Oxidant-induced cell death in lymphocytes: mechanisms of induction and resistance

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av

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Avhandlingen baseras på följande delarbeten:

I. Thorén, F.B., Romero, A.I., and Hellstrand, K.
Oxygen radicals induce poly(ADP-ribose) polymerase-dependent cell death in cytotoxic lymphocytes. *J Immunol* (2006) 176:7301-7307.

II. Thorén F.B., Romero A.I., Hellstrand K.
Oxidant-induced inactivation of natural killer cells and T cells: role of poly(ADP-ribose)polymerase-1. *In manuscript*

III. Thorén F.B., Romero A.I., Hellstrand K.
The $CD16^{-}/CD56^{bright}$ subset of natural killer cells is resistant to oxidant-induced cell death. *J Immunol,* accepted for publication

IV. Romero, A.I., Thorén, F.B., Brune, M., and Hellstrand, K.
NKp46 and NKG2D receptor expression in NK cells with $CD56^{dim}$ and $CD56^{bright}$ phenotype: regulation by histamine and reactive oxygen species. *Br J Haematol* (2006) 132:91-98.

V. Thorén F.B., Betten Å., Romero A.I., Hellstrand K.
Anti-oxidative properties of myeloid dendritic cells: protection of T cells and NK cells from oxygen radical-induced inactivation and apoptosis. *Submitted*

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Abstract
Reactive oxygen species (oxidants, oxygen radicals) produced by the phagocytic NADPH oxidase have pivotal roles in immunity. Patients lacking a functional NADPH oxidase suffer from chronic granulomatous disease, which is characterized by recurring bacterial infections and thus manifesting the importance of reactive oxygen species in host defense against bacteria. However, NADPH oxidase-derived radicals also efficiently inhibit lymphocyte-mediated immunity. Oxidant-induced inactivation of lymphocytes is reportedly a control mechanism for autoreactive lymphocytes and hence prevents autoimmunity. In malignant diseases, oxygen radicals have been proposed to contribute to the characteristic state of anergy of cytotoxic lymphocytes, which prevents immune-mediated rejection of the tumor. Studies of the mechanisms of radical-induced inactivation of lymphocytes may therefore be helpful in understanding the pathophysiology of important disease entities.

The first paper in this thesis shows that oxidant-induced functional inhibition and cell death in cytotoxic lymphocytes is critically dependent on cooperation between a nuclear enzyme involved in DNA repair, PARP-1, and a mitochondrion-derived protein, AIF. The results presented in Paper II demonstrate that pharmacological inhibition of the PARP-1 enzyme not only prevents oxidant-induced cell death, but also preserves functions of cytotoxic lymphocytes, such as cytotoxicity against malignant cells, cytokine production, and proliferation. Paper III shows that subsets of natural killer (NK) cells display differential sensitivity to oxygen radicals: the cytotoxic $CD56^{dim}CD16^{+}$ NK cells were found to be highly sensitive to oxidative inactivation and apoptosis, while the immunoregulatory, cytokine-producing $CD56^{bright}CD16^{-}$ NK cells were highly resistant to the toxicity of oxidants. These data were extended in Paper IV, in which the effect of oxygen radical-producing phagocytes on the expression of the activating NK cell receptors, NKp46 and NKG2D, was investigated. The expression of both receptors was efficiently downregulated on $CD56^{dim}$ NK cells, while the expression remained intact on $CD56^{bright}$ cells. Recent data imply that reciprocal interactions between NK cells and dendritic cells (DCs) are important for the development of adaptive immunity. The results presented in Paper V demonstrate that DCs are equipped with an antioxidative system that efficiently protects cytotoxic cells from oxidant-induced inactivation.

Keywords: reactive oxygen species, cell death, apoptosis, poly(ADP-ribose)polymerase-1, apoptosis-inducing factor, natural killer cells, phagocytes, dendritic cells,

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