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THE ANTIMICROBIAL PEPTIDE rCRAMP IS STRONGLY UPREGULATED DURING EXPERIMENTAL ARTHRITIS IN THE RAT

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Background and objectives Rheumatoid arthritis (RA) is characterised by an inflammatory and destructive infiltration of various immune cells into the synovium of the joint. The first cells to arrive at the site of inflammation and the main cell type in synovial fluid are neutrophil granulocytes that locally release cytotoxic agents, antimicrobial peptides, proteases and other inflammatory mediators, thus fuelling inflammation and damaging tissue. The aim of this project is to elucidate if locally released antimicrobial peptides contribute to the pathogenic events of arthritis.

Materials and Methods Expression of the rat cathelicidin related antimicrobial peptide (rCRAMP) during the course of pristane-induced arthritis (PIA) in Dark Agouti rats was determined in blood, synovial blood, joint extracts, lymph nodes, spleens and livers by Western blotting, immunohistochemistry and fluorescence-activated cell sorting. Formation of neutrophil extracellular traps was analysed by 4'-6-diamidino-2-phenylindole staining. IFN α was determined in sera by ELISA. Autoantibodies to rCRAMP were detected by immunoblot.

Results In PIA, an animal model of arthritis that closely mimics RA, rCRAMP is strongly upregulated in the joints of arthritic animals. Interestingly, the strongest overexpression is seen around onset of clinical arthritis. rCRAMP expression is also upregulated in the blood of pristane-injected rats even before the onset of clinical arthritis. Upregulation after pristane injection can as well be seen in spleen, but not in pristane-draining lymph nodes or the liver. rCRAMP is mainly expressed in His48+ CD62L-granulocytes and a smaller fraction of monocytes. Pristane application induces NETs and causes accumulation of low density neutrophils that copurify with peripheral blood mononuclear cell. The increased expression of rCRAMP coincides with IgG and IgM autoantibodies to rCRAMP and elevated serum levels of type I Interferons in PIA rats.

Conclusion Our results show strong upregulation of rCRAMP coinciding with pathological events in PIA. This might be due to a connection between rCRAMP forming complexes with nucleic acids that are locally released from damaged cells and activation of interferon-producing cells.