Hyaluronic acid in synovial fluid in inflamed joints inhibits neutrophil activation

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Rheumatoid arthritis (RA) and spondyloarthritis (SpA) patients suffer from tissue damage in inflamed joints, generally thought to be caused by among others activated neutrophils in the synovial fluid (SF). However, surprisingly, we found that in these patients synovial neutrophils are inactive, despite the presence of many neutrophil-activating stimuli in SF. This finding suggests that an inhibitor of neutrophil activation is present in SF. Neutrophils were isolated from healthy donor blood and from SF from RA and SpA patients (n=25) and stimulated with activating agents in the absence or presence of increasing concentrations of SF. Degranulation and ROS production were determined to analyze the neutrophil activation status. Neutrophils derived from SF did not show an activated phenotype. However, activation of SF-derived neutrophils in vitro in the absence of SF led to full degranulation and ROS production. Activation of blood-derived neutrophils was dose-dependently inhibited by the presence of SF. This effect is independent of the diagnosis, gender, age, and medication use of the patients from which the SF originates. Furthermore, we showed that when SF was treated with the enzyme hyaluronidase the inhibitory effect of SF on neutrophil activation was reduced, indicating that hyaluronic acid plays a role in the inhibition of neutrophil activation. Together, our data suggest that SF inhibits neutrophil activation and that hyaluronic acid in SF is partly responsible for this. This information may be important for preventing tissue damage in inflamed joints.