TD-02 KIDNEY TISSUE DAMAGE IN MICE WITH SINGLE AND COMBINED ABNORMALITIES IN COMPLEMENT, INTERFERON AND APOPTOTIC CELL CLEARANCE

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Background Lupus nephritis (LN) affects ~70% of systemic lupus erythematosus (SLE) patients and is one of the main contributors to morbidity and mortality. While defective clearance of apoptotic cells (AC), immune complexes, and type 1 interferons (IFN) are strongly implicated in lupus pathogenesis, the precise way that each impacts kidney protection and injury is unknown.

Methods To investigate mechanisms of kidney injury in a lupus-like disease model, we created C57BL/6 mice with defective clearance of AC (Mfge8^{-/-}) and anti-chromatin antibodies (sle1) that were also deficient in either C1q [C1q Triple mutant (C1qTM)] or C3 (C3TM). Kidney injury was evaluated by urine albumin/creatinine ratio (UCAR), PAS staining, and immunofluorescence (IF) staining. The effect of IFN-I on disease was studied in C3TM mice by a single injection of an adenovirus expressing IFN α (AdV-IFN α).

Results Sle1 mice deficient in MFGE8 developed significantly higher titers of autoantibodies directed at lupus antigens compared to sle1 mice alone. When MFGE8^{-/-} Sle1 mice also had C1q or C3 deficiency, a further increase in anti-DNA (figure 1A) and other autoantibodies was observed. Both TM strains showed AC accumulation in the kidneys (figure 1B) and C1qTM mice had decreased survival. Remarkably, we detected glomerular deposition of C3/C3d in C1qTM (figure 1C) and the membrane attack complex (MAC) in C3TM mice. To dissociate the effects of complement on B cells versus effects on the kidney, we studied antibody mediated kidney injury (Nephrotoxic Nephritis, NTN) in mice deficient in AC clearance and complement proteins [double knockout (DKO)

(Mfge8^{-/-}C1q^{-/-} or Mfge8^{-/-}C3^{-/-}) mice]. NTN in C1q DKO and C3 DKO mice revealed a significantly elevated UACR compared to the single mutants. IF analyses also revealed glomerular C3/C3d deposition in C1qDKO mice and MAC deposition in C3DKO mice. A single injection of AdV-IFN α accelerated kidney damage in C3TM mice, resulting in increased anti-dsDNA IgG titers, UACR, and PAS staining.

Conclusions These findings demonstrate that early component complement deficiencies have two distinct effects: they promote enhanced B cell autoreactivity and they protect against kidney disease. Increased glomerular C3/C3d deposition in C1qTM and NTN C1qDKO mice suggest activation of the lectin or alternative complement pathways. Increased MAC deposition in C3TM and NTN C3DKO mice indicates that a C3-independent mechanism leads to distal complement activation and MAC formation. These data prompt models of tissue injury in low complement states that will require assessment in human SLE and provide rationale for targeted therapeutics that are not currently used.

TD-03 CONVOLUTIONAL NEURAL NETWORKS IDENTIFY *IN SITU* ADAPTIVE IMMUNE CELL ARCHITECTURES IN HUMAN LUPUS

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Background Adaptive immunity is driven by antigen-restricted cell:cell interactions. In mice, two-photon excitation microscopy (TPEM) has revolutionized our understanding of immune cell architectures. However, TPEM has several limitations: most notably it can only be used to study manipulated animal model systems and not human disease. Previously, we demonstrated that by quantifying the distance between B cells and T cells in multichannel confocal images of human tissue (Cell Distance Mapping, CDM) we could identify cognate interactions. However, CDM used fixed filters and could not

Abstract TD-02 Figure 1

accurately capture cell shape. We postulated that this might be important as T cells adopt different shapes when scanning for antigen and after recognizing MHC class II-restricted peptides.

Methods We implemented a deep convolutional neural network (DCNN) that accurately identified both cell position and shape. The DCNN output was then analyzed with a tuned convolutional neural network (TNN) to identify distance and cell shape features that best discriminated between different T cell populations relative to dendritic cells (DCs). We refer to this analysis pipeline as CDM³.

Results In mice, CDM³ discriminated between cognate and non-cognate T cell interactions with DCs with a sensitivity and specificity similar to most TPDM measures. In human lupus nephritis, CDM³ both confirmed that myeloid DCs present antigen to CD4⁺ T cells *in situ* and identified plasmacytoid DCs as an important antigen presenting cell in severe inflammation.

Conclusions CDM³ provides a novel tool for quantifying *in situ* adaptive immune cell networks broadly applicable to the study of human diseases including autoimmunity and cancer.

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TD-04 PLAQUENIL DISCONTINUATION IS ASSOCIATED WITH INCREASED DAMAGE ACCUMULATION IN SLE

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Background There is ample evidence demonstrating that hydroxychloroquine (HCQ) prevents lupus flares, increases long-term survival, and protects against irreversible organ damage in SLE (Pons-Estel Arth Care Res 2010). However, in recent years, ophthalmology guidelines have encouraged providers to limit cumulative HCQ exposure to prevent ocular toxicity. We examined whether a) HCQ use in our UCLA cohort has changed over time and b) whether patients who discontinue HCQ accumulate damage at a different rate than continuous or never users.

Methods SLE subjects participating in our longitudinal 'Biomarkers of Atherosclerosis' carotid ultrasound cohort were evaluated. Medication use (and reasons for disuse) were recorded at cohort entry, and at each subsequent study visit.

303 SLE subjects participated in the baseline study (2004–2006), 229 in the 2nd follow-up (2008–2010), and 102 in the 3rd follow-up exam (2015–present).

For continuity, SLICC Damage Index (SDI) was measured at baseline, 3 years, and 5 years after cohort entry.

Results At baseline, 69.8% of patients were taking HCQ, 62.1% at first follow-up, and 58.6% at second follow-up ($p=ns$). Patient preference and physician preference were the most common reasons for HCQ non-use. Less than 3% of subjects who discontinued HCQ did so due to concern for eye toxicity at baseline and first follow-up, but this increased to 7.4% at second follow-up.

We compared SDI at baseline in patients who were never HCQ users ($n=29$), vs previous users ($n=93$), vs continuously users ($n=181$). We found evidence of SLE-related damage ($SDI \geq 1$) in 75.9% of never HCQ users, 74.1% of previous users, and 52.4% of subjects on HCQ at baseline ($p=0.001$, Chi-Square). At 5 years, we found $SDI \geq 1$ in 94.7% of never HCQ users, 82.7% of previous users vs 68.2% of subjects on HCQ at baseline ($p=0.004$, Chi-Square).

Conclusions Although the frequency HCQ use in our longitudinal SLE cohort has decreased slightly over the last 13 years, the percentage of subjects who discontinued HCQ due to eye-related eye toxicity has increased recently. Further studies will be required to determine whether this increase is due solely to cumulative HCQ dose vs more frequent detection because of adherence to ophthalmology testing guidelines vs earlier detection due to more sensitive testing modalities. Our data also demonstrate that damage accumulation is similar in subjects who previously used HCQ and those who never used, and higher compared to continuous users, suggesting continuous HCQ use may be important for damage prevention in SLE.

TD-05 DYNAMIC CONTRAST ENHANCED MRI (DCE-MRI) DEMONSTRATES HIPPOCAMPUS PERMEABILITY IN SLE

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Background Cross-reactive, anti-dsDNA/N-methyl D-aspartate receptor antibodies (DNRAb) have been associated with cognitive impairment in SLE. The mouse model demonstrates selective effects of DNRAb on hippocampal neurons following blood brain barrier (BBB) breach.¹ We previously identified abnormal hippocampal glucose hypermetabolism in SLE patients that correlated with serum DNRAb titers and poor performance on neuropsychological (NP) testing.² However, little is known about how antibodies access brain in humans. We evaluated BBB permeability (BBBP) in SLE and healthy control (HC) subjects with DCE-MRI and hypothesized that regions with abnormal hypermetabolism would also demonstrate altered BBBP.

Methods 6 SLE subjects with no history of NP symptoms and 6 age and gender matched HCs underwent NP testing using the Automated Neuropsychological Assessment Metric (ANAM) computerized battery and DCE-MRI on a 3.0 tesla magnet. MRI sequences were acquired according to standard protocols; permeability imaging used DCE technique with axial 3D-SPGR T1-WI sequences and 80 cine phases using TR=25 ms, TE=3.8 ms, FOV=24 mm, and matrix size of 128 × 256. Magnevist Gadolinium contrast, 0.1 mmol/kg IV, was dosed at 5 cc/sec following a 5 sec delay. Post-processing of images into BBBP parameters of K-trans (mL/100 gm/min) and VE (mL/100 gm) was performed using Olea Sphere 2.2 and 2.3 with the Tofts extended permeability model. This