Interestingly, p16Ink4a seems to be associated with CD8 T cell infiltration, renal cell compartments. Cellular senescence is the irreversible arrest of the cell immunity but also hosts pathogenic mechanisms determining renal disease. Decision are hence eagerly sought, as are novel therapeutic targets. It is clear that lupus kidney is not simply a passive target of systemic autoimmunity but also hosts pathogenic mechanisms determining renal disease severity. These likely involve both the infiltrating immune and resident renal cell compartments. Cellular senescence is the irreversible arrest of the cell cycle through the accumulation of cyclin dependent kinase (CDK) inhibitors such as p16Ink4a (CDKN2A). Senescent cells nevertheless remain metabolically active and undergo morphological and physiological changes, including the acquisition of a pro-inflammatory, pro-fibrotic senescence-associated secretary phenotype (SASP). Aberrant accumulation of senescent cells has been observed in renal aging and pathology. We recently described the presence of p16Ink4a-positive cells (a senescence hallmark) in LN renal biopsies, and their association with baseline disease severity and 5 year outcome. In addition, we observed a spatial co-distribution between tissue-infiltrating CD8 T cells, senescent kidney cells, suggesting a functional genetic interaction between them.

Objectives: We hypothesize that cellular senescence may contribute to tissue damage in a few different ways: (a) Presentation of senescence-associated antigens that attract and activate CD8 T cells. Alternatively, CD8 T cells may be sequestered to the kidney by other means, and may contribute to senescence-induction through the secretion of certain cytokines; (b) Secretion of pro-fibrotic, pro-inflammatory molecules, and/or (c) Functional incapacitation of kidney cells, particularly renal progenitor cells, responsible for repairing and restoring kidney function upon damage. In parallel with our work on patient samples, we aim to establish a relevant pre-clinical model in which we may test for the effects of senescence and senescence-directed interventions, on kidney damage.

Methods: Here, we assess for whether the B6.Sle1.Sle2.Sle3 spontaneous lupus-prone mouse may serve as an appropriate model in which to study the role of cellular senescence. We evaluated the presence and distribution of p16INK4a-positive cells by immunohistochemistry, and tested for an association with CD8 T cell infiltration and renal and systemic disease, in a cohort of 21 B6.Sle1.Sle2.Sle3 female mice. This is now being followed-up by a systematic, longitudinal study for the time of onset of different renal and systemic disease parameters, as compared to the detection of renal cell senescence in this well-characterized model.

Results: As observed in renal biopsies from LN patients, staining for p16INK4a-positive cells was heterogenous between mouse kidney samples. Interestingly, p16INK4a seems to be associated with CD8 T cell infiltration, renal impairment and damage, independently of age. This will now be confirmed using the "senescence-associated β-galactosidase" assay, the other classic measure of cellular senescence.

Conclusion: We report the occurrence of cellular senescence, and its correlation with CD8 T cell infiltration and disease severity, in the B6.Sle1.Sle2.Sle3 mouse model of lupus. These mice provide a platform for preclinical research, which to test for the role of cellular senescence in the pathogenesis of LN in vivo (by the induction vs. selective elimination of senescent cells). They also serve as an alternative source (alongside patient samples) of cells for in vitro functional assays to test for the effects of senescent renal cells on CD8 T cells and vice versa.

REFERENCES:

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