On the role of innate cell interactions in inflammation and leukemia

Akademisk avhandling

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av

Rebecca Riise

Fakultetsopponent: Professor Per-Arne Oldenborg,

Institutionen för integrativ medicinsk biologi vid Umeå universitet, Umeå

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I. **Riise, RE**; Bernson, E; Aurelius, J; Martner, A; Pesce, S; Della Chiesa, M; Marcenaro, E; Bylund, J; Hellstrand, K; Moretta, L; Moretta, A; Thorén, FB.
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Submitted.

II. Thorén, FB; **Riise, RE**; Ousbäck, J; Della Chiesa, M; Alsterholm, M; Marcenaro, E; Pesce, S; Prato, C; Cantoni, C; Bylund, J; Moretta, L; Moretta, A.
Human NK cells induce neutrophil apoptosis via an NKp46- and Fas-dependent mechanism.
Journal of Immunology 2012; 188: 1668-1674.

III. Aurelius, J; Martner, A; **Riise, RE**; Romero, AI; Palmqvist, L; Brune, M; Hellstrand, K; Thorén, FB.
Chronic myeloid leukemic cells trigger poly(ADP-ribose) polymerase-dependent inactivation and cell death in lymphocytes.
Journal of Leukocyte Biology 2013; 93: 155-160.

IV. Martner, A; Rydström, A; **Riise, RE**; Aurelius, J; Anderson, H; Brune, M; Foá, R; Hellstrand, K; Thorén, FB.
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OncoImmunology 2015; 10.1080/2162402X.2015.1041701.

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ABSTRACT

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Rebecca Riise

Department of Infectious Diseases, Institute of Biomedicine
The Sahlgrenska Academy at University of Gothenburg, Sweden

Inflammatory cells of the innate immune system launch rapid and powerful effector responses in the combat against infectious pathogens. However, these inflammatory mediators may cause excessive damage to the host and, therefore, require rigid control systems to maintain the delicate balance between prompt clearance of infections and the risk of developing immunopathology. Natural killer (NK) cells form a part of a multifaceted network of innate interactions with myeloid cells during the course of immune responses. These complex patterns of reciprocal interplay have capacity to potentiate or inactivate immunity. The first paper of this thesis describes how interaction between NK cells and neutrophils contributes to the activation of adaptive responses. In paper II, we demonstrated that NK cells negatively regulate neutrophil functions by accelerating neutrophil cell death via NKp46 and the death receptor Fas. The results presented in paper III show that leukemic myeloid cells avoid elimination by NK cells by inducing lymphocyte cell death and that inhibition of the nuclear enzyme PARP-1 restores NK cell anti-leukemic effector functions. In paper IV, the crosstalk between NK cells and myeloid cells was targeted in patients with acute myeloid leukemia who received immunotherapy with histamine dihydrochloride and low-dose interleukin-2 aiming to prevent leukemic relapse. The treatment was found to trigger expansion of NK cell subtypes in blood and to induce enhanced NK cell expression of natural cytotoxicity receptors. These features of NK cells were associated with reduced risk of relapse. In summary, this thesis work may expand the knowledge of cellular crosstalk in immunity and suggests that communication between innate immune cells may be targeted for therapeutic purposes.

Keywords: Innate immunity, neutrophils, NK cells, caspase-1, apoptosis, myeloid leukemia, ROS, immunotherapy

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