prednisone allowed to 15 mg/d; Non responder = not meeting previous definitions.

Results A total of 127 patients were included: 48 (38%) with pure proliferative LN (class III or IV), 41 (32%) with mixed LN (III or IV +/- V), and 38% (30%) with pure membranous LN. Response was complete in 34 (27%), partial in 29 (23%), and none in 64 (50%). There were no urinary biomarkers at baseline that predicted response. We then analyzed the changes in urinary proteins at 3 months compared to baseline. Patients who responded at 1 year showed an early decline in 51 urinary proteins led by CD163, IL-16, and macrophage mannose receptor (CD206) (figure 1A) which matched the proteomic signature associated with histological activity (figure 1B). No changes were observed in nonresponders. The decline of several urinary biomarkers at 3 months outperformed a decline in UPCR (clinical standard) in predicting the 1 year response (figure 2A). In particular, a decline of CD163 predicted 1 year response in ROC analysis with an area under the curve (AUC) of 83% compared to an AUC of 75% for UPCR decline (figure 2B). In proliferative LN, urinary biomarkers displayed superior performance with an AUC of 91%, 86%, and 78% for the decline of CD206, CD163, and UPCR, respectively (figure 2C-D). Pathway enrichment analysis identified leukocyte activation, neutrophil degranulation, and matrix degradation as the main pathways reduced at 3 months in responders.

Conclusion An early decline in urinary biomarkers of histological activity is associated with proteinuric response at 1 year. These findings indicate that effective immunosuppression induces by three months an immunological response in the kidney that can be noninvasively monitored in the urine. Biomarkers of immunological response outperformed early decline of UPCR, the standard of care, in predicting 1-year proteinuric response, especially in proliferative LN. Because biomarkers of immunological response parallel intrarenal activity, they could detect early treatment response/failure and allow early treatment changes. They could serve as surrogate endpoints in clinical trials. Longitudinal studies are needed to confirm that this immunological response is a better predictor of long-term kidney function preservation than proteinuric responses.

Lupus Nephritis

1113 THE TRANSCRIPTOMIC LANDSCAPE OF NEPHRITIC KIDNEYS REVEALS MECHANISMS FOR END ORGAN RESISTANCE TO DAMAGE IN LUPUS-PRONE MICE

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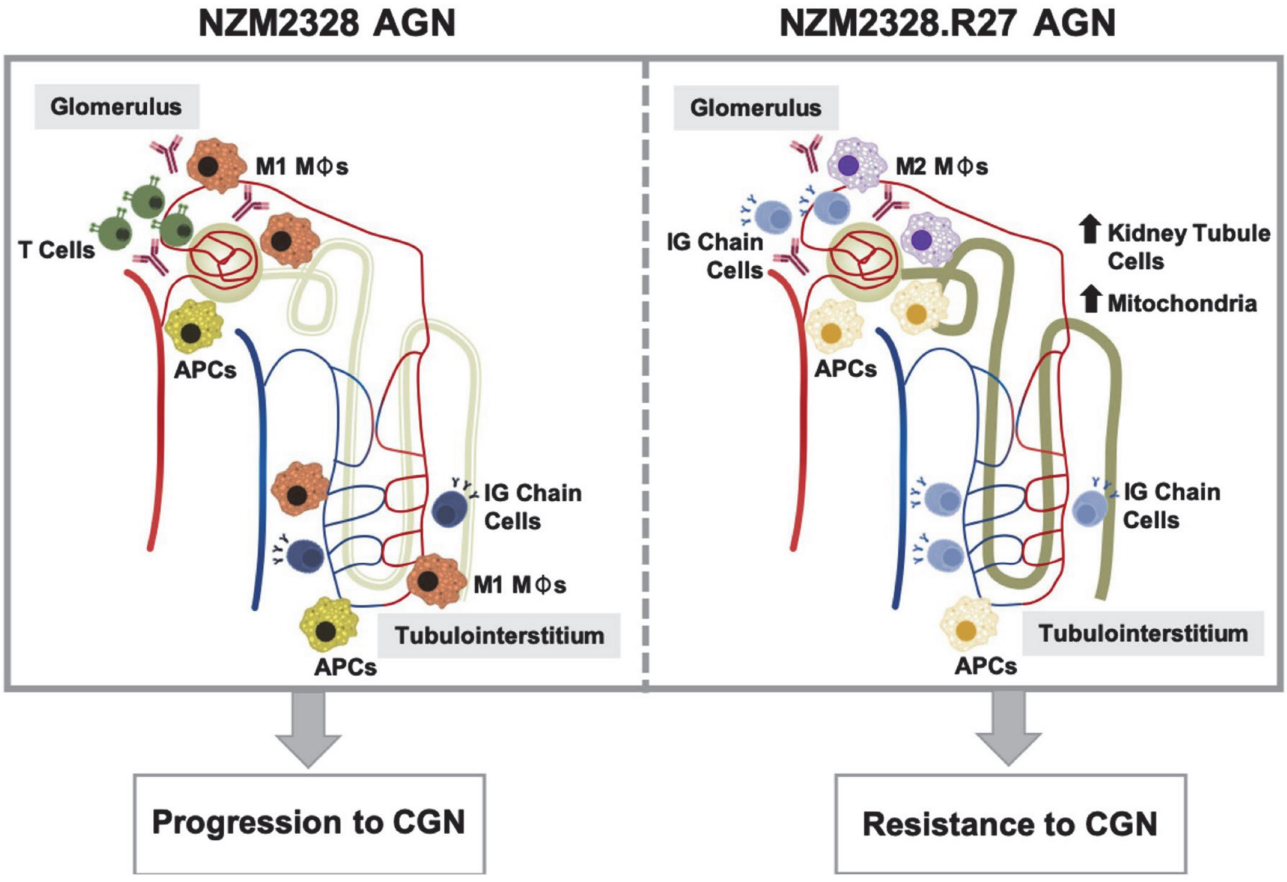
Background Pathologic inflammation is a major driver of kidney damage in lupus nephritis (LN), but the immune mechanisms of disease progression and risk factors for end organ damage are poorly understood. Previous studies established the NZM2328 lupus-prone mouse strain as a model for human proliferative glomerulonephritis (GN). These studies determined that disease in female NZM2328 mice presents in acute (AGN) and chronic (CGN) stages, each of which was associated with genetic loci (*Agnz1* and *Cgnz1)*. In addition, male mice and the congenic NZM2328.R27 strain were found to be resistant to the development of chronic nephritis. To characterize molecular profiles through the development of LN, we carried out gene expression analysis of micro-dissected kidneys from lupus-prone NZM2328 mice at different stages of disease severity and examined male and R27 mice as a means to define pathogenic processes associated with disease progression. Gene expression analysis of human LN patients was carried out to determine whether similar molecular profiles could be identified in human LN kidneys.

Methods Kidneys from NZM2328 and R27 mice were harvested and the stage of GN was confirmed by histological classification at regular intervals of disease progression. Tissues from young mice, before disease development, were used as a control for diseased mice. Laser capture microdissection was used to isolate glomeruli and tubulointerstitial tissue from control and diseased mice. Total RNA was extracted and hybridized to Affymetrix Mouse Clariom D (NZM2328 and R27 female) or Mouse 430 v2.0 (NZM2328 male) arrays. Differential expression (DE) analysis, gene set variation analysis (GSVA), and linear regression were utilized to define the stages of GN in NZM2328 mice and identify immune populations and processes associated with disease progression. Human orthologs of selected murine gene signatures were utilized for GSVA of two gene expression datasets from kidneys of human LN patients.

Results Gene expression profiling identified a continuum of inflammatory processes associated with progression from acute inflammatory to chronic destructive disease initiated in the glomeruli and progressing to the tubules. AGN mice exhibited evidence of immune cell infiltration including enrichment of inflammatory M1-like macrophages and activated lymphocytes (figure 1). We also uncovered a newly recognized transitional (TGN) stage in which we observed the greatest level of immune activity and that served as a critical checkpoint driving progression to the CGN stage and de-enrichment of kidney tissue cells. Male mice exhibited minimal immune infiltration in the glomeruli resulting in non-progressive renal pathology. Immune infiltrates in the glomeruli of R27 mice expressed a regulatory gene signature and especially a dominance of M2-like macrophages. Moreover, R27 mice manifested an enhanced kidney tubule signature, with evidence of increased mitochondrial and metabolic activity consistent with a functional resistance to cellular damage. The robust tubule signature was associated with the absence of an immune/inflammatory gene signature. Numerous genes in the R27 genetic region were upregulated in NZM2328 nephritic kidneys and could contribute to the protective effect of this interval on the evolution of LN. The gene expression profiles of human LN were similar to those noted in the NZM2328 mouse suggesting comparable stages of LN progression.

Conclusion Transcriptome analysis revealed distinct immune profiles for AGN, after initial IC deposition in the kidney glomerulus, TGN in which inflammatory cell and pathway enrichment is at its peak, and CGN in which the accumulated insults result in irreversible damage to the kidney tissue. In addition, we identified distinct mechanisms of resistance to chronic disease based on differences in gender and genetics. Using a gene expression-based clustering approach, we identified a core set of gene signatures able to classify disease stages



Abstract 1113 Figure 1 Graphical model of AGN in NZM2328 and R27 mice. Model summarizing differences in immunologic gene signature enrichment between female NZM2328 and R27 mice with AGN and their proposed impact on the development of chronic disease.

of murine GN into molecular endotypes that effectively translate to human LN patients. Therefore, this work provides a foundation for improved classification of LN based on molecular endotypes and illustrates the applicability of murine models to better understanding human disease.

Lay Summary Systemic lupus erythematosus (SLE) is an autoimmune disorder that can affect a variety of tissues, including the kidney. Lupus nephritis (LN) is one of the most severe organ manifestations of SLE and affects approximately 40% of adult lupus patients with 10-20% of patients developing end-stage renal disease (ESRD). Therefore, there remains a need to understand the risk factors for chronic disease and the stages of inflammation leading to ESRD in greater detail. Mice that develop spontaneous lupus-like disease serve as important tools for understanding lupus pathology and testing potential therapies for lupus patients. Previous studies have established the NZM2328 lupus-prone mouse strain as a model for human LN. We have used gene expression analysis of NZM2328 mice at different stages of disease to understand the pathogenesis of lupus nephritis and, in particular, immune populations and processes associated with the progression from acute to chronic disease. We characterized molecular profiles associated with acute inflammatory and chronic, destructive disease as well as a transitional stage with the highest degree of immune activity ultimately leading to kidney damage and end stage disease. We also identified mechanisms of resistance to chronic disease based on differences in gender and genetics, which altered the nature of inflammation in the kidneys of diseased mice. In addition, we demonstrated similarities in gene expression profiles between human lupus and lupus-prone mice that provide evidence for the applicability of mouse models to better understanding disease progression in human lupus patients.

1114 PARENCHYMAL INFγ RESPONSE REGULATES MURINE LUPUS NEPHRITIS IN A PD-L1 INDEPENDENT FASHION

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Background/Purpose Lupus nephritis is the most common life-threatening end-organ complication of SLE. Interstitial infiltrates, specifically T cells, are major predictors of disease outcomes. We recently determined that kidney-infiltrating T cells (KITs) are suppressed after kidney infiltration and exhibit an exhausted phenotype. We hypothesize that one mechanism of suppression is an IFNγ inducible immunosuppressive on the tissue parenchyma. Previously we and others have shown that PD-L1 is upregulated on the parenchyma of lupus nephritis patients and lupus-prone mice. KITs have high expression of PD1 when compared to lymphoid T cells from the same mouse. Furthermore, IFNγ is the major inducer of PD-L1.

Therefore, we postulated that IFNγ induces a protective program mediated by PD-L1 which results in suppresses immune destruction of the kidney in lupus nephritis.