Mechanisms of leukemia-induced immunosuppression

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Tor Bjurström, Medicinaregatan 3B, Göteborg, torsdagen den 7 juni 2012, kl 09.00

av Johan Aurelius

Fakultetsopponent:
Professor Hans-Gustaf Ljunggren
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Avhandlingen baseras på följande delarbeten:

I. Martner, A; **Aurelius, J**; Rydström, A; Hellstrand, K; Thorén, FB. *Redox remodeling by dendritic cells protects antigen-specific T cells against oxidative stress.*
J Immunol 2011;187 6243-6248.

II. **Aurelius, J**; Thorén, FB; Akhiani, A; Brune, M; Palmqvist, L; Hansson, M; Hellstrand, K; Martner, A. *Monocytic AML cells inactivate anti-leukemic lymphocytes: role of NADPH oxidase/gp91^{phox} expression and the PARP-1/PAR pathway of apoptosis.*
Blood 2012; May 1. [Epub ahead of print].

III. **Aurelius, J**; Martner, A; Brune, M; Palmqvist, L; Hansson, M; Hellstrand, K; Thorén, FB. *Remission maintenance in acute myeloid leukemia: impact of functional histamine H_2 receptors expressed by leukemic cells*.
Submitted 2012.

IV. **Aurelius, J**; Martner, A; Romero, AI; Riise, RE; Palmqvist, L; Brune, M; Hellstrand, K; Thorén FB. *Chronic myeloid leukemic cells trigger poly(ADP-ribose) polymerase-dependent inactivation and cell death in lymphocytes.*
Submitted 2012.

V. Akhiani, AA**; Aurelius, J**; Movitz, C; Hellstrand, K; Thorén FB. *Reactive oxygen species trigger ERK pathway-dependent parthanatos in cytotoxic lymphocytes.*
Submitted 2012.

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Mechanisms of leukemia-induced immunosuppression

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Abstract

This thesis aimed to define the role of reactive oxygen species (ROS), produced by the NADPH oxidase of myeloid cells, in the regulation of lymphocyte function with focus on ROS-induced dysfunction of natural killer (NK) cells and T lymphocytes in myeloid leukemia. In **Paper I**, a novel mechanism is presented by which specifically activated T lymphocytes evade inactivation by ROS after antigen presentation. Antigen-presenting dendritic cells were found to induce ROS-neutralizing thiols on the surface of antigen-specific T cells, but not on T cells that lacked antigen specificity. These findings may explain why antigen-specific T cells remain viable under conditions of oxidative stress. **Paper II** shows that subsets of leukemic cells recovered from patients with acute myeloid leukemia (AML) produce and release ROS via a membrane-bound NADPH oxidase, and that ROS-producing leukemic cells initiate a PARP-1-dependent pathway of cell death (parthanatos) in NK cells and T cells. The results presented in **Paper III** demonstrate that treatment of AML patients with a NADPH oxidase inhibitor (histamine dihydrochloride) was preferentially efficacious among patients with monocytic leukemias (FAB classes M4 and M5), in which cells of the leukemic clone expressed a ROS-producing NADPH oxidase and functional histamine H_2 receptors. The results presented in **Paper IV** imply that malignant cells recovered from patients with chronic myeloid leukemia utilize the ROS/PARP-1 axis to induce NK cell parthanatos and that PARP-1 inhibition maintains functions of T cells and NK cells under conditions of oxidative stress. **Paper V** aimed to define the intracellular pathways of ROS-induced PARP-1 activation with ensuing cell death in lymphocytes. The results suggest that the mitogen-activated protein kinase ERK1/2 is involved in ROS-induced signal transduction and that ERK1/2 is activated upstream of PARP-1 in ROS-dependent lymphocyte parthanatos.

Keywords: Reactive oxygen species, NK cells, T cells, ROS, PARP-1, Acute myeloid leukemia, AML, immunosuppression, immunotherapy
ISBN: 978-91-628-8481-9