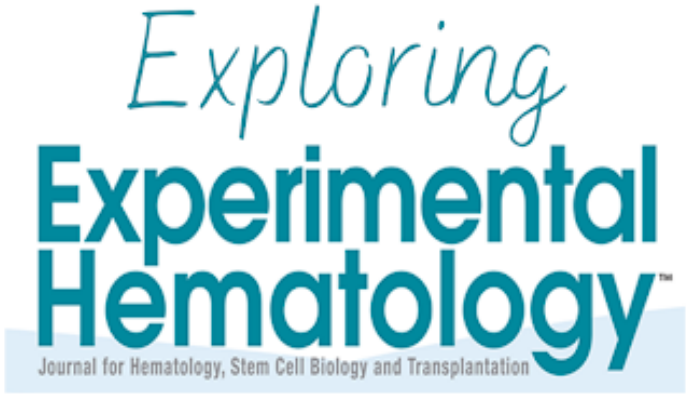
simply blood
Deconstructing Blood Cell Research
Building the Hematology Community

Exploring Experimental Hematology: Journal Crossover Series II

- April 08, 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.*

Molecular insight into Diamond-Blackfan anemia (DBA), and a detection strategy for clinical diagnosis of DBA and other inherited bone marrow failure syndromes

Inherited bone marrow failure syndromes (IBMFs) are a group of complex genetic diseases that display comparable major complications such as (pan)cytopenia, bone marrow failure, and increased risks for myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Although a majority of patients receive proper diagnoses, many patients lack specific syndromic diagnoses in part due to incomplete identification of the underlying etiology of IBMFs. Therefore, further studies into the genetic, molecular, and clinical aspects of IBMFs are needed. Two recent complementary papers published in *Experimental Hematology* and *Hemasphere* contribute to these efforts.

Diamond-Blackfan anemia (DBA), one of several IBMFs, is characterized by red blood cell aplasia, which leads to a reduction in erythroid progenitors and impaired erythroid cells, and cancer susceptibility. DBA is

autosomal dominant and is frequently caused by mutations in several ribosomal genes, including RPL11, leading to impaired ribosomal biosynthesis. Activation of the "ribosomal stress" response, which triggers the p53 pathway, has been proposed as a mechanism contributing to DBA. However, it is not clear whether the p53 pathway directly leads to anemia. Other genetic mutations independent of the ribosomal genes were found in GATA1 and TSR2 genes and results in erythroid failure observed in DBA. Thus, the mechanism in the pathogenesis of DBA remains to be fully studied in erythroid cells.

In *Experimental Hematology* ("Single-cell analysis of erythropoiesis in Rpl11 haploinsufficient mice Diamond reveals insight into the pathogenesis of Blackfan anemia", February 2021), Doty et al. characterized the erythroblast populations and identified the gene expression changes in the early erythroid precursor populations of Rpl11 haploinsufficient mice. A previous study showed that the inducible Rpl11-null allele mouse model recapitulates the human DBA disorder insofar as anemia, inefficient/impaired erythroid maturation, and predisposition to cancer. The authors induced the deletion of Rpl11 in mice by treatments of tamoxifen and subsequently, analyzed the development of anemia in the peripheral blood for 16 weeks post deletion. Next, the authors identified the erythroblast populations in the bone marrow (femurs and tibias) or total splenocytes by flow cytometry. Flow sorted BFU-E, CFU-E, pro-, and basophilic erythroblasts populations were used for single-cell RNA sequencing. Additionally, the authors complemented their studies using the Flvcr1-deleted mouse model, which has a disrupted heme export function, that displays DBA phenotype including, macrocytic anemia, and a block in erythroid development. Heme content and reactive oxygen species (ROS) were determined in erythroid precursor cells by spectrofluorometry and flow cytometry, respectively. The major findings were that early erythroid precursors have excess heme and high ROS that contribute to cellular toxicity and the impairment of erythroid differentiation. Single-cell analysis revealed upregulation of the Cdkn1a pathway, p53 stabilization pathway, p53-dependent and p53-independent G1/S DNA damage pathways, while downregulation of GATA1 target genes and genes in the mitotic spindle pathway were observed predominantly at the earliest stages of erythroid differentiation.

On the clinical side, determining the proper DBA or other IBMFs diagnoses for patients remains challenging because patients present a wide range of syndromes and at the same time, display overlapping phenotypes among IBMFs. Genetic screening is a critical tool in determining the right diagnosis for optimal clinical treatment. Although conventional genetic analysis is available to screen for frequently mutated genes, this approach is not always feasible for IBMFs where large numbers of genes are involved and whose clinical manifestation reflects several syndromes. Next-generation sequencing (NGS) is revolutionizing the platform for genetic diagnosis of IBMFs. However, sufficient numbers and appropriate selection of gene sets in NSG panel design are needed to maximize the potential of this technique.

In a recent issue of *Hemasphere* ("Next-generation Sequencing in Bone Marrow Failure Syndromes and Isolated Cytopenias: Experience of the Spanish Network on Bone Marrow Failure Syndromes", January

2021), Gálvez et al. developed two NGS panels to screen for IBMFs in a cohort of patients with suspected IBMFSs without a molecular diagnosis. The authors designed two NSG panels to comprehensively cover 145 IBMFs associated genes with the first panel screening for 129 IBMF related genes that have been described as of 2016, and the second NGS panel included 16 additional genes. NSG sequencing was conducted using DNA samples extracted from the peripheral blood obtained from undiagnosed patients (n=214) in Spain. Patients were divided into two groups based on the suspected type of IBMFs: classified and unclassified. Bioinformatic tools were applied for quality control, detection of copy number variation, and referencing to several databases. With this approach, the authors detected 104 candidate variants in 35 genes and identified differences in the diagnostic rates between classified (48%) and unclassified (24%) IBMFs groups. Additionally, the percentage of molecular diagnosis between NSG panels was similar. Importantly, the study identified the diagnosis in 91 patients – an overall molecular diagnosis rate of 44%; and amended the clinical classification of six patients to reflect their genetic diagnosis.

Cumulatively, these reports address the molecular and clinical aspects in understanding DBA and other IBMFs. The work by Doty et al. that revealed the altered pathways in early erythroid populations in a DBA mouse model suggests that therapeutic intervention should be focused on targeting the early erythroid precursors. Although additional functional analyses are needed, their work also discusses candidate pathways that may be crucial for DBA pathogenesis. Correspondingly, the study by Gálvez et al. that described the genetic screening panels and the utility of an NSG-sequencing platform as a tool for proper IBMFs diagnosis, emphasizes the genetic heterogeneity underlying IBMFs and the need for additional studies in the molecular bases of IBMFs, which will aid in proper detection and clinical management.

Charmaine Soco
PhD Candidate
Department of Hematology & HCT
Irell & Manella Graduate School of Biological Sciences
Beckman Research Institute, City of Hope

Exp Hematol. 2021 Feb 22:S0301-472X(21)00092-8. doi: 10.1016/j.exphem.2021.02.010.
Single-cell analysis of erythropoiesis in Rpl11 haploinsufficient mice reveals insight into the pathogenesis

of Diamond-Blackfan anemia.
Doty RT, Yan X, Meng C, Lausted C, Tian Q, Abkowitz JL.
Single-cell analysis of erythropoiesis in Rpl11 haploinsufficient mice reveals insight into the pathogenesis of Diamond-Blackfan anemia – PubMed (nih.gov)

Hemasphere. 2021 Mar 9;5(4):e539. doi: 10.1097/HS9.0000000000000539.
Next-generation Sequencing in Bone Marrow Failure Syndromes and Isolated Cytopenias: Experience of the Spanish Network on Bone Marrow Failure Syndromes.
Gálvez E, Vallespín E, Arias-Salgado EG, Sánchez-Valdepeñas C, Giménez Y, Navarro S, Río P, Bogliolo M, Pujol R, Peiró M, Nevado J, Zubicaray J, Sebastián E, Catalá A, Beléndez C, Díaz de Heredia C, Galera A, Badell I, Madero L, Perona R, Sastre L, Surrallés J, Bueren J, Lapunzina P, Sevilla J.
Next-generation Sequencing in Bone Marrow Failure Syndromes and Isolated Cytopenias: Experience of the Spanish Network on Bone Marrow Failure Syndromes – PubMed (nih.gov)

Experimental Hematology ISEH Research

Popular posts from this blog

ISEH 2025 Society Award Winners

- *March 11, 2025*

On behalf of the Awards Committee, ISEH would like to congratulate the recipients of the 2025 ISEH Society Awards which will be presented at the ISEH 54th Annual Scientific Meeting . Donald Metcalf Award Winner - Constanze Bonifer The recipient of the 2025 Donald Metcalf Award is Dr. Constanze ⋯

READ MORE

Message from the President: 2021 Society Updates

- *March 25, 2021*

Dear Friends and Colleagues, I write this message reflecting upon what was an unprecedented time for hematology and hematology researchers. Looking back on last year, I am truly amazed by how our Society reacted to our member's experiences with lab shutdowns, socioeconomic upheaval in reaction ⋯

READ MORE

Lab Spotlight: Vanuytsel Lab

- *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 ⋯

READ MORE