P102 SENESCENCE OF RENAL RESIDENT CELLS IS ASSOCIATED WITH IMPAIRED RENAL FUNCTION IN LUPUS NEPHRITIS

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Background Renal fibrosis is a feared complication of Lupus Nephritis (LN), and is associated with irreversible loss of kidney function. In our previous experiments, we found that intrarenal infiltration by immune effectors in LN correlates with the development of renal fibrosis. Here, we wondered whether cellular senescence, through its typical secretome (known as senescence-associated secretory phenotype or SASP) or through the accumulation of functionally incompetent cells, are part of the renal functional impairment and fibrotic process in LN.

Methods Microarray data (Illumina HumanHT-2 v4 Expression BeadChip), obtained by our group from 32 human LN kidney biopsies and 8 controls were mined using GeneSpring software in order to study the expression of SASP-associated transcripts. Senescent cells were identified in human LN kidney biopsies using an anti-p16 antibody (Roche Diagnostics). Evaluation of glomerular activity and chronicity indices, glomerular and interstitial fibrosis was performed using conventional or quantitative scores on HE- PAS- and Red Sirius-stained sections. Clinical and biological data were retrieved from the medical files of the patients.

Results Mining of microarray data obtained from 32 LN kidney biopsies indicated that SASP-associated transcripts (e.g. IGFB4, VCAM1, TGFb2, COL1A2, MMP7) were significantly overexpressed in kidney biopsies characterized by the presence of adaptive immune cell infiltrates in the interstitium and lower renal function. Expression of SASP-associated transcripts correlated significantly with the expression of b galactosidase (GLB1), a key regulator of the senescence process.

In a pilot experiment, we stained LN renal biopsy sections using anti-p16 antibodies, in order to detect the presence of senescent cells. We found a positive stain in podocytes and renal tubular cells from 8 LN patients. The number of positive cells correlated positively with the number of intrarenal CD8-positive cells and the amount of fibrosis in these samples, while it correlated negatively with renal function (eGFR).

Conclusion Our data show that the presence of senescent podocytes and renal tubular cells in LN kidney biopsies correlates with fibrotic changes and impaired renal function. Characterization of senescent cells in a larger cohort of LN biopsies is ongoing. Our observations are in line with the hypothesis that inflammation-accelerated senescence links the presence of activated adaptive immune effectors in the lupus kidney and the development of fibrosis.

P103 ABERRANT DNA DAMAGE RESPONSE OF B CELL POPULATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background SLE patients demonstrate increased levels of DNA damage, defective DNA repair and polymorphisms in genes required for maintaining genomic stability. Effective DNA damage response is crucial for the generation of antibodies by B cells while excessive production of autoantibodies is a universal feature of the disease. We sought to investigate DNA damage response/repair a) in total B cells and their subtypes in several tissues of a murine SLE model and b) in transcriptomic data derived by B cell subtypes from the peripheral blood of SLE patients.

Methods Flow Cytometry analysis was performed for total B cells or their subtypes combined with γH2AX DNA damage marker in blood, spleen, lymph nodes and bone marrow (BM) of NZBW/F1 murine SLE model (pre-diseased, n=5/diseased, n=4) and in the blood of SLE patients (n=7) compared to healthy controls (HC, n=9). Gene set enrichment analysis (GSEA) was performed in a published B cell populations transcriptomic dataset[1] derived from the blood of SLE patients (n=9) compared to HC (n=12).

Results Increased γH2AX expression was identified in B cells from blood and BM of diseased mice compared to pre-diseased ($p=0.02$) as well as from blood of SLE patients with high disease activity compared to HC ($p=0.02$). Deregulated γH2AX expression levels were detected in distinct B subtypes of diseased mice ($p<0.05$). GSEA showed significant enrichment of DNA damage response/repair pathways in B subtypes from the blood of SLE patients compared to HC (**table 1**).

Abstract P103 Table 1 Enriched DNA damage response/repair Gene Ontology processes and pathways in SLE B cell populations

B CELL SUBTYPE	GENE ONTOLOGY PROCESSES & PATHWAYS RELATED TO DNA DAMAGE RESPONSE & REPAIR (GSEA, FDR<0.25)
Resting Naive ($CD19^+IgD^+CD27^-MTG^-CD24^+CD38^+$)	• DNA DAMAGE RESPONSE SIGNAL TRANSDUCTION BY P53 CLASS MEDIATOR • INTRINSIC APOPTOTIC SIGNALING PATHWAY IN RESPONSE TO DNA DAMAGE • NUCLEOTIDE EXCISION REPAIR PREINCISION COMPLEX STABILIZATION • G2M CHECKPOINT • MISMATCH REPAIR
Transitional 3 ($CD19^+IgD^+CD27^-MTG^+CD24^{mid/+}CD38^-$)	• ATM PATHWAY • G2M CHECKPOINT • BASE EXCISION REPAIR AP SITE FORMATION • DNA DAMAGE TELOMERE STRESS INDUCED SENESCENCE
Activated Naive ($CD19^+IgD^+CD27^-MTG^+CD24^-CD38^-$)	• G2M CHECKPOINT • GENOTOXIC DAMAGE 4HR
Isotype-Switched Memory ($CD19^+IgD^-CD27^+$)	• CELL CYCLE CHECKPOINT • G2 DNA DAMAGE CHECKPOINT • DNA REPAIR
Double-Negative ($CD19^+IgD^-CD27^-CXCR5^-$)	• BASE EXCISION REPAIR • NUCLEOTIDE EXCISION REPAIR • MISMATCH REPAIR • DNA REPLICATION

Conclusions NZBW/F1 murine SLE model presents with increased DNA damage in blood- and BM-derived total B cells and subtypes. Peripheral B cells and distinct B subpopulations show aberrant DNA damage response and repair in SLE patients.