Redox reactions in cancer: impact and regulation

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Avhandlingen baseras på följande delarbeten:

I. Martner A, **Grauers Wiktorin H**, Lenox B, Ewald Sander F, Aydin E, Aurelius J, Thorén FB, Ståhlberg A, Hermodsson S, Hellstrand K. Histamine promotes the development of monocyte-derived dendritic cells and reduces tumor growth by targeting the myeloid NADPH oxidase.
J Immunol 2015;194(10):5014-5021

II. **Grauers Wiktorin H**, Nilsson MS, Kiffin R, Ewald Sander F, Lenox B, Rydström A, Hellstrand K, Martner A. Histamine targets myeloid-derived suppressor cells and improves the anti-tumor efficacy of PD-1/PD-L1 checkpoint blockade.
Accepted for publication in Cancer Immunology Immunotherapy 2018

III. Kiffin R, **Grauers Wiktorin H**, Nilsson MS, Aurelius J, Aydin E, Lenox B, Nilsson JA, Ståhlberg A, Thorén FB, Hellstrand K, Martner A. Anti-leukemic properties of histamine in monocytic leukemia: The role of NOX2.
Front Oncol 2018;8(JUN):218

IV. **Grauers Wiktorin H**, Nilsson T, Aydin E, Hellstrand K, Palmqvist L, Martner A. Role of NOX2 for leukaemic expansion in a murine model of BCR-ABL1$^+$ leukaemia.
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Redox reactions in cancer: impact and regulation

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Abstract

The reduction-oxidation (redox) reaction involves a change in the oxidation state of molecules where a molecule that donates an electron is oxidized and a molecule that accepts an electron is reduced. The NADPH oxidase of myeloid cells, NOX2, is a major source of oxidants in the form of reactive oxygen species (ROS), which are short-lived oxygen derivatives. NOX2-derived ROS have been ascribed a pivotal role in the elimination of pathogens and may be toxic also to host cells and tissues. ROS may also act as signaling molecules and thus regulate biological processes such as cell cycle proliferation, differentiation, cell death, blood vessel formation, and immunity. The purpose of this thesis was to contribute to the understanding of the impact and regulation of redox reactions in cancer with focus on the role of NOX2. The studies have comprised cells and animals that were genetically or pharmacologically deprived of NOX2 activity, and attempts were made to define the significance of the findings in a clinical setting. The results presented in **paper I** imply that ROS may inhibit the maturation of monocytes into antigen-presenting dendritic cells, which may favor tumor growth *in vivo*. **Paper II** reports that treatment of mice with the NOX2 inhibitor histamine dihydrochloride (HDC) resulted in reduced expansion and reduced immunosuppressive activity of myeloid-derived suppressor cells. Treatment of mice with HDC also improved the efficacy of checkpoint inhibitors to reduce the growth of murine lymphoma and colon cancer. The results of **paper III** suggest that HDC, by targeting NOX2-derived ROS, promotes the differentiation of acute myeloid leukemia (AML) cells *in vitro* and *in vivo*, thus implying that the intrinsic formation of ROS by AML cells contributes to their malignant features. In **paper IV** it is reported that functional NOX2 is relevant to the induction of chronic myeloid leukemia by murine *BCR-ABL1*$^{+}$ cells. In conclusion, these results support that NOX2 is a conceivable therapeutic target in cancer.

Keywords: Cancer, immunotherapy, reactive oxygen species, NOX2, histamine dihydrochloride, myeloid-derived suppressor cells, checkpoint inhibition, acute myeloid leukemia, chronic myeloid leukemia

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