Göteborg, 2024

Multiomic profiling of leukemic stem cells in myeloid leukemia: implications for immunotherapy

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3

Torsdagen den 29 februari, klockan 9.00

av **Hana Komic**

Fakultetsopponent: Bjørn Tore Gjertsen
University of Bergen, Norway

Avhandlingen baseras på följande delarbeten

I. **Komic H[*],** Schmachtel T[*], Simoes C[*], Yu W[*], Nilsson MS, Gonzales C, Jolly A, Rolfson O, Prosper F, Bönig HB, Paiva B, Thorén FB, Rieger MA. Continuous measures of early molecular steps in human bone marrow stem cell differentiation trajectories. *In manuscript.* [*]Equal contribution

II. Nilsson MS[*], **Komic H[*]**, Gustafsson J, Sheybani Z, Paul S, Rolfson O, Hellstrand K, Wennström L, Martner A[#], Thorén FB[#]. Multiomic single-cell analysis identifies von Willebrand factor and TIM3-expressing *BCR-ABL1*$^{+}$ CML stem cells. *bioRxiv 2023.09.14.557507; doi: https://doi.org/10.1101/2023.09.14.557507.* [*, #] Equal contribution

III. **Komic H[*],** Nilsson MS[*], Wennström L, Hellstrand K, Thorén FB[#], Martner A[#]. Single cell proteo-transcriptomic profiling reveals altered characteristics of stem and progenitor cells in patients receiving cytoreductive hydroxyurea in early-phase chronic myeloid leukemia. *Submitted* [*, #] Equal contribution

IV. **Komic H[*],** Hallner A[*], Hussein BA, Badami C, Wöhr A, Hellstrand K, Bernson E, Thorén FB. HLA-B[*]44 and the Bw4-80T motif are associated with poor outcome of relapse-preventive immunotherapy in acute myeloid leukemia. *Cancer Immunol Immunother.* 2023; 72(11):3559-3566. [*]Equal contribution

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

GÖTEBORGS UNIVERSITET

Göteborg, 2024

Multiomic profiling of leukemic stem cells in myeloid leukemia: implications for immunotherapy

Hana Komic

Department of Medical Biochemistry and Cell Biology, Institute of Biomedicine, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Abstract

Despite the extensive array of therapies available for treating hematological malignancies, a major challenge in hemato-oncology lies in therapy resistance, which primarily is caused by residual resistant leukemic stem cells (LSC). In order to eliminate leukemic cells, it is crucial to understand the molecular mechanisms enabling their survival and to identify specific targetable markers for LSC to spare healthy cells. While tyrosine kinase inhibitors (TKI) provide a favorable prognosis for patients with chronic myeloid leukemia (CML), a fraction of patients suffers from disease progression or relapse upon treatment discontinuation. Acute myeloid leukemia (AML) on the other hand is a complex disease and despite development of novel therapies, survival prognosis remains poor. A common denominator for these diseases is the therapy-resistant LSC that propagate and cause a relapse. Hence, the main goal of this thesis was to identify novel targets on residual LSC by dissecting the heterogeneity among hematopoietic stem and progenitor cells (HSPC) in healthy and diseased conditions.

In **Paper I** we provide a comprehensive molecular map of early human HSPC differentiation. Detailed analyses of immature cell compartments identified novel HSC markers, including CD273/PD-L2. Functional validation showed that $CD273^{hi}$ cells have a quiescent profile and delayed *in vitro* differentiation, compared to $CD273^{low}$ cells. Furthermore, we revealed changes in the distribution of the most immature cells and lineage differentiation propensities upon ageing. **Paper II** focused on detailed multiomic profiling of the $CD34^{+}$ cells in bone marrow samples of CML patients. The most important finding of this study was the detection of two novel LSC markers, von Willebrand factor (*VWF*) and TIM3. **Paper III** aimed at understanding the effects of short-term hydroxyurea (HU) treatment on HSPC in CML patients. The results implicate HU-induced increased the frequency of erythroid progenitors and accumulation of cell subsets with S/G2/M phase-related gene profile. With **Paper IV**, we aimed to investigate the impact of HLA-B genotypes on outcome during histamine dihydrochloride (HDC) and interleukin 2 (IL-2) immunotherapy. The HLA-$B^{*}44$ allele, which is a weak ligand to the inhibitory NK cell receptor, KIR3DL1, was found to be associated with poor survival.

Our results suggest that a strong ligand-receptor interaction induces enhanced NK cell function, which may result in better leukemia control and prolonged survival. In summary, the results from this thesis could serve as basis for a development of targeted treatment for TKI-resistant LSC in CML and relapse-preventive approaches in AML.

Keywords: hematopoiesis, HSC, LSC, CML, AML, immunotherapy

ISBN 978-91-8069-591-6 (PRINT) http://hdl.handle.net/2077/79334
ISBN 978-91-8069-592-3 (PDF)