China’s top 10 hematological advances in 2021 lists the key developments in hematology in China for that year

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Abstract
The China’s top 10 hematological advances in 2021 was announced at the 2nd Annual Meeting of Chinese Alliance for Societies of Hematology on January 16, 2022.

Keywords: 2021, China, Hematological advances

The China’s top 10 hematological advances in 2021 list key developments in hematology and beyond of last year. The China’s top 10 hematological advances in 2020 was released on January 30, 2021, at the first China Blood Development Conference, which now has been renamed as Annual Meeting of Chinese Alliance for Societies of Hematology (CASH). Aiming to be China’s largest professional meeting to promote research, clinical care, education, training, and advocacy in hematology, the 1st CASH meeting was well received, with the number of audience reached more than 300,000 around the world. The 2nd CASH was virtually held on January 14–16, 2022, with more than 400,000 attendees. After receiving submission of hematological discoveries by China researchers of 2021, the candidates were assessed and ranked by CASH science committee members using a numerical system. During the 2nd CASH the results were announced.

1. HEMATOPOIETIC STEM CELL HETEROGENEITY IS ASSOCIATED WITH THE PATHOGENESIS AND THERAPEUTIC RESPONSE OF MYELOPROLIFERATIVE NEOPLASMS (MPNs)

The JAK2V617F+ MPNs, harboring the same JAK2 mutation in hematopoietic stem cells (HSCs), display diverse phenotypes, including polycythemia vera, essential thrombocythemia (ET), and primary myelofibrosis. This scenario constitutes an instructive paradigm for analyzing the pathological consequences of stem cell heterogeneity. The research from Lihong Shi’s team provided the single-cell gene expression profiling with parallel mutation detection of HSCs, demonstrating that the megakaryocyte (MK)-primed HSC subpopulation expanded significantly with enhanced potential in untreated ET patients, which were driven primarily by JAK2 mutation and the elevated IFN (interferon) signaling.1 During therapy for ET, mutant HSCs were preferentially targeted in the Mk-primed HSC subpopulation. Mechanistically, the homozygous mutant HSCs were forced to re-enter quiescence, while their heterozygous counterparts underwent apoptosis. Thus, this study provides important insights by linking the pathogenic and therapeutic consequences of a malignant disease with stem cell heterogeneity.

2. EXTRAMEDULLARY DEVELOPMENT OF INNATE LYMPHOID CELLS (ILCs)

The origin of tissue-resident lymphocytes, including liver type 1 innate lymphoid cells (ILC1s), remained unclear. Recently, the study from Zhigang Tian’s team illustrated that an IFN-γ-dependent loop drives liver ILC1 development in situ from hematopoietic progenitor in adult liver, highlighting the contribution of extramedullary hematopoiesis to regional immune composition within the liver.2

3. RNA EDITOME REVEALS EDITED AZIN1 AS A NOVEL REGULATOR IN HEMATOPOIESIS

Posttranscriptional modifications of RNA are ubiquitous and serve as regulatory layers implicated in a variety of physiological and disease phenotypes. Adenosine-to-inosine (A-to-I) RNA editing and the catalyzing enzyme adenosine deaminase are both essential for hematopoietic development and differentiation. However, the RNA editome during hematopoiesis and the underlying mechanisms were poorly defined. The research from Tao Cheng’s team provided transcriptome-wide editing data for 12 murine cell types and delineated an essential role for Azin1 RNA editing in HSCs.3,4 This work constitutes a valuable resource for further study of RNA editing on a more general basis.
4. FUNCTIONAL AND SPATIAL DIVERGENCE IN MURINE MEGAKARYOPOIESIS

It is not known whether the diverse functions of MKs are executed by a single population or by distinct subsets of cells. The research from Qianfei Wang's and Jiaxi Zhou's team found that cellular heterogeneity of mouse bone marrow existed within three distinct subpopulations that possess gene signatures related to platelet generation, HSC niche interaction, and inflammatory responses, uncovering new molecular, spatial, and functional heterogeneity within MKs in vivo and demonstrating the existence of a specialized MK subsystem that may act as a new type of immune cell.1,6

5. CHASING THE EARLIEST HUMAN ILCs OR PROFILING THE SPATIOTEMPORAL DEVELOPMENT OF EARLY HUMAN ILC

ILCs are considered as innate equivalents of T cells. They play critical roles in tissue homeostasis, early defense against pathogens, and tissue repair. However, their developmental hierarchy in early human fetus remains largely elusive.

Bing Liu's team used single-cell RNA sequencing and functional validation to explore the ILC development in human fetal tissues.7 The development trajectory from hematopoietic stem and progenitor cells, through two stages of lymphoid progenitors, to ILC progenitor in fetal liver is revealed, followed by the specification and maturation stages to generate three subgroups of lymphoid progenitor cells in lymphoid and nonlymphoid tissues. Intriguingly, the novel lymphoid progenitors were characterized by expression of IL-3RA undergoing ILC lineage specification in fetal liver. The IL-3RA+ lymphoid progenitors in fetal liver showed T, B, ILC, and myeloid potentials, while IL-3RA- lymphoid progenitors were predominantly B-lineage committed. They also determined the heterogeneity and tissue distribution of each ILC subpopulation, revealing the proliferating characteristics shared by the precursors of each ILC subtype. Meanwhile, a novel unconventional ILC2 subpopulation (CRTH2+CCR9+ ILC2) was identified in fetal thymus which may be involved in thymus organogenesis and T-cell development. Collectively, their study illuminated the precise cellular and molecular features underlying the stepwise formation of human fetal ILC hierarchy with remarkable spatiotemporal heterogeneity.

6. DECODING THE DYNAMICS AND MECHANISM OF RNA m6A MODIFICATION IN MAINTAINING HEMATOPOIETIC HOMEOSTASIS

The research from Haojian Zhang's team delineated a comprehensive RNA m6A landscape across hematopoietic hierarchy through developing a super-low-input m6A-seq strategy for rare cells, and identified IGF2BP2 as a key factor for preserving HSC function by regulating mitochondrial activity.8 This study uncovered a conserved and complicated role of m6A in controlling hematopoietic trajectory.

7. DONOR-DERIVED CD7 CAR-T CELLS EFFECTIVELY TREATED t/r T-ALL WITH MANAGEABLE SAFETY PROFILE

Xiaoming Feng's team reported the first phase I trial of donor-derived CD7 chimeric antigen receptor (CAR) T-cell therapy in patients with t/r T-ALL. This therapy demonstrated a high rate (90%) of complete remission with a manageable safety profile.9

8. SUPER-ENHANCER LANDSCAPE REVEALS XBP1s ADDICTION AS AN ACHELLES' HEEL OF LEUKEMIA STEM CELLS (LSCs)

LSCs are often persistent in chronic myelogenous leukemia (CML) and are resistant to tyrosine kinase inhibitor treatment. This leads to relapse in patients, requiring alternative strategies to overcome this disease. The research from Jinxuan Pan’s team explored the epigenetic regulation in LSCs and found that the maintenance of CML LSCs was highly dependent on SE-associated oncogene XBP1.10 The identification of LSC reliance on super-enhancer transcription suggests a potential targeting strategy for CML.

9. NOVEL THERAPY FOR CARDIAC LIGHT-CHAIN AMYLOIDOSIS

Doxycycline has been recommended as an adjuvant to standard systemic therapy for light-chain amyloidosis in the latest National Comprehensive Cancer Network guideline. However, the advantage of doxycycline has not been validated in randomized trial. Jian Li's team designed and performed the first randomized trial to evaluate the value of doxycycline in light-chain amyloidosis.11 The results showed that doxycycline failed to prolong progression-free survival or overall survival in cardiac light-chain amyloidosis. Therefore, doxycycline should not be recommended for treatment of light-chain amyloidosis.

10. A SERIES OF STUDIES OF A NOVEL FULLY HUMAN B-CELL MATURATION ANTIGEN-SPECIFIC CAR-T CELLS (CT103A) IN PATIENTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

The impressive efficacy of CT103A, including time to response, overall response rate, and durability, was corroborated by robust expansion and prolonged persistence of CT103A. The expansion and clinical benefits of CT103A did not seem to be influenced by prior murine B-cell maturation antigen (BCMA) CAR-T. CT103A is safe and highly active in patients with relapsed/refractory multiple myeloma (RRMM) and can be developed as a promising therapy for RRMM. The research from Jianfeng Zhou's team also provided the recommendations of viral management in patients receiving BCMA-targeting CAR T-cell therapy.12-14

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