Göteborg, 2023

PRIMING AND ACTIVATION OF NEUTROPHILS FROM BLOOD AND TISSUE

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hörsal Arvid Carlsson, Medicinaregatan 3, onsdagen den 3 maj, klockan 9:00

av **Lisa Davidsson**

Fakultetsopponent:

Docent Robin Kahn

Medicinska fakulteten vid Lunds Universitet

Avhandlingen baseras på följande delarbeten

I. A simple skin blister technique for the study of in vivo transmigration of human leukocytes. **Davidsson L**, Björkman L, Christenson K, Alsterholm M, Movitz C, Thorén FB, Karlsson A, Welin A, Bylund J. *J Immunol Methods 2013; 393 (1-2): 8-17*

II. Neutrophil recruitment to inflamed joints can occur without cellular priming. Björkman L, Christenson K, **Davidsson L**, Mårtensson J, Amirbeagi F, Welin A, Forsman H, Karlsson A, Dahlgren C, Bylund J. *J Leukoc Biol. 2019; 105 (6): 1123-1130*

III. In vivo transmigrated human neutrophils are highly primed for intracellular radical production induced by monosodium urate crystals. **Davidsson L**, Dahlstrand Rudin A, Sanchez Klose FP, Buck A, Björkman L, Christenson K, Bylund J. *Int J Mol Sci. 2020; 21 (11): 3750*

IV. Neutrophil ROS production is primed in blood neutrophils from gout patients. **Davidsson L**, Dahlstrand Rudin A, Christenson K, Björkman L, Bylund J. *In manuscript.*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN

GÖTEBORGS UNIVERSITET

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Priming and activation of neutrophils from blood and tissue

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Avdelningen för Reumatologi och Inflammationsforskning, Institutionen för Medicin, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2023

Abstract

Inflammation is a powerful process, involved in many disease states, as well as in physiological situations. Neutrophils, the main characters of this thesis, are potent immune cells with the capacity to regulate inflammatory responses. In health, circulating blood neutrophils are regarded as quiescent, with limited responsiveness to stimuli. When needed to combat infection, or during, e.g., flares of inflammatory disease, neutrophils have to leave the circulation to reach the inflamed tissue. The process of passing through, i.e., transmigrate, the blood vessel wall is believed to functionally alter and pre-activate the neutrophils, an event referred to as priming. Primed neutrophils are able to respond forcefully to activating stimuli, including the performance of efficient phagocytosis, maximal release of microbicidal molecules, production of reactive oxygen species (ROS) and formation of neutrophil extracellular traps (NETs). In certain disease states also circulating blood neutrophils can be primed, due to the presence of, e.g., proinflammatory cytokines or bacterial products in the bloodstream. While properly regulated priming of tissue neutrophils is beneficial for fighting bacteria, priming of neutrophils in the circulation often results in adverse outcomes, since uncontrolled neutrophil activation can damage the surrounding vasculature. Priming is thus to be seen as a control mechanism, important in the regulation of neutrophil activation. Despite tissue neutrophils being the main effector cells, blood neutrophils represent the main source of knowledge on neutrophil biology, due to the simplicity of obtaining these cells. The overall aim of this thesis was to increase the current knowledge on neutrophil priming and activation, complex processes that participate in regulating inflammation, in blood and tissue, in health as well as in inflammatory disease. In **paper I,** a simple skin blister technique to obtain and study *in vivo* transmigrated neutrophils was described and characterized. In **paper II,** in contrast to neutrophils obtained from skin blisters and skin chambers (two *in vivo* models of aseptic inflammation) and the leading dogma, synovial fluid neutrophils derived from patients with inflammatory arthritis were shown to display no, or only mild, signs of priming. In **paper III**, the interactions between neutrophils and monosodium urate (MSU) crystals, triggers of the inflammatory disease gout, were studied. Neutrophil ROS production induced by the crystals was shown to be strictly intracellular and clearly primed in tissue neutrophils derived from skin chambers. NET formation induced by the crystals was not dependent on ROS and not primed in any of the studied tissue neutrophils. In **paper IV,** blood neutrophils from gout patients were shown to be primed for baseline and MSU crystal triggered ROS production, while NET formation and receptor expression were similar between neutrophils from gout patients and controls. In conclusion, this thesis highlights the complexity of neutrophil priming and activation and the changes that neutrophils undergo during transmigration to different inflamed tissues.

Keywords: neutrophil, priming, gout, inflammation, transmigration, neutrophil extracellular traps (NETs)

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