Immune escape in chronic leukemia

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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, PO. 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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