CELL DEATH AND CLEARANCE
– STUDIES OF HUMAN NEUTROPHILS FROM BLOOD AND TISSUE

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen, våning 3 i Mikrobiologihuset, Guldhedsgatan 10A, Göteborg

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av
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Avhandlingen baseras på följande arbeten:

I K Christenson, L Björkman, C Tängemo, and J Bylund
Serum Amyloid A inhibits apoptosis of human neutrophils via a P2X7-sensitive pathway independent of formyl peptide receptor-like 1
Journal of Leukocyte Biology (2008) 83(1):139-48

II A Karlsson*, K Christenson*, M Matlak, Å Björstad, KL Brown, E Telemo, E Salomonsson, H Leffler, and J Bylund
Galectin-3 functions as an opsonin and enhances macrophage clearance of apoptotic neutrophils
*Glycobiology (2009) 19(1):16-20. *=joint first authors*

III K Christenson, L Björkman, J Karlsson, M Sundqvist, C Movitz, DP Speert, C Dahlgren, and J Bylund
In vivo transmigrated neutrophils are resistant to antiapoptotic stimulation
Journal of Leukocyte Biology (2011) epub ahead of print

VI K Christenson, L Björkman, C Movitz , and J Bylund
Cell death processes in neutrophils from synovial fluid
In manuscript

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Abstract:
Neutrophils are phagocytic cells that typically migrate from circulation to tissues in order to combat microbial invasion. The journey from blood to tissue involves mobilization of intracellular organelles which results in modifications of surface markers (e.g., exposure of receptors involved in adhesion, chemotaxis and phagocytosis) that render neutrophils a primed/activated phenotype distinct from that of resting blood neutrophils. Neutrophils contain a substantial arsenal of tissue destructive factors, which could be hazardous for the environment if released in an uncontrolled fashion. Therefore, neutrophil apoptosis and clearance of the dead bodies is of outmost importance and a necessity for resolution of the inflammation.

Apoptosis of neutrophils can be modulated *in vitro;* typically pro-inflammatory danger signals delay apoptosis. The acute phase protein serum amyloid A (SAA) delayed neutrophil apoptosis *in vitro*, an effect that was blocked by inhibition of the receptor P2X7. Blocking of P2X7 also inhibited prolonged survival mediated by other stimuli indicating that P2X7 is not an actual SAA receptor, but instead involved in anti-apoptotic signaling in general. Clearance of apoptotic cells can also be modulated *in vitro*, e.g., by opsonization. This was shown for Galectin-3 that increased the clearance of apoptotic neutrophils by monocyte-derived macrophages. Galectin-3 enhanced the proportion of macrophages that engulfed apoptotic cells but also the number of ingested neutrophils in each macrophage.

Apoptosis is well studied in resting neutrophils purified from peripheral blood, but how the process is modulated in tissue neutrophils is relatively unknown. We investigated the apoptotic process in tissue neutrophils from two different inflammatory settings, skin chambers on healthy subjects and synovial fluid from patients with inflammatory arthritis. Skin chamber neutrophils were totally resistant to anti-apoptotic stimulation, which was in stark contrast to neutrophils from synovial fluid that responded well to anti-apoptotic stimulation. Also, neutrophils from skin chambers showed an activated phenotype, while neutrophils from synovial fluid surprisingly displayed a phenotype similar to that of resting blood neutrophils. Thus, the tissue neutrophils in our studies behaved fundamentally different. If this means that every inflammatory setting is unique remains to be evaluated in future studies.

Key words: neutrophils, apoptosis, transmigration, phagocytes

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