NIH roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

II-19 ELEVATED PLASMA CELL-FREE MITOCHONDRIAL DNA DEFINES A SUBGROUP OF LUPUS PATIENTS WITH MEMBRANOUS LUPUS NEPHRITIS

[1]**David R Fernandez***, [2]Maria A Pabon, [1]Mikhail Olferiev, [2]Ana C Hernandez, [2]Faryal Malick, [1]Leila Khalili, [2]Kiichi Nakahira, [2]Augustine MK Choi, [1]Mary K Crow. *[1]Hospital for Special Surgery, New York, NY, United States; [2]Weill Cornell Medical College, New York, NY, United States*

10.1136/lupus-2016-000179.49

Background Systemic lupus erythematosus (SLE) is an autoimmune disease with protean manifestations, characterised by production of antibodies against nucleic acids and upregulation of type I interferon-inducible genes in a majority of SLE patients. The principal drivers of this interferon signature are still not well understood. Recent work has shown that oxidised mitochondrial DNA released by neutrophils can stimulate plasmacytoid dendritic cells to produce interferon-α.[1] We hypothesised that cell-free mitochondrial DNA might contribute to type I interferon production in SLE, and we sought to examine whether cell-free mtDNA levels were increased in SLE patients relative to controls, or during disease flares.

Materials and methods A retrospective analysis was performed using banked plasma samples from 164 patients in our SLE cohort along with 57 banked plasma samples from healthy donors. DNA was isolated from the plasma samples and real-time quantitative PCR was performed, amplifying a target sequence in the mitochondrially-encoded gene NADH dehydrogenase I, as previously published.[2] In-depth clinical phenotyping of SLE patients in the cohort was performed and used to define subgroups of SLE patients, as well as the specific disease manifestations present during flares.

Results No significant difference was seen in cell-free mtDNA in plasma from SLE patients versus healthy donors (HD – 3060.3 copies/uL, N = 57, SLE - 3845.5 copies/uL, N = 164, p = 0.22). However, cell-free mtDNA levels were elevated in a subset of SLE patients with a history of membranous lupus nephritis, including those with a component of proliferative nephritis (WHO class V/III+V/IV+V), relative to patients with proliferative nephritis alone (WHO class III or class IV) (5313.9 copies/uL, N = 34 vs. 2062.5 copies/uL, N = 17, p = 0.02). A subset of 70 patients had multiple samples collected at visits before, during, and after flares of disease activity. Cell-free mtDNA levels rose at the peak of disease activity as assessed by SLEDAI score in 11/16 flares of class V/III+V/IV+V nephritis (p = 0.04), while it only did so in 4/11 of the remaining nephritis flares. In contrast, cell-free mtDNA rose at the peak of disease activity in only 4/20 flares where alopecia was present (p = 0.02).

Conclusions Cell-free mtDNA levels are elevated in a subset of SLE patients with a history of membranous nephritis, and were more likely to rise during flares of membranous nephritis versus other types of disease flares.

Acknowledgements Supported by a Lupus and Antiphospholipid Centre of Excellence Research Fund Award

REFERENCES

1 Lood C, *et al*. Neutrophil extracellular traps enriched in oxidised mitochondrial DNA are interferogenic and contribute to lupus-like disease. *Nat Med* advance on, 2016
2 Nakahira K, *et al*. Circulating mitochondrial DNA in patients in the ICU as a marker of mortality: derivation and validation. *PLoS Med* 2013;**10**:e1001577; discussion e1001577

II-20 RELEVANCE OF MOUSE LUPUS MODELS OF LUPUS NEPHRITIS TO PROGRESSION OF CKD

[1]Celine C Berthier, [1]Matthias Ketzler, [2]**Anne Davidson***. *[1]Internal Medicine, Nephrology, University of Michigan, Ann Arbour, USA; [2]Feinstein Institute for Medical Research, Manhasset NY 11030, USA*

10.1136/lupus-2016-000179.50

Background Lupus nephritis progresses to chronic kidney disease (CKD) in an unacceptably high proportion of affected individuals. It is difficult to predict who is at risk for this complication and may therefore need more intensive therapy. Risk for progression of CKD in humans is associated with an interstitial molecular signature containing 68 genes (Ju W *et al*, Sci Transl Med, 2015). Of these, a decrease in renal expression of EGF with a concomitant increase in urinary EGF improves the ability to predict CKD expression.

Materials and methods To determine whether these 68 genes can be used in pre-clinical studies to model disease and therapeutic responses, we analysed microarray data of kidneys from three mouse lupus strains at various disease stages and after remission induction. Renal macrophage gene expression was assessed using RNASeq.

Results 64/68 genes have mouse gene IDs and 61/64 are represented on the mouse microarray chip. Of these 49 (80.3%) were regulated in the same direction as in humans in at least one strain (38 in NZM2410 mice, 44 in NZW/BXSB mice, 33 in NZB/W mice and 28 common to all three strains). Few genes were unique to a single strain: of these, collagen genes were uniquely expressed in nephritic NZW/BXSB mice. To determine which genes could distinguish early from established disease we compared the profiles of newly proteinuric NZB/W mice to those of NZB/W mice with established disease. 9 genes, including EGF and TIMP1 only became abnormally regulated during established disease, confirming their association with CKD progression. Most of the CKD associated genes normalised after immunosuppression but tended to drift back to their abnormal values during impending relapse. Some of the abnormally regulated genes are derived from macrophages/DCs. Using RNASeq analysis of isolated renal macrophages from NZB/W mice we showed that macrophage restricted C1qa has a similarly high expression level in young and nephritic renal macrophages. Therefore the increased renal expression of this gene can be used as a biomarker of increased macrophage infiltration, a known poor prognostic feature in human lupus nephritis.

Conclusions Mice with lupus nephritis have a strikingly similar pattern of CKD-related gene expression to humans and these genes can be used to track therapeutic responses. Downregulation of EGF and upregulation of TIMP1 are markers of progressive disease in mice as in humans and C1qa can be used as a marker of macrophage infiltration. The fibrosis signature is best modelled in NZW/BXSB mice.