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Deconstructing Blood Cell Research
Building the Hematology Community

Exploring Experimental Hematology: Journal Crossover Series I

- February 18, 2021

In a bid to connect the research being published in *Experimental Hematology* with the wider hematological community, we have begun to identify related pairs of recently published articles from other journals and in this entry, we focus on an article published in the European Hematology Association's journal *HemaSphere.*

Novel approaches to understanding ALL treatment and subclone diversity

Acute lymphoblastic leukemia (ALL) results from malignant transformation of lymphoid progenitor cells, and is a blood cancer found predominantly in the pediatric population. Clinical prognosis for children diagnosed with ALL are amongst the best outcomes for all blood cancers, with about 90% of all patients

surviving their disease. However, the remaining children who are refractory to therapy or suffer relapse still represent a significant clinical problem due to the high incidence of this disease in the pediatric population. As such, there remains tremendous importance in identifying the molecular mechanisms of treatment response and new targets for therapy in these children. Two recent complementary papers published in *Experimental Hematology* and *Hemasphere* tackle these issues in novel ways.

In *Experimental Hematology* ("Detection of chemotherapy-resistant patient-derived acute lymphoblastic leukemia clones in murine xenografts using cellular barcodes", November 2020), Jacobs et al. used lentiviral barcoding to track the origins of ALL treatment resistance. The research team transduced patient-derived B-ALL cells and a B-ALL cell line and transplanted the transduced cells into immunodeficient mice. The authors then sampled cells at the time of transplantation and 4-weeks after exposure to different chemotherapeutic agents that form the backbone of ALL chemotherapy regimens (methotrexate, dexamethasone, vincristine). The cell populations were then subjected to next-generation sequencing to quantify how treatment influenced barcode diversity. The major findings were that chemotherapy reduces the clonal complexity of ALL tumor samples, initiating a selection bottleneck which facilitated the outgrowth of sublcones with genetic or epigenetic mechanisms of adaptation. Earlier detection of these therapy-resistant subclones may inform future adaptation of treatment and possible prevention of relapse.

Whereas the Jacobs et al. study identified the mechanisms of how ALL cells become resistant to treatment, a major question still remains about alternative therapies that could be applied to eradicate subclones from patients that are resistant to up-front chemotherapy. In a recent issue of *Hemasphere* ("ARHGEF4 Regulates an Essential Oncogenic Program in t(12;21)-Associated Acute Lymphoblastic Leukemia", September 2020), Virely et al. identify molecular mechanisms that sustain ALL and are clinically actionable. The authors studied ALL driven by the t(12;21) chromosomal translocation which results in expression of the ETV6-RUNX1 fusion oncoprotein. This genetic event is associated with approximately 25% of ALL cases. The study team has previously shown that ETV6-RUNX1+ ALL is specifically associated with over-expression of the guanine nucleotide exchange factor ARHGEF4. In the present study, the authors now demonstrate that over-expression of ARHGEF4 is dependent on the ETV6-RUNX1+ oncoprotein, and over-expression of ARHGEF4 increases activity of the Rho-subfamily GTPase CDC42. Perhaps most importantly, pharmacological inhibition of CDC42 induced cell death in ETV6-RUNX1+ leukemia cells and this was associated with suppression of STAT3-regulated survival programs.

Cumulatively, the complimentary studies of ALL highlight mechanisms of treatment resistance and relapse, and identify new therapeutic opportunities for these patients.

Exp Hematol. 2020 Nov;91:46-54. doi: 10.1016/j.exphem.2020.09.188. Epub 2020 Sep 15.
Detection of chemotherapy-resistant patient-derived acute lymphoblastic leukemia clones in murine xenografts using cellular barcodes
Sabrina Jacobs 1, Albertina Ausema 1, Erik Zwart 1, Ellen Weersing 1, Gerald de Haan 1, Leonid V Bystrykh 1, Mirjam E Belderbos 2

Detection of chemotherapy-resistant patient-derived acute lymphoblastic leukemia clones in murine xenografts using cellular barcodes - PubMed (nih.gov)

Hemasphere. 2020 Sep 11;4(5):e467. doi: 10.1097/HS9.0000000000000467. eCollection 2020 Oct.
ARHGEF4 Regulates an Essential Oncogenic Program in t(12;21)-Associated Acute Lymphoblastic Leukemia
Clemence Virely 1, Luca Gasparoli 1, Maurizio Mangolini 1, Katherine Clesham 1, Sarah Inglott 2, Darren Edwards 3, Stuart Adams 2, Jack Bartram 3, Sujith Samarasinghe 3, Philip Ancliff 3, Ajay Vora 3, Jasper de Boer 1, Owen Williams 1

ARHGEF4 Regulates an Essential Oncogenic Program in t(12;21)-Associated Acute Lymphoblastic Leukemia - PubMed (nih.gov)

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- *November 14, 2024*

Each month, Simply Blood spotlights a lab contributing to the fields of hematology, immunology, stem cell research, cell and gene therapies, and more. Get to know groups doing cutting edge research from around the world! This month, we are featuring the Vanuytsel Lab which is based out of the Center for …

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