On the role of Natural Killer cell immunogenetics for the outcome of immunotherapy in acute myeloid leukemia

Akademisk avhandling

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Fredag den 4 mars 2022 kl. 9.00

av **Brwa Ali Hussein**

Fakultetsopponent: Mattias Carlsten, Karolinska Institutet, Stockholm, Sverige

Avhandlingen baseras på följande delarbeten:

I. 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. Blood 2019;133(13):1479-1488.

II. Hussein BA, Hallner A, Wenneström L, Brune M, Martner A, Hellstrand K, Bernson E, Thorén FB. Impact of NK cell activatory gene variants on receptor expression and outcome of immunotherapy in acute myeloid leukemia. Frontiers in Immunology. 2021;12:796072

III. Hussein BA*, Kristenson L*, Pesce S, Hallner A, Nilsson M, Nilsson S, Brune M, Hellstrand K, Elin Bernson, Tang KW, Thorén FB. An NKG2A gene polymorphism skews the NK cell repertoire, impacts NK cells function and affects the outcome of immunotherapy in acute myeloid leukemia. In manuscript. *Authors equally contributed

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Abstract

Numerous studies have revealed that natural killer cells have fundamental roles as effector cells in myeloid leukemias. Thus, understanding NK cell-related biomarkers that influence outcome are warranted. This thesis comprises in-depth dissection of how NK cell biology impacts on survival during histamine dihydrochloride/IL-2 therapy in acute myeloid leukemia (AML), with an emphasis on role of genetics of NK cell receptors and HLA. We studied AML samples from the Re:Mission trial using flow cytometry and PCR-based techniques. In addition, various *in vitro* NK cell functional assays have been performed using healthy donors and CRISPR-edited cell lines. In ***paper I***, we sought to examine the effects of an HLA-B dimorphism, which affects HLA-E presentation, on NK cell function and on NK cell responses to leukemic cells. Results suggested that individuals with a presentable HLA-B variant harbored better-educated NKG2A^{+} cells. Furthermore, AML patients with this variant showed superior clinical outcome after HDC/IL-2 therapy in comparison to patients with non-presentable HLA-B leader peptides. In ***paper II***, we investigated the potential impact of gene variants of NKG2D, DNAM-1 and NKp30 on receptor expression and survival of AML. Findings demonstrated that an NKG2D SNP was associated with increased expression and better clinical outcome of HDC/IL-2 immunotherapy. However, this polymorphism is in linkage disequilibrium with other polymorphisms in adjacent genes. Thus, in ***paper III***, we first aimed to determine the clinical impact of NKG2A variants on outcome of AML after immunotherapy; secondly, to define whether the NKG2A gene variants affect function of NK cells. AML patients with high-expressing NKG2A alleles had a more immature NK cell repertoire, higher granzyme B content and superior clinical outcome. Taken together, this thesis provides new insights into NK cell biology, and their potential applicability to predict outcome of immunotherapy in AML.

Keywords: Natural killer cells, acute myeloid leukemia, immunotherapy, HDC/IL-2, NKG2A, NK education, SNPs, NK activating receptors, HLA class I

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