Impact of NK cell repertoires on immunotherapy in acute myeloid leukemia

Akademisk avhandling

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Elin Bernson

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University of Minnesota

Avhandlingen baseras på följande arbeten:

I. **Bernson E**, Hallner A, Sander F E, Wilsson O, Werlenius O, Rydström A, Kiffin R, Brune M, Foà R, Aurelius J, Martner A, Hellstrand K, Thorén F B.
Impact of killer-immunoglobulin-like receptor and human leukocyte antigen genotypes on the efficacy of immunotherapy in acute myeloid leukemia.
Leukemia, 2017; Epub ahead of print

II. **Bernson E**, Hallner A, Sander F E, Nicklasson M, Nilsson M, Christenson K, Aydin E, Liljeqvist J-Å, Brune M, Foà R, Aurelius J, Martner A, Hellstrand K, Thorén F B.
Cytomegalovirus regulates autoreactive NK cells and prognosticates the outcome of IL-2-based immunotherapy in acute myeloid leukemia.
Submitted

III. Hallner A, **Bernson E**, Hussein B A, Sander F E, Brune M, Foà R, Aurelius J, Martner A, Hellstrand K, Thorén F B.
Impact of HLA-B -21 dimorphism on clinical outcome of IL-2-based immunotherapy in acute myeloid leukemia.
In manuscript

IV. **Bernson E***, Christenson K*, Pasanen M, Amirbeagi F, Bylund J, Thorén F T.
Dynamic modulation of NK cell receptor ligands in inflammatory neutrophils.
In manuscript

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Impact of NK cell repertoires on immunotherapy in acute myeloid leukemia

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ABSTRACT

Natural killer (NK) cells are lymphocytes endowed with cytotoxicity against aberrant cells, including transformed and virus-infected cells. NK cell function is dictated by a fine-tuned interplay between activating and inhibitory receptors expressed on the NK cell surface. While the different activating receptors interact with unique ligands present on healthy or transformed cells, inhibitory NKG2A and killer immunoglobulin-like receptors (KIRs) invariably recognize HLA class I molecules. The purpose of this thesis was to elucidate how interactions between inhibitory NK cell receptors and HLA class I impact on anti-leukemic functions of NK cells and on NK cell-mediated termination of inflammation. In a phase IV trial, 81 AML patients received histamine dihydrochloride and low-dose interleukin-2 (HDC/IL-2) for the prevention of recurrence of leukemia after the completion of chemotherapy. The trial comprised immunophenotyping of serial blood samples along with KIR/HLA genotyping and assessment of cytomegalovirus (CMV) serostatus. Results from papers I and II imply a beneficial role of NK cell subsets that are less inhibited by HLA while prior CMV infection, which promotes the expression of additional KIRs, impacted negatively on relapse risk and survival. Additionally, a single nucleotide polymorphism in *HLA-B* that dictates NK cell inhibition to be preferentially mediated by NKG2A impacted positively on outcome in this trial (paper III). The relevance of the interplay between activating and HLA-mediated inhibitory signaling was further illustrated in a non-malignant setting in paper IV, where modulation of NK cell receptor ligands expressed by inflammatory neutrophils was associated with enhanced susceptibility to NK cell cytotoxicity. In conclusion, these studies support i) that low-grade KIR-mediated inhibition of NK cells is relevant for the benefit of relapse-preventive immunotherapy in AML and ii) that NK cells participate in the resolution of inflammation.

Keywords: Natural killer cells, Acute myeloid leukemia, Immunotherapy, Killer-cell immunoglobulin-like receptor, human leukocyte antigen class I molecules

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