

Immune escape in chronic leukemia

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Avhandlingen baseras på följande delarbeten:

- I. Akhiani, A. A., O. Werlenius, J. Aurelius, C. Movitz, A. Martner, K. Hellstrand, and F. B. Thorén. 2014. Role of the ERK pathway for oxidant-induced parthanatos in human lymphocytes. *PLoS one* 9: e89646
- II. Werlenius, O., R. E. Riise, M. Simpanen, J. Aurelius, and F. B. Thorén. 2014. CD20 antibodies induce production and release of reactive oxygen species by neutrophils. *Blood* 123: 4001-4002
- III. Werlenius, O., J. Aurelius, A. Hallner, A. A. Akhiani, M. Simpanen., A. Martner, P.O. Andersson, K. Hellstrand, and F. B. Thorén. Reactive oxygen species induced by therapeutic CD20 antibodies inhibit NK cell-mediated ADCC against primary CLL cells. *Submitted*
- IV. Aurelius, J., O. Werlenius, A. Hallner, R. E. Riise, L. Möllgård, M. Brune, A. Martner, F. B. Thorén, and K. Hellstrand. Immunosuppressive properties of malignant monocytes in chronic myelomonocytic leukemia: role of reactive oxygen species. *In manuscript*



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ABSTRACT

Reactive oxygen species (ROS) are produced by myeloid cells as a mechanism of defense against infection, but also to resolve inflammation, as ROS can induce cell death in T cells and NK cells. ROS production may also be deployed as a mechanism by which myeloid cells suppress anti-leukemic lymphocytes to promote malignant progression. The aim of this thesis was to define the role of myeloid cell-derived ROS in chronic leukemias as a putative target of immunotherapy. In **paper I**, the transductional pathways leading to ROS-induced lymphocyte death were investigated and found to involve the ERK1/2 mitogen-activated protein kinase (MAPK). These results challenge the view of ROS-induced cell death being a direct consequence of ROS-inflicted DNA damage. **Papers II and III** demonstrate that anti-CD20 monoclonal antibodies (mAbs) triggered ROS production by monocytes and neutrophils, which translated into reduced NK cell-mediated antibody-dependent cytotoxicity (ADCC) towards autologous leukemic cells derived from patients with chronic lymphocytic leukemia (CLL). The anti-oxidative agent histamine dihydrochloride (HDC) was found to restore ADCC by preventing ROS formation from adjacent monocytes, suggesting that anti-oxidative therapy might increase the efficacy of therapeutic mAbs. In **paper IV**, monocytic leukemic cells obtained from patients with chronic myelomonocytic leukemia (CMML) were shown to suppress T cells and NK cells by producing ROS. HDC counter-acted the suppression of lymphocytes by preventing ROS formation, and augmented the anti-leukemic activity of NK cells. Collectively, these results suggest that myeloid cell-derived ROS may be operational in CLL and in CMML as a mechanism of immune escape and that immunotherapy by anti-oxidative intervention should be further investigated in these forms of chronic leukemia.

Keywords Immune escape, immunotherapy, reactive oxygen species, chronic lymphocytic leukemia, chronic myelomonocytic leukemia, MAPK

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