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 β 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.

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.