to therapeutic applications. Finally, we have shown that IRS can prevent skin lesions following mechanical injury by blocking PDC activation in the skin environment. The lead IRS inhibitor, called DV1179, has entered a human clinical trial and its safety was assessed in multiple ascending doses in healthy volunteers and lupus patients, however no effect on IFN response was observed in lupus patients.

Conclusions These data provide a new understanding of the role of self-recognition of DNA and RNA by TLR as an important parameter during inflammatory response. These data also stress the potential of blocking PDC activation to increase patient's response to corticosteroid treatment although the use of oligonucleotide based inhibitors did not reduce the IFN signature in lupus patients. Other approaches could be tested as well.

II-16 PROTECTION OF LUPUS NEPHRITIS BY IRHOM2 DEFICIENCY IN *FCRγIIB-/-* MICE

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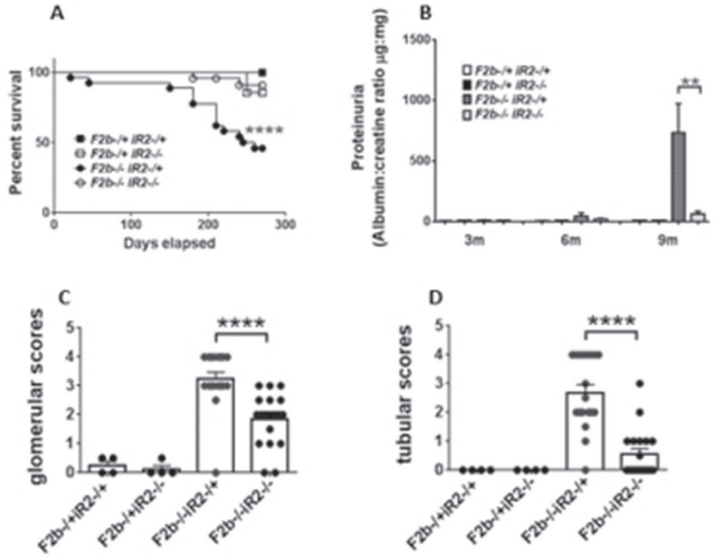
10.1136/lupus-2016-000179.46

Background Lupus nephritis (LN) is a major cause of morbidity and mortality in lupus. A disintegrin and metalloprotease 17 (ADAM17), is a principal membrane-anchored metalloprotease that cleaves a large spectrum of membrane-bound proteins into their soluble forms. Inactive rhomboid protein 2 (iRhom2), a newly identified regulator of ADAM17, controls maturation and function of ADAM17. Interestingly, in iRhom2$^{-/-}$ mice, loss of ADAM17-dependent shedding activity is limited to the immune organs. Accumulating evidence has shown increased protein shedding and possibly activation of ADAM17 in lupus. Among ADAM17 substrates, tumour necrosis factor α (TNF-α) and heparin-binding EGF (HB-EGF) have been reported to play important roles in mediating renal damage in lupus. We hypothesised that the activation of iRhom2/ADAM17 pathway plays a role in the pathogenesis of lupus nephritis.

Materials and methods We crossed *iRhom2*$^{-/-}$ mice with the well-established *FcRγIIB-/-* lupus-prone mice, and assessed development of lupus-like syndrome in these mice.

Results We found that *iRhom2* deficiency protects *FcRγIIB*$^{-/-}$ mice from severe kidney damage (Figure 1), with minimal impact on the production of anti-double stranded (ds) DNA antibodies and renal deposition of immune complex and complement C3. In the absence of iRhom2, glomerular and tubule-interstitial structures were preserved, and massive inflammatory infiltrates including myeloid and CD4^{+} T cells were alleviated in the lupus kidneys. Protection of kidney injury by *iRhom2* deficiency is associated with reduced EGFR signalling and ERK1/2 activation in the kidneys of *FcRγIIB*$^{-/-}$ mice. Transcriptome analysis of the whole kidneys as well as kidney macrophages from *FcRγIIB*$^{-/-}$ mice identified genes encoding pro-inflammatory cytokine/chemokines, fibrosis and tissue remodelling highly upregulated, and many of these genes were significantly reduced in the absence of *iRhom2*. In addition, kidney biopsies from patients with lupus nephritis show intense staining for HB-EGF, an EGFR ligand, in areas of crescents.

Conclusions Our findings here provide the first evidence that iRhom2, a major regulator of ADAM17, plays a critical role in the pathogenesis of LN. The role of iRhom2 in a spontaneous chronic mouse model of LN, *FcRγIIB*$^{-/-}$ mice, appears to be targeting at the effector arm of the disease, rather than affecting the process of autoimmunity development. iRhom2 may be a potential therapeutic target in LN.



Abstract II16 Figure 1 *iRhom2* deficiency protects *FcγRIIB-/-* mice from developing severe kidney injury. *FcγRIIB-/-* mice crossed with *iRhom2-/-* mice were assessed for survival and kidney injury. Survival **(A)** and proteinuria **(B)** were plotted at each age. Pathological scores were illustrated for glomerular **(C)** and tubular-interstitial area **(D)** respectively. (A) survival, Chi square test. (B) proteinuria, student *t*-test. (C, D) pathological scores, non-parametric Mann Whitney test. ** $P < 0.005$, **** $P < 0.0001$

Acknowledgements Work supported by Lupus Research Institute (JES and CB) and Barbara Volcker Centre of Hospital for Special Surgery (XQ).

II-17 LUPUSHDL PROMOTES PRO-INFLAMMATORY RESPONSES IN MACROPHAGES THROUGH LOX1R BINDING AND ABROGATION OF ATF3 ACTIVITY

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10.1136/lupus-2016-000179.47

Background Recent evidence indicates that high-density lipoprotein (HDL) exerts vasculoprotective activities by promoting activating transcription factor 3 (ATF3), leading to down-regulation of TLR-induced inflammatory responses. SLE is associated with increased cardiovascular disease (CVD) risk not explained by the Framingham risk score. Recent studies have indicated oxidised HDL as a possible contributor. We investigated the potential mechanisms by which lupus HDL may lose its anti-inflammatory effects and promote immune dysregulation.

Methods and results Compared to control HDL, SLE HDL activates NF_KB, promotes inflammatory cytokine production, and fails to block TLR-induced inflammation in control macrophages. This failure of lupus HDL to block inflammatory responses is due to an impaired ability to promote ATF3 synthesis and nuclear translocation. SLE HDL-induced pro-inflammatory responses in macrophages are dependent on its binding to lectin-like oxidised low-density lipoprotein receptor 1 (LOX1R), which promotes suppression of ATF3 activity in a ROCK1/2 kinase-dependent manner. This inflammation can be modulated *in vivo* as lupus-prone mice exposed to the HDL mimetic ETC-642 show improved ATF3 induction and significant abrogation of pro-inflammatory cytokines

Conclusions Lupus HDL promotes pro-inflammatory responses, increased NFκB activity and decreased ATF3 synthesis and activity, in a LOX1R- and ROCK1/2 kinase-dependent manner. ETC-642 inhibited both *in vitro* and *in vivo* SLE HDL-induced inflammation.

Acknowledgements Funded by Intramural Research Program at NIAMS and by Lupus Research Institute.

II-18 CELL-BASEDTHERAPY IN SYSTEM LUPUS ERYTHEMATOSUS (SLE): EFFECTS ON NEUTROPHIL NETTING

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10.1136/lupus-2016-000179.48

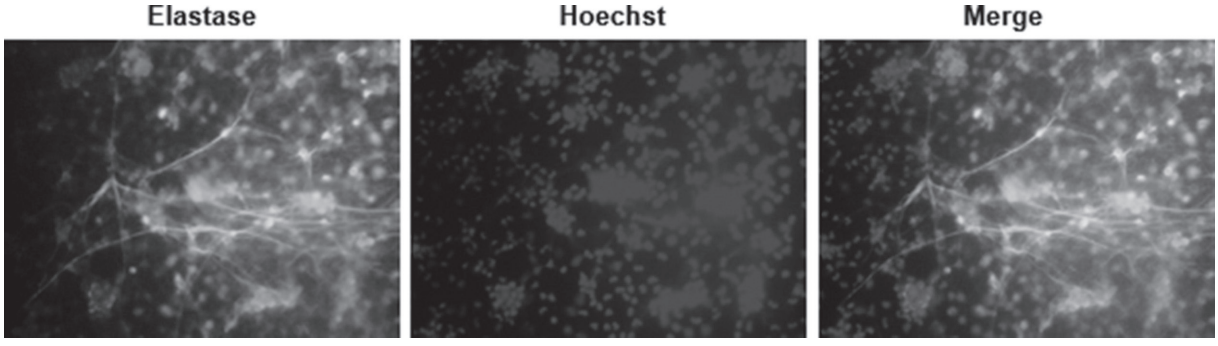
Background Evidence that mesenchymal stem cells (MSCs) derived from bone marrow, fat and umbilical cord can be used to treat refractory SLE and SLE nephritis is growing. MSCs were originally described as cells from bone marrow that have the capacity to differentiate into bone, cartilage and fat. More recently it has been recognised that all MSCs are peri-cytes and that their greatest potential is because they are pleiotropic and can both sense and repair their environment. We hypothesised that MSCs can reduce neutrophil activation in SLE by inhibiting neutrophil netting thus reducing induction of T-helper follicular cells that promote the development of long-living plasmablasts that can secrete autoantibodies.

Materials and methods We studied neutrophils derived from healthy donors and patients with SLE. Neutrophils were isolated using MACSxpress™ Neutrophil Isolation Kit (Miltenyi) and onto coverslips in 24-well plates and incubated for 1–2 hours with conditioned medium derived from MSCs or control medium. Netting was induced by culture *ex vivo* with 20 nM PMA for 2 hours. Coverslips were fixed in 4% paraformaldehyde and NETs were quantified using anti-human antibody directed against neutrophil elastase colocalizing with extracellular DNA using Hoechst 33342.

Results To date we have optimised the conditions of our assay. Studies are ongoing to determine the effect of MSCs and/or their products on neutrophil netting. Figure 1: seen below are netting neutrophils induced as described above. Assays are underway to determine the effect of MSCs on SLE netting neutrophils *ex vivo*.

Conclusion The possibility that MSCs and/or their products could act both on innate and adaptive immune responses in SLE is appealing. Demonstration of the effect of MSCs on neutrophils is critical in understanding the potential therapeutic role of MSCs in SLE and SLE related organ damage.

Acknowledgements This work has been supported by the Lupus Foundation of America and by the by the Clinical and Translational Science Collaborative of Cleveland, UL1TR000439 from the National Centre for Advancing Translational Sciences (NCATS) component of the National Institutes of Health and



Abstract II-18 Figure 1 Neutrophil Elastase colocalized with extracellular DNA. Control neutrophils were isolated from peripheral blood and stimulated with 10nM PMA for 2 hr at 370C. Cells were fixed and stained for detection of neutrophil Elastase (green) and DNA was labeled with Hoechst 33342 (blue).