Immunotherapy and immunosuppression in myeloid leukemia

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Björn Folkow, Medicinaregatan 11, Göteborg

Torsdagen den 29 november 2018 kl. 9.00

av **Alexander Hallner**

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Avhandlingen baseras på följande delarbeten:

I. Aurelius J*, **Hallner A***, Werlenius O, Riise R, Möllgård L, Brune M, Hansson M, Martner A, Thorén FB, Hellstrand K. NOX2-dependent immunosuppression in chronic myelomonocytic leukemia. *Authors contributed equally
Journal of Leukocyte Biology 2017; 102: 459-466

II. Rydström A*, **Hallner A***, Aurelius J, Sander FE, Bernson E, Kiffin R, Thoren FB, Hellstrand K, Martner A. Dynamics of myeloid cell populations during relapse-preventive immunotherapy in acute myeloid leukemia. *Authors contributed equally
Journal of Leukocyte Biology 2017; 102: 467-474

III. Bernson E, **Hallner A**, Sander FE, Wilsson O, Werlenius O, Rydström A, Kiffin R, Brune M, Foà R, Aurelius J, Martner A, Hellstrand K, Thorén FB.
Impact of killer-immunoglobulin-like receptor and human leukocyte antigen genotypes on the efficacy of immunotherapy in acute myeloid leukemia.
Leukemia 2017; 31: 2552-2559

IV. Bernson E, **Hallner A**, Sander FE, Nicklasson M, Nilsson MS, Christenson K, Aydin E, Liljeqvist JÅ, Brune M, Foà R, Aurelius J, Martner A, Hellstrand K, Thorén FB.
Cytomegalovirus serostatus affects autoreactive NK cells and outcomes of IL2-based immunotherapy in acute myeloid leukemia.
Cancer Immunology Research 2018; 6: 1110-1119

V. **Hallner A**, Bernson E, Hussein BA, Sander FE, Brune M, Aurelius J, Martner A, Hellstrand K, Thorén FB. The HLA-B -21 dimorphism impacts on NK cell education and clinical outcome of immunotherapy in acute myeloid leukemia.
Submitted

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Immunotherapy and immunosuppression in myeloid leukemia

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Abstract

Acute myeloid leukemia (AML) and chronic myelomonocytic leukemia (CMML) are potentially life-threatening blood cancers characterized by the expansion of malignant myeloid cells in bone marrow and other organs. This thesis aimed at contributing to the understanding of the role of natural killer (NK) cells in AML and CMML with focus on the potential impact of the immunosuppression exerted by reactive oxygen species (ROS) formed by the myeloid cell NOX2 enzyme. The thesis work has comprised *in vitro* studies of interactions between NK cells and primary myeloid leukemic cells along with analyses of NK cell repertoires in a clinical trial using a NOX2 inhibitor, histamine dihydrochloride (HDC) in conjunction with the NK cell-activating cytokine interleukin-2 (IL-2) for the prevention of relapse of AML after the completion of chemotherapy. **Paper I** reports that the functions and viability of cytotoxic lymphocytes, including NK cells, were compromised by ROS produced by leukemic myeloid cells recovered from patients with CMML. The results are thus suggestive of a novel mechanism of leukemia-induced immunosuppression in this disease. **Paper II** analyzed aspects of myeloid cell populations in AML using blood samples from a clinical phase IV trial where AML patients (n=84) received HDC in conjunction with IL-2. The results imply that HDC may exert anti-leukemic efficacy by facilitating the maturation of myeloid cells, which impacts on the efficiency of immunotherapy with HDC/IL-2. In **papers III** and **IV** we explored the role of killer cell immunoglobulin-like receptors (KIR) for the relapse and survival of AML patients receiving HDC/IL-2. The results suggest that a subset of immature NK cells with low KIR expression may determine clinical outcome. In **paper IV** we further analyzed results from the above-referenced phase IV trial and observed that a past cytomegalovirus (CMV) infection predicted high relapse risk and poor survival, presumably by reducing the pool of immature NK cells. The results of **paper V** suggest that a dimorphism in the leader peptide of HLA-B is relevant to NK cell-mediated killing of AML cells and to the outcome of immunotherapy. In conclusion, this thesis work presents novel aspects of myeloid cell-induced immunosuppression in AML and CMML and identifies NK cell subsets of potential relevance to the benefit of immunotherapy with HDC/IL-2.

Keywords: Natural killer cells, acute myeloid leukemia, histamine dihydrochloride, immunotherapy, reactive oxygen species, chronic myelomonocytic leukemia, NK cell education, NKG2A, HLA, KIR

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