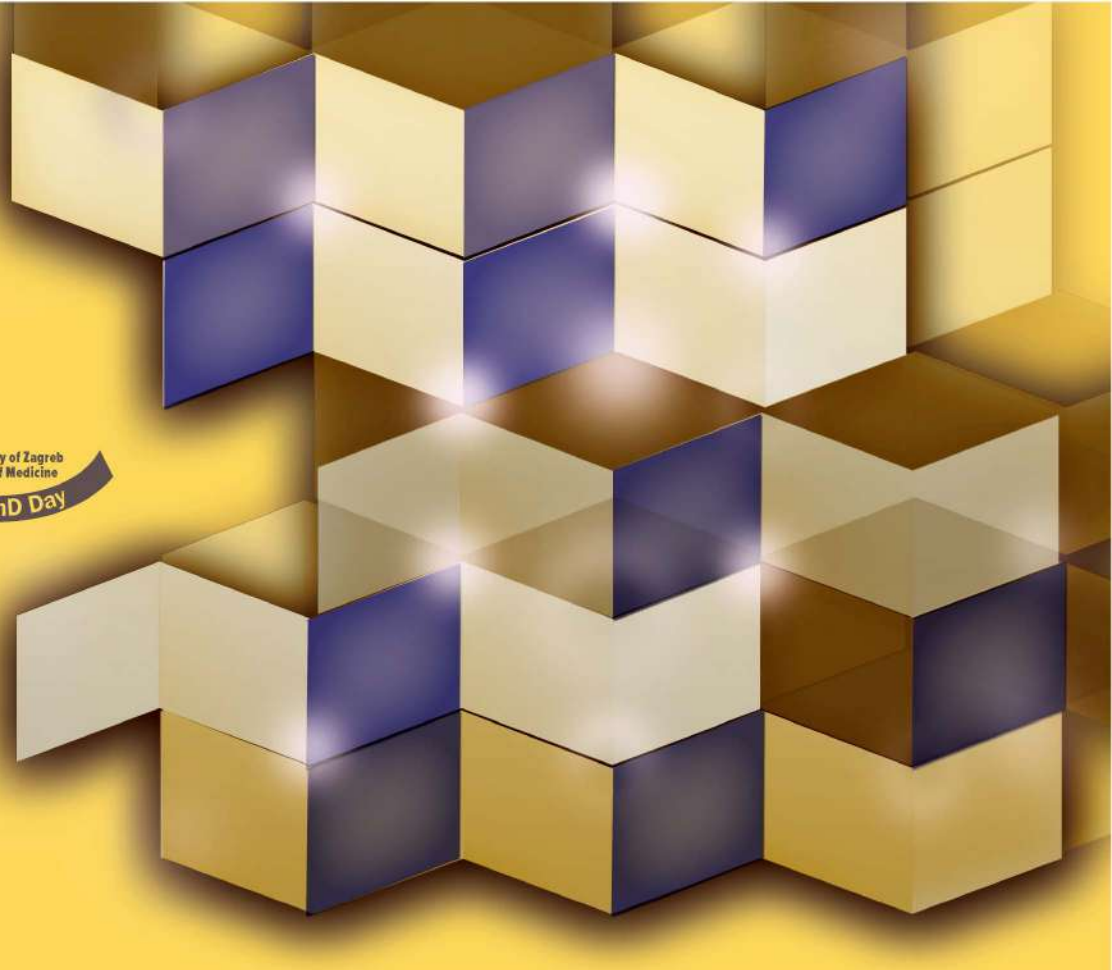

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Basic medical sciences - Preliminary research results

Poster Title: Ubiquitin E3 ligase Mid1 mediates subchondral bone resorption in a mouse model of rheumatoid arthritis

PhD candidate: Nina Lukač

Part of the thesis: Cellular and molecular mediators of subchondral bone destruction in arthritis

Mentor(s): Assoc. Prof. Nataša Kovačić, MD PhD

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Introduction: Subchondral bone resorption often accompanies synovial joint inflammation in rheumatoid arthritis (RA) and causes disability which is not reversible by currently available therapeutics. Using antigen-induced arthritis (AIA), a murine model of RA, we have shown that mice deficient for Fas gene (Fas -/-) develop an ameliorated form of AIA characterized by the absence of subchondral bone resorption. This non-resorptive arthritis is marked by a lower frequency of synovial myeloid cells, which down-regulate Mid1 gene. The objective of the study was to evaluate the role of Mid1 in bone resorption in AIA.

Materials and methods: C57BL6 wild-type (WT) and Fas-/- mice were immunized with methylated bovine serum albumin (mBSA) emulsified in complete Freund's adjuvant, and arthritis was induced by subsequent intra-articular injection of mBSA. Bone resorption was assessed by micro-CT. Synovial myeloid (CD11b+Gr-1+) cells from Fas -/- and WT mice were sorted using BD FACSAria and their transcriptome was further analyzed by Affymetrix ST 2.0 arrays. Bioinformatics analysis was performed using Bioconductor and differences in gene expression were confirmed by qRT-PCR. WT mice with arthritis were treated in vivo with metformin, which inhibits proinflammatory effect of Mid1, at daily dose 1g/kg, to assess its effect on the development of arthritis.

Results: Mid1 gene was up-regulated in sorted myeloid cells (logFC=2.01, p(BH-adjusted)=0.0003, limma+BH-adjustment) and bulk joint tissue (logFC=8.74, p=0.02, Welch-test) of WT mice in comparison to Fas-/- mice with ameliorated arthritis. Despite its position on X chromosome Mid1 expression in joints was not sexually dimorphic and was up-regulated in both male (logFC=1.92, p=0.006, T-test) and female WT mice (logFC=8.74, p=0.02, Welch-test) with arthritis (WT-AIA). Furthermore, expression was associated with an increase in knee diameter (ρ=0.68, p=0.03, Spearman's rank correlation) as well as with gene expression levels of pro-inflammatory cytokines in joints of mice with arthritis (IL-1: ρ=0.78, p=0.008; IL-6: ρ=0.70, p=0.025; TNF: ρ= 0.78, p=0.008, Spearman's rank correlation). Metformin treatment of WT-AIA mice ameliorated the severity of arthritis assessed by knee diameter (3.68±0.22mm WT-AIA vs. 3.30±0.17mm WT-AIA+metformin, p=0.01, T-test) and visual score (2.33±0.88 WT-AIA vs. 0.5±0.5 WT-AIA+metformin, 0-4 scale, p=0.003, T-test). Arthritis-induced epiphyseal trabecular bone volume loss was not significantly different in metformin treated group in comparison to non-immunized (NI) control group (40.08±4.07% WT-NI vs. 33.44±4.37% WT-AIA+metformin, p=0.056, ANOVA+Tukey-Kramer), whereas it was significantly reduced in non-treated mice with arthritis (40.08±4.07% WT-NI vs. 30.38±4.43% WT-AIA, p=0.004, ANOVA+Tukey-Kramer).

Discussion: Increased expression of Mid1 gene has already been reported to promote allergic airway inflammation, which is dependent on death receptor TRAIL. Results suggest the role of Mid1 as a novel mediator joint inflammation and subchondral bone destruction in arthritis, and a potential therapeutic target for inflammation-mediated joint destruction.

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MeSH/Keywords: Mid1, bone resorption, arthritis

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