

# THE ROLE OF SERUM AMYLOID A IN INFLAMMATORY DISEASE

## - PROINFLAMMATORY MEDIATOR OR INERT BIOMARKER?

Akademisk avhandling  
som för avläggande av medicine doktorexamen vid Sahlgrenska akademien vid  
Göteborgs universitet kommer att offentlig förvaras i föreläsningssalen i  
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Fredagen den 9 april kl.13.00  
av Lena Björkman

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Avhandlingen baseras på följande delarbeten:

- I. Fu H, Björkman L, Janmey P, Karlsson A, Karlsson J, Movitz C, Dahlgren C. The two neutrophil members of the formylpeptide receptor family activate the NADPH-oxidase through signals that differ in sensitivity to a gelsolin derived phosphoinositide-binding peptide. *BMC Cell Biol.* 2004 Dec 29;5(1):50.
- II. Björkman L, Karlsson J, Karlsson A, Rabiet MJ, Boulay F, Fu H, Bylund J, Dahlgren C. Serum amyloid A mediates human neutrophil production of reactive oxygen species through a receptor independent of formyl peptide receptor like-1. *J Leukoc Biol.* 2008 Feb;83(2):245-53.
- III. Björkman L, Raynes JG, Shah C, Karlsson A, Dahlgren C, Bylund J. The proinflammatory activity of recombinant serum amyloid A is not shared by the endogenous protein in circulation. *Arthritis Rheum.* 2010. *Accepted for publication.*
- IV. Björkman L, Christenson K, Ekwall-Hultgård A-K, Dahlgren C, Bylund J. Activation status of neutrophils in the joints of patients with rheumatic disease. *In manuscript.*

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# **THE ROLE OF SERUM AMYLOID A IN INFLAMMATORY DISEASE – PROINFLAMMATORY MEDIATOR OR INERT BIOMARKER?**

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**Abstract:** Neutrophils are phagocytes of the innate immune system with prominent roles in host defense and are also believed to be important in autoimmune diseases such as rheumatoid arthritis (RA) by accumulating in inflamed joints and contribute to tissues destruction. Neutrophils differentiate in the bone-marrow and are mature cells when entering circulation with a cytoplasm packed with granules that contain toxic substances in addition to receptors that can be up-regulated to the cell surface during activation. Migration into the affected tissue is directed by mediators from the inflamed site which guides neutrophils along a chemotactic gradient and transfers the cell from resting- into a primed state. The inflammatory process triggers a systemic acute phase response characterized by the production of acute phase proteins (APP). The most prominent APP is serum amyloid A (SAA), the concentration of which can increase thousand fold in response to infection, aseptic inflammation or trauma. Patients with RA often have chronically elevated SAA in blood and joints and SAA has been implicated in the pathogenesis of RA. Recombinant SAA (rSAA) has been suggested to possess proinflammatory activities and act as a chemoattractant for neutrophils via a receptor called FPR2. A peptide (PBP10) with intracellular inhibitory activity was shown to allow discrimination between neutrophil signals mediated by FPR2 and the closely related FPR1. Next, the receptor specificity for rSAA was studied by use of PBP10 and another FPR2 specific inhibitor WRW4. rSAA affinity for FPR2 in transfected cell lines was corroborated and rSAA indeed activated primary human neutrophils. However, FPR2 was not responsible for mediating activation of primary human neutrophils by rSAA. Next, proinflammatory activity of rSAA was compared to that of endogenous SAA in circulation of RA patients. Using a sensitive marker for neutrophil activation in peripheral blood, endogenous SAA in circulation lacked proinflammatory activity and thus differed functionally from rSAA. Synovial neutrophils from patients with inflammatory arthritis and elevated SAA in joint fluid were next studied with respect to activation status. Synovial neutrophils displayed a surprisingly resting phenotype despite having transmigrated from peripheral blood to a compartment with endogenous SAA. Endogenous SAA, both in circulation and in joints, lack the proinflammatory properties present in the recombinant molecule.

Key-words: neutrophils, serum amyloid A, rheumatoid arthritis  
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