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Targeting residual malignant cells in myeloid leukemia

Akademisk avhandling

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

Måndagen den 5 juni 2023, klockan 9.00

av **Malin Nilsson**

Fakultetsopponent: Marcus Järås, Lunds universitet, Sverige

Avhandlingen baseras på följande delarbeten:

I. **Nilsson MS**, Hallner A, Brune M, Nilsson S, Thorén FB, Martner A, Hellstrand K. Complete remission after the first cycle of induction chemotherapy determines the clinical efficacy of relapse-preventive immunotherapy in acute myeloid leukaemia. *Br J Haematol. 2020;188(4):e49-e53.*

II. **Nilsson MS**, Hallner A, Brune M, Nilsson S, Thorén FB, Martner A, Hellstrand K. Immunotherapy with HDC/IL-2 may be clinically efficacious in acute myeloid leukemia of normal karyotype. *Hum Vaccin Immunother. 2020;16(1):109-111.*

III. **Nilsson MS***, Komic H*, Sheybani Z, Paul S, Rolfson O, Hellstrand K, Wennström L, Martner A#, Thorén FB#. Multiomic single-cell analysis of the $CD14^{-}$ $CD34^{+}$ HSPC compartment in chronic myeloid leukemia identifies von Willebrand factor and TIM3-expressing *BCR-ABL1*$^{+}$ leukemic stem cells in aberrant myeloid-biased hematopoiesis. *In manuscript.*

IV. Komic H*, **Nilsson MS***, Wennström L, Thorén FB#, Martner A#. Single-cell proteo-transcriptomic profiling of leukemic stem and progenitor cells in patients receiving cytoreductive hydroxyurea in early-phase chronic myeloid leukemia. *In manuscript.*

*,# Authors contributed equally.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

GÖTEBORGS UNIVERSITET

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Targeting residual malignant cells in myeloid leukemia

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Abstract

Malignant cells persisting during treatment prevent cure in many patients with myeloid leukemia. In acute myeloid leukemia (AML), the failure to eradicate the leukemic clone during conventional chemotherapy is associated with leukemic relapse, mostly with dismal survival outcome. Chronic myeloid leukemia (CML) is often successfully treated with targeted tyrosine kinase inhibitors (TKI). However, persisting treatment-resistant leukemic stem cells (LSC) put the patients at risk for acquired TKI resistance, relapse, or disease progression. This thesis encompasses studies ultimately aimed at facilitating the elimination of residual malignant cells in myeloid leukemia. AML is a heterogeneous disease in which subpopulations of patients may benefit from distinct treatment approaches. In **papers I and II**, we identified younger patients in first complete remission with chemotherapy-sensitive, normal karyotype AML (without *FLT3* mutation) as a new target group that may benefit from relapse-preventive immunotherapy with histamine dihydrochloride (HDC) and low-dose interleukin 2 (IL-2). In this group of patients, HDC/IL-2 may help prevent the expansion of residual leukemic cells and thus improve the chances of long-term relapse-free survival. In **paper III**, we performed an unprecedently detailed multiomic single-cell characterization of the $CD34^+$ stem and progenitor cell (SPC) compartment in CML bone marrow and compared it to that of healthy bone marrow. Through development of a method allowing detection of pathognomonic *BCR-ABL1* expression at the single-cell level, we identified a group of LSC displaying a TKI-resistance phenotype and defined novel expression patterns within this group of cells, including expression of von Willebrand factor and TIM3. Additional findings carried implications for the understanding of differences between leukemic and normal hematopoiesis and the phenotypic definition of CML LSC. **Paper IV** addressed effects of cytoreductive hydroxyurea (HU) treatment on CML SPC. The results revealed HU-induced hemoglobin expression in erythrocyte progenitors and signs of treatment-induced S phase arrest at all maturation stages within the CML SPC compartment. Taken together, the results presented in this thesis may have implications for future relapse-preventive treatment decisions in AML and studies of the TKI-resistant LSC population in CML, thus contributing to the targeting of residual disease in the two primary forms of myeloid leukemia.

Keywords: acute myeloid leukemia, chronic myeloid leukemia, histamine dihydrochloride, hydroxyurea, leukemic stem cells

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