to adapt to infection, and produce an efficient immune response. Through a series of laboratory and translational experiments, they discovered that susceptibility to these mutations during B lymphopoiesis was exacerbated by strong inflammatory stimuli driving leukemic clonal evolution especially for subtypes of childhood leukemia due to in utero ETV6-RUNX1 fusion.
Using data from 207 children with pre-B ALL enrolled in Children’s Oncology Group protocol P9906, they identified that 34 of 40 recurrent genes which were mutated, deleted or rearranged in leukemia cells were targets of comparable mouse AID. The remaining 6 abnormal genes were targets of RAG1-RAG2 activity alone. Marrow and blood samples from an additional 215 patients with pre-B ALL enrolled in Eastern Cooperative Oncology Group trial E2993 revealed that higher-than-median AICDA and RAG1 mRNA expressions at diagnosis were associated with relapse and poor overall survival compared to lower-than-median expression.

In healthy human stem cells in vitro, they discovered that AID and RAG proteins were active in pre-B cells. In healthy mouse B cell precursors, specifically, small pre-BII cells were found to have increased genetic vulnerability to these enzymes and blocking interleukin-7 receptor (IL-7R) expression, further increased this premature AID protein expression. In small pre-BII cells from marrow samples, AICDA mRNA expressions were higher in patients with mutations that result in absence of IL-7R signaling than in healthy control cells. They also demonstrated that IL-7R signaling protected the early B cell genome from premature expression of AID through STAT5- and Akt-dependent pathways. Finally, in pre-B cell clones of 72 children with ALL, there was evidence of ongoing, coordinated AID and RAG1-RAG2 activity in all subgroups with notably more activity in those with the ETV6-RUNX1 lesion. This was further supported by demonstrating that wild type (AICDA+/− RAG1+/+) mice with ETV6-RUNX1 transduced pre-B cells subjected to IL-7 withdrawal and lipopolysaccharide inflammation developed leukemia more rapidly compared to AICDA deficient or RAG deficient mice.