that is partially TNF α -mediated. This suggests that the timing of exposure to S100A8/A9 is an important determinant for monocyte-to-osteoclast differentiation.

Disclosure of Interest None declared.

P075

TARGETING NF-KB SIGNALLING IN B CELLS: A POTENTIAL NEW TREATMENT MODALITY FOR ANCA-ASSOCIATED VASCULITIS

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Career situation of first and presenting author Post-doctoral fellow.

Introduction The pivotal role of B cells in the pathogenesis of autoimmune diseases such as ANCA-associated vasculitis (AAV) is well-established and further substantiated by beneficial therapeutic effects of rituximab (anti-CD20 B cell targeted therapy). However, this results in prolonged B cell depletion while long-lived plasma cells are not targeted. Thus, there is a need for novel therapeutics targeting the B-cell lineage in AAV. NF- κ B signalling pathways that act downstream of various B cell surface receptors, including the B cell receptor, CD40, BAFFR and TLRs, are crucially involved in B cell responses and may be suitable as novel targets.

Objectives To identify whether inhibition of NF- κ B signalling by novel pharmacological inhibitors is effective in targeting B cell responses in general and more specifically blocks (auto) antibody production and plasmablast differentiation in B cells from AAV patients.

Methods PBMC and sorted B cells from AAV patients and healthy donors were cultured with T cell-dependent (anti-IgM + anti CD40 + IL-21) and T cell-independent (CpG + IL-2) stimuli. NF- κ B signalling was targeted in these cultures by small molecule inhibitors of NF- κ B inducing kinase (NIK, non-canonical NF- κ B signalling) and Inhibitor of κ B kinase β (IKK β , canonical NF- κ B signalling). Downstream NF- κ B signalling and nuclear NF- κ B translocation was determined by Western blot and confocal imaging. Effects on B cell proliferation and differentiation were determined by CFSE dilution assays and flow cytometric analysis of B cell markers. (Auto)antibody production was measured by ELISA.

Results In B cells of AAV patients and healthy donors, targeting of NIK and IKK β effectively inhibited downstream non-canonical or canonical NF- κ B signalling, respectively. In a B cell stimulation assay, NIK and IKK β inhibition significantly reduced T cell-dependent (anti-IgM + anti-CD40 + IL-21) and T cell-independent (CpG + IL-2) B cell proliferation. In addition, B cell differentiation towards plasmablasts (CD27++/CD38+) and functional antibody production was attenuated by both NIK and IKK β inhibitors. Interestingly, the effects of NIK inhibition appeared to be B cell-specific as T cell proliferation was largely unaffected.

Conclusions These data demonstrate that inhibition of NF- κ B signalling in AAV B cells results in the modulation of various

B cell responses. Ongoing studies will indicate whether targeting of NF- κ B signalling in B cells may be an effective novel treatment modality for AAV.

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SYNOVIAL TISSUE FROM RHEUMATOID ARTHRITIS PATIENTS SHED THEIR ANTI-INFLAMMATORY – AND EFFEROCYTOSIS RECEPTOR MER

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

Introduction We recently showed that the tyrosine-protein kinase MER, a member of the TAM (TYRO, AXL, MER) receptor family plays a protective role in mouse models of rheumatoid arthritis (RA).^{1 2} In both humans and mice, MER can be proteolytically cleaved and this soluble MER (sMER) acts as a decoy receptor for the TAM receptor ligands Growth Arrest-Specific 6 (GAS6) and Protein S. A recent study showed that sMER correlates with disease activity and bone destruction in RA patients.³ In this study, we measured whether sMER was also increased in the circulation of arthritic mice and in synovial fluid and conditioned medium of synovium explants from RA patients.

Methods KRN serum transfer arthritis was induced and mice were sacrificed at day 7 of full blown arthritis. Ankle joints were immunostained for MER (n=15) and sMER levels were measured in serum at day 0 and 7 (n=13). Human synovial explants of RA (n=15) and osteoarthritis (OA)(n=17) patients were immunostained for MER. Synovial explants were cultured 24 hours and released sMER and GAS6 was measured by ELISA. The level of sMER, sAXL, GAS6, IL-6, TNF α , IL-1 β was measured in synovial fluid of RA (n=21) and OA patients (n=11) by ELISA or multiplex array.

Results Serum sMER levels were increased in arthritic mice whereas the amount of MER⁺ synovial cells was unaltered. In human RA synovium, numerous MER⁺ macrophages were present in the lining and sublining. We found significantly enhanced sMER and GAS6 in the synovium culture media (p=0.0045 and 0.0177) and synovial fluid (p=0.0001 and 0.0189) of RA patients as compared to OA patients. Soluble AXL levels in synovial fluid of RA and OA patients was high but did not differ (p=0.5256). In synovial fluid of RA patients, sMER and GAS6 did not correlate with TNF α (Pearson r=0.5587) or IL-1 β (Pearson r=-0.1667), and negatively correlated with IL-6 (Pearson r=-0.9608).

Conclusions Systemic sMER levels are enhanced in experimental arthritis, in line with the observation of Xu et al in RA patients. Synovial shedding of MER was higher in RA- than in OA patients, but this was not reflected by differences in MER positive synovial cells. As sMER acts as a decoy