**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 I 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 Triplet 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 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-IFNα 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.

**Abstracts**

**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

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**Abstract TD-02 Figure 1**

A72 LUPUS 2018;5(Suppl 2):A1–A81
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 CDM.

Results In mice, CDM discriminated between cognate and non-cognate T cell interactions with DCs with a specificity similar to most TEM measures. In human lupus nephritis, CDM 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 CDM 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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