16 A DISEASE-MODIFYING ROLE FOR MUCOSAL IGA ANTIBODIES TO CITRULLINATED ANTIGENS?

Anna Svärd,[1,2] Alf Kastbom,[2] Yngve Sommarin,[3] and Thomas Skogh[2] *[1]Rheumatology clinic/CKF, Falun Hospital, Sweden; [2]Rheumatology unit, IKE/Linköping university, Sweden; [3]EuroDiagnostica AB, Malmö, Sweden*

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Objective The aim of this study was to investigate whether immunoglobulin A (IgA) antibodies to cyclic citrullinated peptides (CCP) can be detected in saliva of patients with established rheumatoid arthritis (RA) and if it relates to clinical manifestations.

Methods Salivary samples were collected (by 'passive drooling') from 63 consecutive patients with established RA at a visit to the rheumatology outpatient clinic (Falun, Sweden), and from 20 healthy persons (hospital staff). The samples were centrifuged and kept frozen at –70°C until analysis. IgA-class

anti-CCP antibodies in saliva were analysed by adaptation of a commercial ELISA (Immunoscan RA, Euro-Diagnostica AB, Malmö, Sweden) using polyclonal rabbit antihuman α-chain specific antibodies conjugated with horseradish peroxidase (DakoCytomation, Glostrup, Denmark) as secondary antibody.To ensure specificity of the reaction, a corresponding ELISA was set up to analyse IgA antibodies to control antigen (cyclic arginine peptide, CAP), and anti-CCP/anti-CAP ratios were calculated. Also, inhibition studies were performed by preincubation of sera with soluble CCP or CAP. Clinical and laboratory data on disease activity, that is, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), and 28-joint count disease activity score (DAS28) as well as radiological outcome (occurrence or absence of erosions as judged by a radiologist in diagnostic routine) were achieved retrospectively via the patients' medical records.

Results Background reactivity against CCP was found in virtually all patients and healthy subjects, whereas a positive anti-CCP/anti-CAP ratio (≥1.5) was found in 14 out of 63 RA patients (22%) and in one healthy subject (5%). Salivary IgA-reactivity with CCP was dose-dependently inhibited by soluble CCP (but not with CAP) in sera with anti-CCP/anti-CAP ratios ≥1.5. No IgG-reactivity to CCP was found in saliva, although all patients with salivary IgA anti-CCP tested IgG anti-CCP-positive in serum. Furthermore, less than half of those testing IgA-positive in saliva were IgA anti-CCP positive in serum, strongly arguing against passive leakage of anti-CCP antibodies from blood to saliva. The patients testing positive for salivary IgA antibodies had lower average disease activity measures (CRP, ESR, DAS28) at presentation and fewer developed bony erosions within 6 years after presentation (p=0.043, Fisher's exact test).

Conclusion Salivary IgA antibodies to citrullinated proteins were found in a subset of IgG anti-CCP positive RA patients. In contrast to their serum counterparts, salivary IgA antibodies may associate with a milder/less destructive disease course. This accords with the notion that secretory IgA antibodies exert anti-inflammatory actions, and that they may be associated with induction of systemic tolerance (oral tolerance). The possible disease-modifying role of mucosal immunity to citrullinated proteins needs further investigation!