

Biologic effects of serum amyloid A in rheumatoid arthritis

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Summary

A-SAA closely reflects measures of disease activity in patients with inflammatory arthritis. A-SAA is produced by the liver and, unlike other acute phase proteins, by inflamed synovial tissue, which may be the reason for the close correlation with disease activity. A-SAA, like TNF, can induce many of the proinflammatory activities associated with pannus formation and joint destruction in inflammatory arthritis.

THE ACUTE PHASE RESPONSE

Inflammation is associated with altered plasma levels of several proteins. Some of these plasma protein levels, such as apolipoprotein A-1 (apo A-1), may decrease, while others including fibrinogen, haptoglobin, complement components, and C-reactive protein (CRP) increase. Acute phase proteins are produced predominantly by the liver and have a critical role in host defence mechanisms. Serum amyloid A (SAA) is an acute phase protein whose serum levels may increase more than 1000-fold following an acute inflammatory stimulus. In a clinical study of patients with early inflammatory arthritis, A-SAA was found to be superior to other conventional measures of the acute phase response in relation to differential diagnosis, association with clinical features, and response to treatment.

SERUM AMYLOID A AND THE ACUTE PHASE RESPONSE

SAA is a family of small homologous apolipoproteins that range from 12-14 kDa. They are encoded by different genes with high allelic variation, and high degrees of homology between species. The SAA proteins in mam-

mals are well conserved throughout evolution. There are four SAA genes in the human genome. SAA1 and SAA2 are specific to the acute phase response and are collectively termed acute phase SAA (A-SAA). They share over 95% nucleotide identity in their exon, intron and promoter regions. SAA 3 is known to be a pseudogene (a DNA sequence which, despite being largely homologous to a transcribed sequence elsewhere in the genome, is not transcribed) in humans; SAA4 is constitutively expressed in humans, and is not hyperinducible. SAA1 and SAA2 are coordinately regulated and are arranged 'head-to-head' in a gene cluster, which also contains SAA3 and SAA4 on chromosome 11p15.1. Following secretion by hepatocytes, A-SAA associates rapidly with the high-density lipoprotein fraction 3 (HDL₃), from which it displaces apo A-1. Serum levels of A-SAA reach concentrations ranging up to 1mg/ml. Extrahepatic production of A-SAA has also been observed in several normal human tissues. Abundant production of A-SAA by fibroblast-like synoviocytes (FLS) and endothelial cells (ECs) isolated from synovial tissue samples obtained from patients with rheumatoid arthritis (RA) and other inflammatory arthropathies has been recently described.

SERUM AMYLOID A RECEPTORS

A-SAA can bind to formyl peptide receptor-like 1 (FPRL1), a seven-transmembrane G protein-coupled receptor (a receptor which spans the membrane seven times) that was first identified on human mononuclear phagocytes. FPRL1 is also expressed on non-phagocytic cells, including hepatocytes, and is highly inducible by a number of cytokines, including interleukin-13 (IL-13) and interferon- γ (IFN- γ), in epithelial cells. In addition

to A-SAA, FPRL1 also interacts with a diverse array of other exogenous and endogenous ligands that are involved in inflammatory and host defence mechanisms. The lipid metabolite lipoxin A₄ (LxA₄) also binds to FPRL1, which antagonises the inflammatory response. Thus, A-SAA-induced monocyte and neutrophil migration to inflamed tissues is mediated through FPRL1. A-SAA is also known to induce MMP production by synovial tissue FLS, but it is not known if this is mediated through FPRL1-binding. At nanomolar concentrations, LxA₄ inhibited interleukin-1 β (IL-1 β)-induced MMP-3 production. FPRL1 mRNA expression has also been demonstrated in inflamed human synovial tissue, in isolated FLS, and in synovial ECs. The level of FPRL1 mRNA expression was similar in the various arthropathies that were examined. The demonstration of both A-SAA and an A-SAA receptor, FPRL1, in RA synovial tissue suggested that A-SAA might have a biologic role in the pathophysiology of inflammation.

THE BIOLOGIC EFFECTS OF SERUM AMYLOID A

A-SAA mRNA expression by FLS and synovial endothelial cells (ECs), and A-SAA protein production by FLS and synovial tissue macrophages, has been demonstrated in several categories of inflammatory arthritis. A-SAA and FPRL1 mRNA were coordinately up-regulated by pro-inflammatory cytokines. We have demonstrated that recombinant human A-SAA can induce both MMP-1 and

MMP-3 production by FLS isolated from RA synovial tissues. Studies from our laboratory have also demonstrated that A-SAA significantly up-regulates ICAM-1 and VCAM-1 expression on isolated RA synovial fibroblasts and ECs, and increases PBMC adhesion to these cells. A-SAA can induce EC migration and increase EC tube formation. Finally, we report that A-SAA promotes these pro-inflammatory mechanisms through the NF κ B and MAPK signaling pathways. These findings support a novel role for A-SAA as a central mediator of synovial inflammation and matrix degradation. A-SAA and its signaling pathways should be considered as potential therapeutic targets in the treatment of RA.

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