Substantial amounts of anti-SAA1 Abs were observed in serially diluted IVIg, while there were 4-fold less anti-AGP Abs detected (Figure 2), which corresponds also to the ratio found in HBD (Figure 1).

Conclusion: Serum IgG Abs against SAA1 and AGP present in HBD, patients with systemic autoimmune diseases and in IVIg can be simultaneously quantified using a customized bead-based multiplex assay. These natural autoAbs found in IVIg could be endogenous immune-regulators of the acute phase response.

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THU0041 MESENCHYMAL STEM CELLS OF DIFFERENT ORIGINS EXHIBIT UNIQUE RESPONSES TO DIFFERENT INFLAMMATORY STIMULI

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Background: Mesenchymal stromal/stem cell (MSC) - based therapies represent promising avenues for treatment of various inflammatory and autoimmune diseases. Currently, a variety of fetal and adult tissues represent a good source of MSC, however further characterization of their effects, especially in an inflammatory environment, is needed.

Objectives: Firstly, to characterize MSC from different origins, namely bone marrow (BM), adipose tissue (AT) and umbilical cord (UC), after stimulation with TNF α , IL-1 β and serum amyloid A (SAA). Secondly, to determine the effects of MSC secretome on migration, proliferation and apoptosis of lung fibroblasts.

Methods: BM-, AT- or UC-MSC were isolated each from 3 healthy donors. The expression and secretion of analytes were studied in each cell type at basal level and following TNF α - (1 ng/ml), IL-1 β - (1 ng/ml) and SAA- (12 μ g/ml) stimulation using qPCR (SDF, CCL5, VCAM, PDE, PGC, IDO, VEGF, IGF) and Luminex technology (IL-6, IL8, MCP-1, ICAM, CH3L1, MMP1, MMP3, tenascin, uPA, HGF, VEGF), respectively. Normal healthy lung fibroblasts (NHLF) were used in the wound scratch assay and treated for 24h with 20% of MSC-conditioned media. For evaluation of BM-, AT- and UC conditioned media effects on proliferative and apoptotic activity, Ki-67-immunolabeled mitotic cells and caspase-3-immunolabeled cells were counted using fluorescence microscopy.

Results: Treatment of MSC with pro-inflammatory cytokines increased mRNA levels of SDF, CCL5, VCAM1, PGC and IDO, while levels of PDE-5A were down-regulated. The greatest increase in expression was observed in TNF α -stimulated MSCs, namely of two immunomodulatory molecules, CCL5 and IDO in AT-MSC (4396- and 928-fold change increase respectively). Secretome analysis showed highest secretion levels of IL-6, IL-8 and MCP1 after IL-1 β -activation in all 3 tissue sources. AT- and BM-derived conditioned media increased NHLF scratch closure, while UC-MSC decreased it. In non-inflammatory conditions, UC-, BM- and AT-MSCs conditioned media decreased the number of mitotic events in NHLF by an average of 40%. Importantly, only the conditioned medium derived from inflammatory cytokine-treated AT- and BM-MSC significantly decreased the mitotic rate of NHLF ($p < 0.01$). The number of apoptotic cells increased 3- to 8-fold after treatment with all MSC conditioned media, with UC-MSC showing the highest effect ($p < 0.01$).

Conclusion: Our results highlight specific roles of MSC from different tissue origins, as well as their response to environmental inflammatory stimuli and suggest that source selection might be critical for the success of treatment approaches in different diagnoses.

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THU0042 EFFECT OF SPLEEN TYROSIN KINASE (SYK)-INHIBITORS ON RHEUMATOID ARTHRITIS SYNOVIAL FIBROBLASTS

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Background: The spleen tyrosine kinase (syk) is an intracellular protein kinase involved in signal transmission processes of immune cells and non-hematopoietic cells, such as fibroblasts. Various syk-inhibitors are therefore currently being tested in preclinical and clinical studies, e.g. for the treatment of different types of cancer as well as autoimmune diseases. In preclinical studies, the syk inhibitor fostamatinib showed a pronounced anti-inflammatory effect on synovial fibroblasts (SF) from patients with rheumatoid arthritis (RA). These cells play an important role in the pathogenesis of RA by mediating matrix destructive processes. On the other hand, clinical trials have been only moderately successful due to the side effects and the limitation regarding increase in dosage. However, further inhibitors such as RO9021 or TAK-659 have been developed. They are characterized by a more specific kinase profile and therefore side effects could potentially be less severe. Whether these inhibitors also convey an anti-inflammatory effect on RASF has not yet been investigated.

Objectives: This study examines the effect of syk-inhibitors on the inflammatory response and functional behavior of activated RASF.

Methods: RASF were isolated from synovial tissue of patients with known rheumatoid arthritis during joint replacement surgery. RASF were pre-treated with different concentrations of RO9021 and TAK-659 and their vehicle control for 2h and additionally stimulated with IL-1 β (10 ng/ml) for 17h or with oncostatin M (OSM, 100 ng/ml) for 24h. Supernatants were collected and the concentration of IL-6 and MMP3 were determined by ELISA. The measurement of cell viability, cytotoxicity and apoptosis was performed to exclude possible cytotoxic or apoptotic effects of the syk-inhibitors. The RASF proliferation was detected by a BrdU-incorporation assay. The effect of syk-inhibitors on cell migration towards a FCS-gradient was measured by cell culture inserts.

Results: Both TAK-659 and RO9021 showed a significant reduction of the release of the pro-inflammatory cytokine IL-6 and the production of MMP3 in IL-1 β stimulated RASF. However TAK-659 showed a stronger effect on IL-6 reduction (48%, $p < 0.005$) than RO9021 (25%, $p < 0.05$) at 10 μ M. MMP3 decrease was also stronger with TAK-659 (92%, $p < 0.001$) than with RO9021 (59%, $p < 0.001$). This effect was apparently not restricted to IL-1 β because both inhibitors also decreased the OSM-induced IL-6 release of RASF by 85% ($p < 0.01$) with TAK-659 and 30% with RO9021 at 10 μ M. The proliferation of RASF was also reduced by both syk-inhibitors at 5 μ M and higher. The highest effect could be observed with TAK-659 for 80% and with RO9021 by 50% both at 15 μ M. The migration of RASF was also decreased by TAK-659 at 10 μ M ($p < 0.01$, $n = 3$). The effects were not mediated by induction of apoptosis or by cytotoxicity.

Conclusion: The syk-inhibitors TAK-659 and RO9021 at concentrations above 5 μ M reduce the inflammatory response, the migration and proliferation of RASF. If appropriate concentrations can be reached in vivo, these syk-inhibitors could offer a possibility to modulate the aggressive phenotype of RASF.

DISCLOSURE OF INTERESTS:

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THU0043 IL-25 ALLEVIATES RHEUMATOID ARTHRITIS BY INHIBITING TH17 IMMUNE RESPONSE

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Background: Rheumatoid arthritis (RA) is a prevalent common autoimmune disease characterized by chronic inflammation of the joint and synovial hyperplasia and progressive destruction of articular cartilage and bone. Accumulating evidence highlighted that an imbalance between pro-