had nonsignificant results, possibly due to the small sample size, especially for mortality.

The multivariable models were adjusted for baseline covariates including demographic variables (age, sex, location of residence, neighborhood income quintile), indicator of having RA or SLE (not considered for individual RA and SLE patients cases), health resource utilization (hospital visits, physician and specialist visits including rheumatologist, nephrologist, and psychiatrist visits), medication usage (statins, other cardiovascular drugs, hormone replacement therapy, glucocorticoids, anticoagulant therapy, Cox-2 inhibitors, immunosuppressive drugs), comorbidities (hypertension, chronic obstructive pulmonary disease, angina), and the Romano adaptation of the Charlson comorbidity index for administrative data. Also, the time-varying variables of health resource utilization, medication usage, Charlson comorbidity index, and comorbidities were used to calculate weights in marginal structural model.

Conclusions SLE and RA patients' adherent to AM therapy had 53% and 30% lower risk of CVD mortality and incident CVD events, respectively, than partially adherent patients.

500 – Lupus nephritis

501 ANTI-LG3 ANTIBODIES CONTRIBUTE TO MICROVASCULAR LOSS AND FIBROSIS IN LUPUS NEPHRITIS

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Background Lupus nephritis (LN) is a common and serious manifestation of systemic lupus erythematosus (SLE) and 30% of cases, affected patients progress to end stage renal disease (ESRD). Microvascular damage is an emerging contributing factor to LN renal dysfunction leading to end stage renal disease. We have shown that vascular injury derived apoptotic exosomes can trigger SLE autoantibodies as well as autoantibodies targeting perlecan/LG3 (anti- LG3). We have also unraveled biomarkers and effector roles of anti-LG3 in kidney vascular damage in both native and transplanted kidneys. We hypothesize that anti-LG3 responses contribute to microvascular damage of importance in LN development.

Methods Longitudinal bleeds were performed on SLE prone NZB/NZWf1 and control mice. Circulating Anti-LG3 IgG levels were measured by ELISA. 26 weeks old NZB/NZWf1 mice were infused with anti-LG3 or control IgG, every second day for 3 weeks. Kidneys were harvested at sacrifice for renal histology and immunohistochemistry analyses. PTC capillary loss was evaluated with MECA-32 staining and renal interstitial fibrosis aSMA and Collagen IV staining.

Results Elevated levels of anti-LG3 are found in SLE prone mice, compared to control mice. Importantly, NZB/NZWf1 mice passively transferred with anti-LG3 exhibited significantly increased interstitial inflammation, PTC capillary loss, and renal interstitial fibrosis in the absence of glomerular abnormalities (crescents and proliferation), compared to mice transferred with control IgG.

Conclusions These observations suggest that anti-LG3 antibodies are elevated in SLE and show a tropism specific for the interstitial microvasculature, contributing to microvascular loss and fibrosis. A better understanding of the impact of these novel biomarkers and effector will improve identification, prediction, and management of LN.

502 ENVIRONMENTAL ADAPTATION AND TISSUE INJURY IN LUPUS

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Background Tissue injury with progressive damage is a major cause of morbidity and mortality in SLE. Yet, there is limited knowledge of the mechanistic pathways that contribute to tissue injury in lupus. We hypothesize that local environmental factors dictate effector function of tissue-infiltrating immune cells in target organs in SLE, to initiate and sustain damage, with therapeutic targeting of these maladaptive changes able to reverse damage. Our hypothesis is based upon the idea that local microenvironment naturally responds to stress or insult, such as mediated by glomerular immune complex deposition or environmental damage to the skin, with changes in the local microenvironment affecting immune-cell phenotype and function.

Methods and Results To identify tissue-adaptive pathways mediated by the local microenvironment that initiate and sustain organ injury, we dissected tissue-infiltrating T cells in the lupus kidney, building upon the longstanding observation that T effector cells are necessary for the local inflammatory response. For example, tissues become hypoxic as a common denominator as an appropriately physiologic response occurring at sites of pathogen replication or in tumors to ensure lymphocyte survival and effector function. The kidney, naturally hypoxic at the corticomedullary junction and in the medulla, becomes even more hypoxic during inflammation. We demonstrated that upon renal infiltration, T cells adapt to the hypoxic environment, without exhaustion, to ensure their survival and effector capability, with remodeling of metabolic and epigenetic pathways with tissue damage driven by a hypoxia-dependent, transcriptionally regulated inflammatory gene program. Tissue hypoxia was initiated by autoantibody-dependent glomerular immune complex formation, with subsequent renal entry of T cells that environmentally adapt with tissue-damaging effector function of a type 1 (Th1 or Tc1) phenotype. Survival was sustained by genetic and metabolic reprogramming of CD4⁺ and CD8⁺ T cells, including alteration in cell death and energy utilization pathways. Selective genetic, or more practically, pharmacologic blockade of tissue-adaptive pathways dampened activated T-cell function, reversing tissue hypoxia and alleviating established damage. The same pathways are operative in human lupus nephritis.

Conclusions We demonstrate that upon infiltration into the kidney, T cells adapt to the local environment to ensure their survival and effector capability, with remodeling of metabolic pathways. Although beneficial to the host upon local pathogen invasion, such changes in lupus are maladaptive, leading to tissue damage. Understanding phenotypic changes in renal-infiltrating immune cells can lead to therapeutic targeting with disease amelioration.