



HAL
open science

From normal hematopoiesis to malignancies: Highlights from the 2021 Meeting of the Club Hematopoiesis and Oncogenesis

Marie-Bérengère Troadec, Françoise Porteu, Marie-Laure Arcangeli, Adlen Foudi, Dominique Bluteau, Paulo de Sepulveda, Christel Guillouf, Nathalie Mazure, Fabienne Meggetto, Philippe Brunet de la Grange, et al.

► To cite this version:

Marie-Bérengère Troadec, Françoise Porteu, Marie-Laure Arcangeli, Adlen Foudi, Dominique Bluteau, et al.. From normal hematopoiesis to malignancies: Highlights from the 2021 Meeting of the Club Hematopoiesis and Oncogenesis. *Bulletin du Cancer*, 2023, 110 (3), pp.331-335. 10.1016/j.bulcan.2022.12.013 . hal-04266637

HAL Id: hal-04266637

<https://hal.science/hal-04266637v1>

Submitted on 6 Nov 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC0 - Public Domain Dedication 4.0 International License

From normal hematopoiesis to malignancies: Highlights from the 2021 Meeting of the Club Hematopoiesis and Oncogenesis



Summary

This article highlights the presentations from the 2021 scientific meeting of the Club Hematopoiesis and Oncogenesis. This annual meeting focuses on hematopoiesis and oncogenic mechanisms. Various topics were presented: expansion of hematopoietic stem cells with *in vivo* and *ex vivo* strategies, the role of the hematopoietic stem cell niches in aging and leukemic resistance, the crossroad between hematology and immunology, the importance of the metabolism in normal hematopoiesis and hematopoietic defects, solid tumors and oncogenesis, the noncoding genome, inflammation in monocyte differentiation and leukemia, and importantly, the recent advances in myeloid malignancies, lymphoid leukemia and lymphoma.

Keywords Hematopoiesis; Oncogenesis; Leukemia; Myelodysplasia; Metabolism; Inflammation; Immunity

Background

Normal hematopoiesis has to be understood when the time comes to dissect the mechanisms leading to the emergence and the maintenance of hematological malignancies. Knowledge brought from the solid cancer field is also meaningful, as many oncogenic pathways are common. This balanced crosstalk between normal and pathogenic mechanisms is one of the pillars of the annual meeting of the Club Hematopoiesis and Oncogenesis (CHO). Other pillars are opportunities given to young scientists to present their work and conviviality, and this is not an empty word after the cancellation of the previous meeting in 2020 due to Covid-19 pandemic.

The first annual meeting of the CHO took place in 1994, and the general topics of the congress remain unchanged: to gather international and French researchers to present their last results on normal hematopoiesis, oncogenesis related to hematology, and on oncology non-related to hematology. The goal behind this diversity is the scientific cross-fertilization between those fields, as well as an expected porosity between normal and pathological mechanisms.

The 2021 annual meeting of the CHO took place from September 29th to October 2nd, 2021 at presqu'île de Giens in France. During the congress, we heard impressive talks on the latest published

as well as unpublished data. The use of many innovative approaches, including single-cell techniques, omics, 3D-cell and tissue imaging, novel animal models, bioinformatics and modelization allows pushing the limits of our knowledge in the fields of hematopoiesis and oncogenesis. This meeting went through a wide range of topics: basic hematopoiesis and cancer, the role of metabolic pathways in hematopoiesis and malignancies, the role of the different hematopoietic niches, genetics, genome stability, the crossroad between hematology and immunology, inflammation and cell differentiation, myeloid and lymphoid malignancies, etc.

Expansion of hematopoietic stem cells: *in vivo* and *ex vivo* strategies

During embryogenesis, expansion of a small number of hematopoietic stem cells (HSCs) is crucial to sustain definitive hematopoiesis. Understanding these mechanisms has important application in regenerative medicine. The zebrafish model has allowed major advances in the understanding of hematopoiesis. This model organism enabled pioneer genetic studies more than 40 years ago, since the analysis of the hematologic tissue was an easy readout for experiments. Nowadays, tools have evolved but this model remains highly informative for exploring the mechanisms of normal hematopoiesis. Pr. Julien Bertrand from Geneva University in Switzerland gave the opening lecture on how to expand HSCs using zebrafish as a model of investigation. Pr. Bertrand exposed the various molecular and cellular mechanisms governing HSC expansion in the zebrafish embryo, and how they are conserved with mammals. His research led him to dissect the non-cell-autonomous genetic pathways controlling HSC expansion including the prostaglandin E₂ (PGE₂) pathway, and to decipher the cooperation between the vascular niche and myeloid cells to protect, maintain and expand HSCs in the caudal hematopoietic tissue. These studies have been published recently (Cacialli, Nat Comms 2021; Cacialli, EMBO J 2022). A different strategy to expand HSCs was explored by Mathilde Huart from Dr. Philippe de La Grange's and Dr. Zoran Ivanovic's laboratory at Etablissement Français du Sang in Bordeaux in France. Their goal was *ex vivo* HSC expansion before graft. She demonstrated that addition of a c-Jun N-Terminal kinase inhibitor (JNK-IN-8) and the antioxidant molecule alpha-lipoic acid (ALA) increase up to 5-fold the steady state peripheral blood primitive CD34⁺ cell pool during the expansion procedure while preserving the HSC engraftment capacity. In these conditions, the regulation of *ex vivo* HSC self-renewal is modulated by Wnt/ β -catenin pathway.

Hematopoietic stem cell niches: aging, leukemic resistance, and single cell approaches

Hematopoiesis occurs in a very constraint environment. More than an inert microenvironment, the bone marrow niches establish a balanced and reciprocal crosstalk between HSCs and precursor cells; alteration in this crosstalk can result in malignancies. Dr. Maria Carolina Florian, from Bellvitge Biomedical Research Institute in Barcelona in Spain, is interested in the aging of the HSC niche. She found that bone marrow perisinusoidal niches are uniquely preserved and protect HSCs from aging. Changes in the HSC niche are associated to specific alterations of HSC behavior and localization within the bone marrow. She demonstrated that aged "labeling retaining" HSCs (the most quiescent HSC subpopulation with the highest regenerative capacity, and cellular and epigenetic polarity) reside predominantly in perisinusoidal niches. Moreover, she showed that sinusoidal niches are uniquely preserved in shape, morphology and number upon aging.

Dr. Vera Pancaldi from Toulouse Cancer Research Center (CRCT, France) gave a presentation on the integration of data from single cell approaches to characterize the tumor microenvironment. She manipulates immunofluorescence multiplex imaging and multiomics data to define cell identity and phenotype in a spatial context. Dr. Sylvain Lefort from Cancer Research Center in Lyon (CRCL, France) focused on the leukemic properties of the niches. The goal of his group is to understand how leukemic bone marrow microenvironment can support leukemic progression and alters treatment response in myeloid malignancies. They used a standardized 3D human coculture model to track chronic myeloid leukemia (CML) through leukemic stem cell dormancy upon treatment. They also identified that resistant acute myeloid leukemia (AML) cells harbor different intrinsic rigidities and mechano-transduction pathway activation compared to sensitive cells.

At the crossroad between hematology and immunology

Dr. Sandrine Sarrazin, from CIML in Marseille in France, work on the fascinating frontier between hematology and immunity, and reconciled them. She showed that HSCs (Hematopoietic Stem Cells) directly sense cytokines released during infection and inflammation, and pathogen-associated molecular patterns. Her presentation on 'Immunomodulation and immune memory in HSC: new functions for new therapeutic applications?' allowed us to understand how HSCs can directly detect a gram-negative bacterium in a molecular manner, and how HSCs can exhibit immune memory. She concluded that HSCs are not only at the apex of hematopoietic development but also at the heart of the immune response.

Importance of metabolism in hematopoietic defects, solid tumors, and oncogenesis

Cellular metabolism, including oxidative stress, is a key regulator of HSC emergence and maintenance, and mature blood cell differentiation. Some metabolic requirements need to be met by these cells for their normal functions. The metabolic regulation during leukemia development is also subject to intense research. Studies from Dr. Els Verhoeyen from C3 M lab in Nice (France) and CIRI-EVIR lab in Lyon (France) introduced us into the world of immunometabolism. GAPDH is a central enzyme implicated in aerobic glycolysis which also harbors non-glycolytic functions. Based on a transgenic mouse model overexpressing GAPDH exclusively in the T cell lineage, Dr. Els Verhoeyen was able to investigate the role of GAPDH in T cells and T cell malignancies. Her mouse model recapitulated key molecular and pathological features of human angioimmunoblastic T cell lymphoma (AITL). Her group identified a non-canonical NF- κ B pathway activated by GAPDH and demonstrated that a newly developed NF- κ B inducing kinase inhibitor prolonged AITL-bearing mouse survival. Dr. Els Verhoeyen also presented very interesting non-viral vector tools to modify human CD34+ HSCs by gene editing with a high efficacy. She welcomes collaborative works using these tools. Research of Dr. Céline Philippe from Dr. Kevin Rouault-Pierre's laboratory at BARTS Cancer Institute, Queen Mary University of London (UK), also clearly illustrated the importance of the metabolic regulation in hematological malignancies. She demonstrated that vitamin B5 and succinyl-CoA improve ineffective erythropoiesis in *SF3B1* mutated myelodysplasia. The study was initiated by RNA-seq analysis of splicing events on hematopoietic colonies derived from myelodysplastic syndrome *SF3B1*-mutant patients and healthy age-matched donors in which they identified the mis-splicing of the coenzyme A synthase transcript. Dr. Margherita Ghisi from Dr. Jean-Emmanuel Sarry's laboratory at CRCT in Toulouse (France) also connected metabolic reprogramming and RNA splicing in leukemia. The chemoresistance in AML is associated with a high mitochondrial oxidative metabolism coupled with a specific "High OxPHOS" gene signature. She demonstrated that this metabolic adaptation is the consequence of the activation of a prosurvival mitochondrial stress response triggered by the treatments and characterized by the induction of the cAMP-PKA and ATF4 signaling pathways. The data indicate that some specific splicing factors such as PTBP1 may play a role in the metabolic changes. Dr. Géraldine Gentric from Dr. Fatima Mechta-Grigoriou's laboratory at Curie Institute in Paris explored metabolically heterogeneous OxPHOS subgroups in high-grade serous ovarian cancers. In high-OxPHOS tumors, chronic oxidative stress promotes aggregation of PML-nuclear bodies that activate PGC-1 α , electron transport chain

synthesis, and mitochondrial respiration. High-OXPHOS HGSOCs exhibit chemosensitivity, in which increased oxidative stress and PML play key functions.

The noncoding world

The vast majority of mammalian genomes do not encode proteins but are obviously not junk DNA. Dr. Claire Francastel from Université Paris-Diderot in Paris focused on the role of those noncoding genomic regions. She explored the functional links between transcription of DNA repeats, DNA methylation (responsible for silencing repetitive elements and for maintaining genome stability), and molecular and cellular programs. She worked on a rare human genetic disease with chromosomal instability, the Immunodeficiency, Centromeric instability, Facial abnormalities syndrome (ICF), where compromised centromere integrity is directly linked to constitutive alterations of DNA methylation of centromeric DNA repeats. With Dr. Eirini Trompouki from Max Planck Institute of Immunobiology and Epigenetics, in Freiburg (Germany) (now at IRCAN in Nice, France), we continued into the field of repetitive elements from the perspective of developmental and regenerative hematopoiesis. She explained how repetitive elements are transcribed during HSC development and chemotherapy-induced regeneration, how repetitive element RNAs act as signals for innate immune receptors of the RIG-I-like receptor family, and how RNA sensing of repetitive elements actively shapes cellular transitions. Understanding how exposure to ionizing radiations affects HSC function on the long term is a major public health concern. Dr. Emilie Elvira-Matlot in IGR in Villejuif (France) demonstrated that the NF- κ B pathway regulates heterochromatin at intronic young LINE-1 elements and HSC gene expression during irradiation stress. Her results show that ionizing radiations directly affects HSC heterochromatin. She also showed that regulating gene expression through a TNF- α /NF- κ B/H3K9me3/L1Md axis expands the NF- κ B repertoire to HSC genes.

Inflammation in monocyte differentiation and in leukemia

Dr. Elodie Segura from Curie Institute in Paris presented her work on the mechanisms of monocyte differentiation in steady-state and inflammation. Circulating monocytes can differentiate into monocyte-derived macrophages (mo-Mac) or dendritic cells (mo-DC). In this lecture, she questioned the mechanism of balance of mo-DC *versus* mo-Mac fate commitment and identified transcription factors that repress mo-Mac differentiation and enable monocyte to commit to the mo-DC pathway. She proposed potential therapeutic targets to re-direct monocyte differentiation in inflammatory disorders. Inflammation is also a great player in leukemia. Camille Sauter from Dr. Laurent Delva's

and Dr. Romain Aucagne's team at the UMR1231 Inserm/Université de Bourgogne in Dijon identified PRMT2, a protein arginine methyltransferase, as an anti-inflammatory epigenetic factor in acute myeloid leukemia (AML). They found that AML patients with a low PRMT2 expression display an accentuated inflammatory phenotype, leading to poor prognosis and lower survival.

Erythroid lineage, Fanconi anemia, GATA2 syndrome

Erythropoiesis is a complex differentiation process leading to the continuous production of red blood cells in the bone marrow. A large panel of transcription factors is implicated at all stages of erythroid differentiation. In erythroid cells, using Crispr KO cell lines, Dr. Eric Soler from IGMM in Montpellier (France) highlighted the role of some Epithelial-to-Mesenchymal Transition (EMT) transcription factors that are co-expressed in erythroid cells along with known essential erythroid transcription factors such as GATA1, TAL1, LMO2, ET02/CBFA2T3. He focused on a key EMT transcription factor that controls intracellular motility and adhesion programs and enucleation of terminally differentiating erythroid cells. Fanconi anemia is a constitutional genetic disorder characterized by the appearance of an early bone marrow aplasia, frequently followed by development of AML. In order to understand the mechanisms of appearance of a "pre-leukemic" state in Fanconi anemia, Maeva Loock from IGR (Villejuif, France) from Dr. Dominique Bluteau's laboratory identified several genes whose expression are altered in *Fancg*-/- hematopoietic cells and highlighted in particular the overexpression of ZMAT3. This gene encodes an RNA binding protein. Their data demonstrated a strong involvement of ZMAT3 in the regulation of the P53 pathway. Dr. Laetitia Largeaud from CRCT in Toulouse (France) from Dr. Cyril Broccardo and Pr. Eric Delabesse's laboratory explored a new approach to decipher GATA2 deficiency syndrome. She demonstrated that expression of *Gata2* R396Q mutation in mouse impacts qualitatively the Lin⁻Sca-1⁺ Kit⁺ compartment (immature cells) and mimics functional and molecular defects observed in the GATA2 deficiency patients.

Recent advances in myeloid malignancies

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid malignancies. A MDS subgroup share mutations in *SF3B1* gene, encoding a splicing factor. If most of *SF3B1* mutations are associated with ring sideroblast phenotype, the entire pathogenic consequences of the mutations in *SF3B1* are not fully understood. Pr. Michaela Fontenay from Université de Paris, Cochin Institute in Paris focused her effort on the splicing factor SF3B1 and DNA replication in erythropoiesis in MDS. She explored the molecular causes of DNA damage and subsequent DNA repair, and their differences between high-risk and low-risk MDS. Chronic myelomonocytic

leukemia (CMML) is a HSC clonal disorder affecting elderly people and associates features of MDS and myeloproliferative neoplasms. Donia Hidaoui from Dr. Françoise Porteu's laboratory at IGR in Villejuif demonstrated that targeting heterochromatin, using G9A/GLP (two enzymes regulating H3K9me2) inhibitors improves DNMTi (decitabine, DAC or 5-azacytidine) efficacy for CMML treatment. Also in CMML, Dr. Dorothée Selimoglu-Buet from the same team explored the role for mature cells of the leukemic clone using single-cell RNA-seq and spectral cytometry. Results from these analyses may generate new therapeutic strategies. Acute Megakaryoblastic Leukemia (AMKL) when associated with the fusion oncogene ETO2-GLIS2 is characterized by a low mutational burden, very young age at diagnosis and poor prognosis. , Dr. Veronica Alonso-Perez from Dr. Françoise Pflumio's laboratory, CEA IRCM in Fontenay-aux-Roses (France), in collaboration with Dr. Thomas Mercher (IGR, Villejuif) presented the first model of pediatric ETO2-GLIS2-driven AMKL in human CD34⁺ cells and demonstrated that fetal liver and bone marrow cells are the most sensitive cells to transformation. AML are severe hematological malignancies. Pr. Raphael Itzykson from Saint-Louis Research Institute in Paris (France) studied the clonal architecture in AML. He developed the concept of richness and evenness, two distinct dimensions of clonal diversity, which can be explored by genetic annotations of AML samples. Emerging single-cell technologies can be instrumental to decipher clonal architecture. SUMOylation, a protein post-translational modification related to ubiquitylation, plays a critical role in AML response to therapies. Dr. Ludovic Gabellier from Guillaume Bossis's laboratory from IGMM in Montpellier (France) demonstrated that the TAK981, a first in class inhibitor of SUMOylation used in clinical trials for lymphomas and solid tumors, synergizes with AML therapies and induces anti-tumor immune response. Dr. Mathilde Poplineau from Dr. Estelle Duprez's laboratory at CRCM in Marseille revealed a non-canonical EZH2 activity as a main driver of retinoic acid resistance in PLZF/RARA leukemia. The nucleophosmin is a multi-functional nucleolar protein, and its encoding gene *NPM1* is mutated in up to 35% of all AML cases. Dr. Edwige Voisset from Dr. Paulo De Sepulveda's laboratory at CRCM in Marseille highlighted the significant contribution of *NPM1* in genomic stability through the base excision repair (BER) pathway. She also demonstrated the role of PML nuclear bodies to DNA damage repair. Their results suggested a connection between *NPM1* and PML nuclear bodies in AML leukemogenesis. Long noncoding RNAs (lncRNAs) are transcripts larger than 200 nucleotides devoid of coding potential. They may be involved in the control of transcriptional, post-transcriptional

and epigenetic regulations. In AML patients carrying mutations in *NPM1*, Dr. Marina Bousquet from CRCT in Toulouse (France) identified and characterized long noncoding RNAs involved in AML suggesting that lncRNAs could be considered as potent prognostic biomarkers and key players in the pathogenesis of AML. eIF4E3 belongs to the eIF4E family of mRNA translation initiation factors. In AML, Dr. Stéphane Pyronnet from CRCT in Toulouse highlighted the role of eIF4E3-specific translational control in myeloid cell fate and in AML resistance to mTOR inhibitors.

Highlights on lymphoid malignancies and lymphoma

T-cell acute lymphoblastic leukemia (T-ALL) is a hematologic malignancy resulting from acquisition of genomic abnormalities in T-cell progenitors/precursors. Dr. Julien Calvo from Dr. Françoise Pflumio's laboratory at the CEA in Fontenay-aux-Roses (France) demonstrated that CD44 overexpression defines T-ALL quiescent cells and confers an advantage to E-selectin binding compared to proliferative cells. In normal hematopoiesis, cell quiescence and self-renewal activity are tightly regulated and are distinctive characteristics of normal HSCs, whereas more mature cells including B-cell progenitors lack these stem cell properties. Vincent Fregona, in Dr. Bastien Gerby's and Pr. Eric Delabesse's laboratory at CRCT in Toulouse, functionally and molecularly characterized preleukemic stem cells in B-cell acute lymphoblastic leukemia induced by the fusion PAX5-ELN. In particular, he demonstrated that PAX5-ELN fusion protein reprograms aberrant stem cell properties to a subset of B-cell progenitors and converts them into preleukemic stem cells. BTG1 is a recurrently mutated gene in lymphomas, especially in the MCD/C5 subgroup of diffuse large B cell lymphomas (DLBCL), which are associated with poor outcome and frequent extranodal dissemination. Dr. Pierre Sujobert from Université Claude Bernard in Lyon (France) showed that BTG1 inactivation is a targetable driver of lymphomagenesis involved in lymphoma dissemination through the control of the BCAR1-Rac1 pathway.

Conclusion

Overall, this meeting covered many aspects of normal hematopoiesis and its dysfunctions that lead to the emergence of hematological malignancies.

The CHO board members would like to thank the French Cancer Society (SFC) for its important moral and financial support. The CHO 2022 meeting was held on October 12th-15th 2022; the report is in preparation. The next CHO 2023 meeting will be held on October 2023. We invite you to visit our website regularly for updates: <https://www.cho-hemato.fr/> and log in to Twitter to see the latest comments: https://twitter.com/CHO_HEMATO.

Acknowledgements: The organizers are grateful to the following financial supports: Société Française d'Hématologie (SFH), Société Française du Cancer (SFC), Ligue Nationale contre le Cancer, Fondation ARC, SIRIC Socrate, Société Française de Génétique (SFG).

Disclosure of interest: the authors declare that they have no competing interest.

Marie-Bérengère Troadec^{1,2,11}, Françoise Porteu³, Marie-Laure Arcangeli⁴, Adlen Foudi⁵, Dominique Bluteau⁶, Paulo De Sepulveda⁷, Christel Guillouf⁸, Nathalie M. Mazure⁴, Fabienne Meggetto⁹, Philippe Brunet De La Grange¹⁰, Cyril Broccardo⁹

¹Univ Brest, INSERM, EFS, UMR 1078, GGB, 29200 Brest, France

²CHRU Brest, Service de génétique, laboratoire de génétique chromosomique, Brest, France

³Institut Gustave Roussy, INSERM UMR 1287, Villejuif, France

⁴Université Côte d'Azur (UCA), C3M, INSERM U1065, 151 Route de St Antoine de Ginestière, BP2 3194, 06204 Nice cedex 03, France

⁵INSERM UMRS 935, Institut André Lwoff, Villejuif, France
⁶Ecole Pratique des Hautes Etudes, Université PSL, INSERM UMR9019 CNRS/Paris Saclay/Institut Gustave Roussy/EPHE, Villejuif, France

⁷CRCM, INSERM U1068, Institut Paoli-Calmettes, CNRS, Aix-Marseille Université, Marseille, France

⁸INSERM U1170, Institut Gustave Roussy, 94800 Villejuif, France
⁹CRCT, INSERM UMR 1037, CNRS UMR 5071, Toulouse III University-Paul Sabatier, Toulouse, France

¹⁰Établissement Français du Sang Nouvelle Aquitaine, France

Correspondence: Marie-Bérengère Troadec, Service de génétique, laboratoire de génétique chromosomique, CHRU Brest, Brest, France

marie-berengere.troadec@univ-brest.fr

¹¹CHO: <https://www.cho-hemato.fr/>.

Available online: 10 February 2023

<https://doi.org/10.1016/j.bulcan.2022.12.013>