Targeting NOX2 in cancer

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Carl Kylberg, Medicinaregatan 7, Göteborg, tisdagen den 20 mars, klockan 9.00

av **Ebru Aydin**

Fakultetsopponent:
Anna Dimberg
Uppsala universitet

Avhandlingen baseras på följande delarbeten:

I. Martner A, Wiktorin HG, Lenox B, Sander FE, **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), pp.5014-5021

II. **Aydin E**, Johansson J, Nazir FH, Hellstrand K, Martner A. Role of NOX2-derived reactive oxygen species in NK cell-mediated control of murine melanoma metastasis
Cancer Immunol Res 2017; *5*(9), pp.804-811

III. 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
Br J Haematol 2017; doi: 10.1111/bjh.14772. [Epub ahead of print]

IV. **Aydin E**, Hallner A, Wiktorin HG, Hellstrand K, Martner A. NOX2 inhibition reduces oxidative stress and prolongs survival in murine KRAS-induced myeloproliferative disease (*Submitted*)

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Abstract

Reactive oxygen species (ROS) are short-lived, toxic derivatives of oxygen that are produced during mitochondrial respiration and by NADPH oxidases (NOX). By enzymatically generating ROS, the myeloid cell NOX2 plays a critical role in defense against bacteria and other microorganisms. The NOX2-derived ROS have also been ascribed immunosuppressive properties and may damage DNA to induce mutagenesis, but details regarding the role of NOX2 and ROS for the initiation and progression of cancer are partly unexplored. This thesis work utilized genetic and pharmacological tools including transgenic mice, genetically modified cells and pharmacological NOX2 inhibitors to further define the role of NOX2 in cancer. The results presented in paper I implied that a NOX2 inhibitor, histamine dihydrochloride (HDC), promotes the development of monocyte-derived, antigen-presenting dendritic cells to control the *in vivo* growth of a murine lymphoma (EL-4). Paper II was designed to elucidate the impact of NOX2 on the process of metastasis. The results suggested that extracellularly released NOX2-derived ROS from myeloid cells may dampen natural killer (NK) cell-mediated defense against murine melanoma cells to promote hematogenous metastasis. Paper III aimed at defining the role of NOX2 in a mouse model of chronic myeloid leukemia (CML). It was observed that genetic ablation of NOX2 delayed the *in vivo* expansion of leukemic cells carrying the *BCR-ABL1* mutation. In paper IV, it is shown that genetic and pharmacological inhibition of NOX2 delayed the development of myeloproliferation in a murine model of *Kras*-induced myeloid leukemia and, also, that inhibition of NOX2 function may confer protection against oxidative stress and DNA damage in cells of the leukemic clone. In summary, these studies identify NOX2 as a conceivable target in cancer therapy.

Keywords: Reactive oxygen species, cancer, immunotherapy, histamine, NOX2, NK cells, melanoma, metastasis, KRAS, leukemia, MPD, AML, CML

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