A-SAA INDUCES CYTOKINE PRODUCTION AND MATRIX METALLOPROTEINASE ACTIVITY IN ADIPOSE AND RA SYNOVIAL TISSUE

Ronan H Mullan, Jennifer McCormick, Mary Connolly, Chin Teck Ng, Ursula Fearon, Douglas J Veale
Dublin Academic Medical Centre, Dublin

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Background Rheumatoid arthritis (RA) is associated with a significant increase in cardiovascular (CV) mortality. Serum amyloid A (A-SAA), an acute phase protein with cytokine-like properties is increased 1000-fold during inflammation. Previously the authors showed A-SAA correlates with RA disease activity and is produced at high levels in the synovial joint. Elevated A-SAA production has been observed in metabolic syndrome in adipose tissues (AT) of type II diabetics but to date the role and regulation of A-SAA in human AT remains to be fully elucidated.

Aim To examine the relationship of A-SAA to CV risk in RA and whether a common proinflammatory pathway exists for A-SAA in RA and obesity.

Methods Forty RA patients were recruited and assessed at baseline, 0.5, 1 and 4 years. RA disease activity measures and paired serum were collected. Baseline CV risk criteria were obtained and CV events were recorded in follow-up. A-SAA serum levels were quantified by specific ELISA. Adipose tissue was obtained under direct visualisation from patients undergoing bariatric surgery or colonoscopy and primary adipocytes and whole tissue adipose explants were cultured. RA synovial biopsies were obtained at arthroscopy and whole tissue synovial explants established. Cell cultures were incubated in the presence of A-SAA (10–50 μg/ml) and interleukin (IL)-6 and IL-8 production were quantified by specific ELISA. Matrix metalloproteinase (MMP)-2 and -9 activation were assessed by gelatin zymography.

Results RA patients who developed CV events up to 4 years later had significantly higher baseline A-SAA levels (p<0.05) which remained elevated in the follow-up period. No significant difference was found in traditional CV risk factors. A-SAA (10 and 50 μg/ml) increased baseline production of IL-8 from 1.528 588 to 5 194 462 and 10 963 497 pg/ml and IL-6 from 549 564 to 3 392 226 and 6 629 568 pg/ml in adipose tissue explant cultures in vitro. In adipocyte cultures, A-SAA (10 μg/ml) markedly increased levels of IL-8 from 21 495 to 33 333 pg/ml and IL-6 from 4483 to 7566 pg/ml. Furthermore, a dramatic increase in MMP-9 activation was observed in adipose tissue explants, an effect greater than that on MMP-2 activity. Similar to adipose tissue cultures a dramatic upregulation of IL-8 from 1948 to 4739 and 5075 pg/ml production and activation of MMP-2 and 9 was demonstrated in RA synovial explant cultures in response to A-SAA (10 and 50 μg/ml).

Conclusion High serum A-SAA levels are associated with increased cardiovascular events over a 4-year period. Ex vivo/in vitro A-SAA induced similar proinflammatory pathways in synovial and adipose tissue, which may represent common pathogenic pathways in RA and metabolic syndrome.