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ALTERATIONS IN THE SYNOVIAL CELLULAR COMPOSITION ASSOCIATED WITH OSTEORESORPTION IN ANTIGEN-INDUCED ARTHRITIS

Martina Fadljević, Nina Lukač, Igor Radanović, Elvira Lazić Mosler, Darja Flegar, Alan Šućur, Tomislav Kelava, Vedran Katavić, Danka Grčević, Nataša Kovačić

University of Zagreb School of Medicine

Introduction The inflammatory arthritides are chronic joint diseases characterised by synovial infammation and thickening. Most common is rheumatoid arthritis, often accompanied by structural bone damage, in contrast to arthritis associated to systemic lupus erythematosus (SLE), which rarely affects bone. Murine phenotype resembling human SLE may be induced by inactivation of Fas/Fas receptor pathway. Mice with a non-functional Fas gene develop ameliorated form of experimentally induced arthritis, with less severe joint damage and bone destruction. However, the exact cellular interactions and signalling pathways mediating this effect are not fully understood. In present investigation we aimed to compare the cellular composition of synovial compartment in resorptive vs. non-resorptive forms of antigen-induced arthritis (AIA), and to assess the association of altered populations with bone resorption.

Methods Wild-type (WT) and Fas-deficient (Fas -/-) mice were immunized with methylated(m)BSA in complete Freund's adjuvant, followed by intra-articular injection of mBSA. Control mice (ctrl) were intra-articularly injected with PBS. Five weeks post-immunization, arthritis was assessed by histology and micro-CT. After collagenase digestion and labelling, the cellular phenotypes were determined by flow cytometry for the following markers: CD3, CD4, CD8, CD11b, CD29, CD31, CD44, CD45, CD51, CD90.1, CD105, CD140b, CD166, CD200, B220, Gr-1, Sca-1, and TER119.

Results Histologically assessed, arthritis was more severe in the AIA group of WT mice than in the Fas -/- AIA group. Micro-CT analysis revealed metaphyseal trabecular bone loss not only as a result of arthritis, but also as a consequence of systemic immunization in both WT and Fas -/- mice. Epiphyseal trabecular bone from Fas -/- mice was not affected by immunization or arthritis induction. Myeloid (CD11b+/Gr-1+) and macrophage (F4/80+) subpopulations accumulated in the synovial compartment of both WT-ctrl and WT-AIA mice, in comparison to non-immunized (NI) mice, while this up-regulation was absent in Fas-/- mice. Proportions of myeloid cells were negatively associated with the femoral epiphyseal trabecular bone volume (BV/TV, $p<0.05$). Populations containing bone and cartilage progenitors were downregulated in the synovial compartment of WT-AIA mice. A positive association with femoral epiphyseal BV/TV was established in particular for proportions of CD140b+ cells whereas the CD44+ population was negatively associated with femoral epiphyseal BV/TV. Skeletal progenitor population (lin-CD51+CD200+) and bone/cartilage stromal progenitor populations (lin-CD51+CD200-CD105+) were reduced (by absolute numbers) and positively associated with femoral epiphyseal BV/TV.

Conclusions Absence of Fas signalling prevents periarticular bone destruction in a murine model of AIA. Non-destructive arthritis in Fas -/- mice is characterised by decreased proportions of synovial myeloid cells and macrophages, which are strongly negatively associated with bone volume. Mesenchymal cells, containing bone and cartilage progenitors, were more abundant in the joints of Fas -/- mice with non-destructive arthritis, associated with higher bone volume.