P148 JAK-INHIBITION BY BARICITINIB AND TOFACITINIB AMELIORATES PATHOLOGICAL BONE LOSS

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Career situation of first and presenting author Student for a master or a PhD.

Introduction Many cytokines relevant to rheumatoid arthritis (RA) rely on the janus kinase – signal transducer and activator of transcription (JAK-STAT) signaling pathway. The JAK-inhibitors tofacitinib and baricitinib, targeting JAK3/JAK1 and JAK1/JAK2 respectively, have been approved for treatment of RA¹. While currently available therapies reduce inflammation, erosive damage in involved joints is still irreversible. However, preliminary data suggests an influence of JAK inhibition on local bone healing.

Objectives To study the role of JAK-inhibition in osteoblast and osteoclast-mediated bone homeostasis and its capacity to alleviate structural bone damage *in vivo*.

Methods For steady state analysis C57BL/6 (WT) mice received tofacitinib QD by oral gavage for 6 weeks. WT mice of the ovariectomy-induced osteoporosis model (OVX) obtained tofacitinib BID by oral gavage for 6 weeks. For the serum-induced arthritis model (SIA) WT mice received tofacitinib or baricitinib BID by oral gavage for 14 days. Readout covered serum cytokine levels (ELISA), μ CT and mRNA analysis of bone (qPCR) and clinical scoring. Murine osteoclasts (OC) were assessed for differentiation (TRAP staining) and resorption (Von Kossa staining). Murine mesenchymal stem cell (MSC)-derived and primary osteoblasts (OB) were analyzed for differentiation (qPCR) and function (Alizarin red staining).

Results In unchallenged WT mice, treatment with tofacitinib increased trabecular bone density in tibia and reduced RANKL/OPG ratio in serum. These results, along with elevated trabeculae numbers, also applied to spinal bone in tofacitinib-treated OVX mice. In SIA, baricitinib and tofacitinib ameliorated disease manifestation and inhibited trabecular/cortical bone loss. *In vitro* JAK-inhibition exhibited no effect on differentiation and function of OCs. However, it enhanced OCN expression in MSC-derived OBs at day 1 after osteoblastic induction and led to decreased Igf1 and increased Dkk1 expression at day 7. Accordingly, primary OBs showed reduced RANKL expression during JAK-inhibition. Moreover, both MSC- and primary OBs responded to JAK-inhibition with increased mineralization.

Conclusions Our findings indicate that JAK-inhibition by tofacitinib and baricitinib increases bone formation *in vivo*, in both steady-state and pathological conditions, presumably as a result of increased mineralization capacity by osteoblasts.

REFERENCE

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P149/006 HIGHER EXPRESSION OF SIGLEC-7/9 ON GRANULOCYTES AND MONOCYTES HAS A PROTECTIVE ROLE IN RHEUMATOID ARTHRITIS

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Career situation of first and presenting author Student for a master or a PhD.

Introduction Prominent features of rheumatoid arthritis (RA) are pain, joint swelling and erosion induced by massive infiltration of immune cells into the inflamed tissue. Among these immune cells, granulocytes and monocytes play a crucial role. Both express sialic acid-binding immunoglobulin-like lectins (Siglecs) –7 and –9 (in mice Siglec-E), trans-membrane proteins generally transmitting inhibitory signals through immunoreceptor tyrosine-based inhibitory motifs in their cytoplasmic tails. So far, there has been only limited research on the effects of Siglecs in RA.

Objectives To evaluate the potential role of Siglec 7- and –9 during disease progression in RA by comparing the expression on blood leukocytes with disease activity in RA patients. Additionally we monitored Siglec-E knockout mice in an experimental arthritis model.

Methods Blood samples from 45 healthy donors (HD) and 37 RA patients were analyzed by flow cytometry for Siglec-7 and –9 expressions on NK cells (CD14+/CD56+/CD3-), granulocytes (CD16+/CD19-) and monocytes (CD14+/CD16-). Expression was correlated with autoantibody positivity and disease severity.

Siglec-E knockout mice and wildtype controls were used in a serum transfer induced arthritis model and disease manifestation was monitored by measurement of paw swelling. Additionally we performed functional *ex vivo* assays to study Siglec impact on granulocytes and monocytes.

Results There was a diminished Siglec-7/9 expression on NK cells from RA patients, especially in highly CCP positive patients (>500 U/ml), while no differences were observed in neutrophils and monocytes compared to healthy controls. Interestingly we observed a correlation between a higher DAS28 score and lower Siglec-9 expression levels on granulocytes in seropositive patients.

Siglec-E knockout mice displayed higher disease scores and paw swelling in serum transfer induced arthritis, especially at the peak and the resolution phase. Functional studies unraveled that granulocytes are in a more active state if Siglec-7 and –9 are missing.

Conclusions Together our data support that Siglec-7/9 expression negatively correlates with pathogenesis and disease manifestation in RA patients. We showed *in vivo* and *ex vivo*, that Siglecs possess an important role concerning granulocyte and monocyte function and are capable of dampening immune response. Due to their inhibitory potential, Siglecs should be considered as potential therapeutic starting point in future studies.