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Reporting From the First EHA Research Conference: Exciting Science With Panoramic Views

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At the end of October, the beautiful surroundings of Palermo in Italy set the stage for the inauguration of the first European Hematology Association (EHA) Research Conference. This meeting is meant to complement the larger and more translational/clinically oriented EHA Annual Congress by providing a small and intimate framework to share and discuss specific research topics. For this first edition, the focus was on the extrinsic signals and perturbations of normal and malignant hematopoietic stem cells (HSCs).

An aspect that was discussed extensively during the meeting was the role of inflammation at the interface of normal hematopoiesis, aging, and disease. Interesting new insights in this came from the Laurenti group. They performed single cell RNA-seq analysis to compare gene expression of human hematopoietic stem and progenitor cells (HSPCs) isolated from steady-state peripheral blood, mobilized peripheral blood, spleen, and bone marrow.[1] Among other findings, this comparison revealed that peripheral blood HSPCs of healthy individuals possess a unique lineage bias toward the erythroid-megakaryocytic differentiation. This erythroid-megakaryocytic skewing was suppressed in a variety of disease conditions such as essential thrombocythemia, β-thalassemia,[1] chronic lymphocytic leukemia (CLL),[2] and COVID-19. In these disorders, circulating peripheral blood HSPCs shifted their differentiation bias from the erythroid-megakaryocytic lineage toward the myeloid lineage. Interestingly, increased interferon(IFN) responses were observed in peripheral blood HSPCs in these conditions, hence suggesting that inflammation shapes differentiation trajectories in human hematopoiesis.

Over a lifetime, HSCs are exposed to multiple and distinct inflammatory events, but how these impact HSC function on the long-term remained unknown. This aspect has now been explored in the mouse by Michael Milsom. His group exposed mice to distinct types of cumulative inflammatory insults and showed that they irreversibly impaired the self-renewal ability of long-term HSCs.[3] HSCs subjected to multiple rounds of stress, moreover, acquired a number of clinically relevant features of aging, demonstrating that the chronic inflammatory exposure in early life drives premature aging. A reduced clonal complexity was also observed in chronic stress situations. Along this line, Katherine King investigated the causality between inflammation and the emergence of clonal hematopoiesis, an age-related acquisition of mutations in HSCs that confers a selective growth advantage. By performing chimeric transplantation assays, her group demonstrated that interferon gamma (IFNγ) signaling, induced during chronic infections, acts as a selective pressure which promotes the expansion of HSCs with loss of DNA methyltransferase 3 alpha (*Dnmt3a*), one of the most commonly mutated genes in clonal hematopoiesis.[4] On the molecular level, the expansion of *Dnmt3a*-deficient clones originated from the stress-induced apoptosis of wild-type HSC and the massive methylation changes induced in their genome by inflammatory signaling, ultimately leading to their differentiation and loss of self-renewal. By contrast, the *Dnmt3a*-deficient clones were resistant to these changes and retain self-renewal capacity, demonstrating how a pro-inflammatory environment drives clonal hematopoiesis. These findings nicely complemented the work from Cristina Lo Celso in the context of acute myeloid leukemia. Her group showed that INFγ secreted by leukemia-specific cytotoxic T-cells induced differentiation of progenitor-like AML cells into a noncycling progeny. These differentiated cells were unable to propagate the disease but instead allowed its progression in the presence of antitumor T cells as they express high levels of Programmed Cell Death Protein 1 (PDL1). These data support a model whereby inflammation shapes AML hierarchies to face tumor immune-surveillance (reference to https://www.biorxiv.org/content/10.1101/2020.12.21.414649v1) and thus suggest that targeting inflammation may boost immune-based therapies.

As it seems that inflammation, aging, and clonal hematopoiesis are interconnected, what do we know about the mechanisms linking these conditions? The work presented during the meeting by Jennifer Trowbridge provided novel mechanistic insight into this aspect. Her group showed that

the aging hallmarks, which start to accumulate in HSCs by middle age, are due to a decline in the bone marrow-derived insulin growth factor 1 (IGF1). These data demonstrated that the bone marrow microenvironment plays an indispensable role in initiating the aging of functional HSCs.[5] Interestingly, moreover, the Trowbridge group also showed that an aged microenvironment sustains the selective growth advantage of HSCs bearing the clonal hematopoiesis-associated mutation *DNMT3A R882*/+.[6] These data, which provide a causal relationship linking aging and clonal hematopoiesis, open the way to novel strategies to rejuvenate aged long-term HSCs and possibly slow/prevent clonal expansion and its evolution to malignancy. Remarkably, IGF1 stimulation of middle-aged long-term HSCs rescued both the molecular and functional aging hallmarks.

These findings exemplified another topic extensively discussed during the conference, namely evolving into therapeutic perspectives what we have learnt about the signals perturbing hematopoiesis. To this regard, Rebekka Schneider presented important results in the context of primary myelofibrosis, a myeloproliferative neoplasm (MPN) driven by the acquisition of mutation in HSCs, such as point mutations in the gene encoding Janus kinase 2 (*JAK2V617F*). This disease is characterized by bone marrow fibrosis, a process whereby bone marrow hematopoietic cells are gradually substituted by scar tissue. Combining *JAK2V617F* transgenic mice to extensive RNAseq analysis of both murine and patients samples, Rebekka Schneider's group showed that *JAK2V617F* mutant HSCs induce a functional reprogramming of mesenchymal stromal cells (MSCs) during distinct stages of disease development.[7] In the initial prefibrotic stage, MSCs lose their progenitor features and differentiate into matrix secreting myofibroblasts and osteolineage cells. During the fibrotic stage, MSCs acquire a profibrotic and inflammatory phenotype. This reprogramming involves the upregulation of S100A8/S100A9, a heterodimeric complex of the Ca2+ binding protein alarmins, which are actively released during inflammation. This event, marking the onset and progression of fibrosis, could be pharmacologically targeted by tasquinimod, a small-molecule inhibiting S100A8/S100A9 signaling. In preclinically settings, this drug ameliorated MPN development and fibrosis, hence setting the stage for the subsequent evaluation of this drug in a novel clinical trial.

In the context of *JAK2V617F* mutant MPN, exciting results also came from Hugues de The'. His group showed that *JAK2V617F* mutant stem cells could be selectively targeted by enhancing the formation of promyelocytic leukemia (PML) nuclear bodies (PML-NBs). These spherical protein structures, which regulate senescence and p53-associated apoptosis, have a tumor suppressor function in distinct cancers. De The' lab demonstrated the combination of arsenic trioxide, which binds to PML to enforce PML-NBs formation, and interferon alpha (INFα), which increases PML expression, augments the formation of PML-NBs to a greater extent than the single agents alone.[8] In turn, this led to eradication of the MPN stem cell population, which became unable to transplant the disease into secondary recipient mice. These data, which pave the way to a clinical translation, demonstrate the importance of targeting PML not only in the context of PML-retinoic acid receptor alphafusion proteins (such as in acute PML) but also in the context of a wild-type PML. Building upon this, Hugues de The' also demonstrated that NPM1c, the oncogenic form of nucleophosmin (*NPM1)* frequently found in AML, binds to PML hence hampering PML-NBs biogenesis.[9] Since these structures regulates the mitochondrial fitness, this ultimately drives an impaired mitochondrial function in *NPM1c* AML cells. As de The' further elegantly showed, these primed mitochondria could be targeted by the antibiotic actinomycin D, which induced an acute mitochondrial stress and boosted reactive oxygen species (ROS) production in these mitochondria. By doing so, actinomycin D restored PML-NBs formation, ultimately driving p53 activation and senescence. In preclinical assays, actinomycin D potentiated the antileukemic effects of the BCL2 inhibitor venetoclax, hence opening the way to novel clinical trials associating these 2 drugs in *NPM1c* AML patients.

Brian Huntley shared insight in the results of a large CRISPR screen aiming to understand the role of chromatin factors in the hematopoietic system using ex vivo and in vivo models. These studies reveal specificity for a variety of chromatin factors in lineage determination and demonstrated opposing effects for chromatin factors in normal hematopoiesis compared with AML, where several of the key complexes (including MLL-H3K4-methyltransferases, c-BAF-remodelers, and Repressive complexes) were associated with a block in differentiation and a role to maintain leukemic fitness (reference to https://www.biorxiv.org/content/10.1101/2022.08.11.503571v1).

Touching upon only a few aspects, this summary provides a glimpse into the variety of hot topics we shared during the meeting while having an extraordinary panoramic sea view. We hope the participants enjoyed the conference as much as we did and we wait for you all again next year.

AUTHOR CONTRIBUTIONS

MT wrote the article.

DISCLOSURES

The author has no conflicts of interest to disclose.

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