CE-47 MOLECULAR IMAGING OF THE KIDNEY IN LUPUS NEPHRITIS TO CHARACTERISE RESPONSE TO TREATMENT

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Background The response of lupus nephritis (LN) to treatment is assessed by clinical criteria, usually proteinuria and renal function, alone. The consequences of treatment for the kidney at the molecular level have not been explored in human LN, but could have important implications for modifying therapy to improve renal outcomes in LN. In this investigation changes in intra-renal transcript expression were measured and correlated with response in a LN cohort that underwent serial kidney biopsies.
Methods SLE patients suspected of having LN had a kidney biopsy for diagnosis (Bx1) and patients with proliferative LN (n = 19) were induced with high-dose corticosteroids plus either MMF or cyclophosphamide. After completing induction therapy, approximately 6 months, patients had a second kidney biopsy (Bx2) to determine histologic response to therapy. Intra-renal transcript expression was measured in Bx1 and B × 2 using Nanostring technology and a panel of over 500 immune response genes. Patients were segregated by clinical response at 6 months into group of complete responders (n = 5, CR) and a group of non-responders (n = 4, NR). Changes in transcript expression were compared between Bx1 and B × 2 in each responder group and between responder groups.
Results Compared to healthy control kidneys (pre-implantation living donor transplant kidney biopsies, n = 4), the CR group had 21 differentially-expressed transcripts at B × 1 and 28 at B × 2. In contrast the NR had 45 and 103 differentially-expressed transcripts at B × 1 and B × 2, respectively, compared to controls. The profiles of these differentially-expressed genes indicated that the type 1 interferon, the alternative complement and T cell signalling pathways discriminated CR from NR. At B × 1 transcripts regulated by type 1 interferon were overexpressed in CR and NR. During induction therapy the expression of type 1 interferon-inducible genes declined in CR but increased in NR, and additional type 1 genes were activated. Similarly, complement component transcript expression was increased at B × 1 in CR and NR and transcripts for regulators of the alternative pathway were suppressed in NR. At B × 2, these complement transcripts normalised in CR, but increased expression in NR. Transcripts related to T cell signalling became overexpressed at B × 2 in NR; this occurred to a lesser extent in CR. To determine whether changes in intra-renal transcript expression translated to changes in protein expression that could be measured non-invasively, complement component C5a was measured in the urine of an independent cohort of LN patients (n = 34). Urine C5a concentration was significantly higher than normal in CR and NR at LN flare. After treatment urine C5a fell significantly in CR, but remained elevated in NR.
Conclusion These data demonstrate that activity of intra-renal inflammatory genes induced at LN flare begins to fall in patients who respond clinically to induction therapy, but increases in patients who do not respond. The functional profiles of the protein products of these transcripts suggest that non-responders may benefit from interventions targeted at the type 1 interferon, alternative complement and T cell signalling pathways.

CE-48 RESIDENTIAL PROXIMITY TO HIGHWAYS, DNA METHYLATION AND SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Systemic lupus erythematosus (SLE) is a heterogeneous disease in which epigenetic and environmental risk factors have been implicated. DNA methylation can be influenced by environmental exposures. Exposure to motor vehicle emissions has been linked to increase in overall mortality, asthma and increase incidence of rheumatoid arthritis. The focus of this study was to evaluate methylation changes in relationship to residential proximity to highways in patients with SLE.
Materials and methods We studied 307 patients with SLE who were previously enrolled in a Lupus Genetics Project. As a replication cohort, 225 participants from a gene-environment study of asthma were studied. Residence at the time of blood draw was recorded and geocoded. The distance to the nearest roads from the geocoded locations were calculated for the four major Tele Atlas Feature Class Codes (FCC) road classes. The Geographic Data Technology, Inc. (GDT) road network data were used for these calculations. Genome-wide methylation profiling was performed using the Illumina Infinium HumanMethylation 450 BeadChip.
Results Patients residing within a 300 metre radius from a major highway were defined as at high risk for significant hazardous health outcomes[1]. Thirty-eight patients (12.4%) were residing in a high risk area. Multivariate analysis did not reveal any

Abstract CE-48 Table 1 Methylation differences between patients who resided in a high risk vs low risk area

Site	Chr	Gene	Pathway	P value
cg11167637	1	*UBE2U*	Ubiquitin-Conjugating Enzyme E2U	9.7 E-09
cg21204139	1	*UBE2U*	Class I MHC mediated antigen processing and presentation	1.6 E-08
cg26317111	1	*UBE2U*		1.8 E-07
cg02696670	1	*UBE2U*		2.2 E-07
cg11244180	1	*UBE2U*		3.2 E-07
cg12405788	17	*AMAC1L3;ZBTB4*	Acyl-malonyl condensing enzyme 1-like 3	4.3 E-07
cg07455318	14	*CCBC88C*	DAPLE	1.8 E −06
			Negative regulator of the Wnt signalling pathway	