Conversely, regression analyses demonstrated that decreased tricarboxylic acid (TCA) cycle and lipid metabolism signatures reflected decreased kidney cell transcripts, which was confirmed by the negative relationship between the TCA cycle signature and expression of the tubule damage marker, *HAVCR1*.¹ Indeed, similar alterations to metabolism were observed in some less severe LN patients, in which inflammatory cell transcripts were not yet increased.² Although interferon can induce metabolic changes at the transcriptional level,³ examination of metabolic gene expression in the murine interferon alpha-accelerated LN model revealed that metabolic changes were not driven by acute exposure to type I interferon.² Moreover, evaluation of metabolic changes in murine LN following various treatments demonstrated that metabolic gene expression could be restored with immunosuppressive therapy.² Regression analyses in DLE and PSO demonstrated that there was a positive correlation between the glycolysis signature and the keratinocyte signature, whereas in PSO, AD, and SSc the glycolysis signature was positively correlated with the monocyte/myeloid cell signature.

Conclusion These results indicate that altered metabolic dysfunction is a common change in lupus- and inflammatory disease-affected tissues and appears to reflect immunologic damage.

REFERENCES

- Morel L. Immunometabolism in systemic lupus erythematosus. *Nat Rev Rheumatol*. 2017;**13**(5):280–290.
- Kingsmore KM, Bachali P, Catalina MD, et al. Altered expression of genes controlling metabolism characterizes the tissue response to immune injury in lupus. *Sci Rep*. 2021;**11**(1):14789.
- Wu D, Sanin DE, Everts B, et al. Type 1 interferons induce changes in core metabolism that are critical for immune function. *Immunity* 2016;**44**(6):1325–1336.

400 – Innate immunity/cardiovascular disease and lupus

401

TRIM21 AS A REGULATOR OF UVB-DRIVEN IFN RESPONSES IN LUPUS

¹Gantsetseg Tumurkhuu, ¹Gabriela de los Santos, ¹Erica N Montano, ¹Duygu Ercan Laguna, ¹Luisa Akaveka, ²Rachel Abuav, ³Wonwoo Shon, ¹Mariko Ishimori, ¹Daniel Wallace, ¹Caroline Jefferies*. ¹Division of Rheumatology, Department of Medicine; ²Department of Dermatology; ³Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, California

10.1136/lupus-2021-lupus21century.14

Background Patients with systemic lupus erythematosus (SLE) experience photosensitivity, with exposure to ultraviolet light (UV) driving lupus flares, triggering symptoms like joint pain and fatigue, in addition to causing cutaneous lesions. Our previous work has shown that TRIM21, an autoantigen in SLE, functions as a negative regulator on the pathways driving IFN expression. *Trim21*^{-/-} mice develop systemic autoimmunity due to an inability to regulate type I IFNs. These mice also spontaneously develop skin lesions, leading us to hypothesize that *Trim21*^{-/-} mice may have enhanced sensitivity to UV-induced skin inflammation.

Methods Wild type (WT, C57BL/6) and TRIM21 KO mice were irradiated with UVB (100 mJ/cm²) consecutively for 1 and 3 weeks, and blood, spleen and kidney analyzed by qPCR, histology, and flow cytometry. Bone marrow derived macrophages (BMDMs) and mouse skin fibroblasts (MDF) were analyzed by qPCR and western blotting. Peripheral blood

samples from SLE patients were analyzed by qPCR for interferon stimulated genes (ISG) RSAD2, IFI44, IFI44L, IFI27 and used to calculate IFN scores.

Results Macroscopically, both WT and *Trim21*^{-/-} mice developed similar levels of erythema, edema and induction of inflammatory cytokines in response to UVB exposure. However, compared to WT mice, expression of IFN β and ISGs were elevated in the skin of *Trim21*^{-/-} mice following UVB. Most notably after UVB exposure, we observed splenomegaly and enhanced expression of ISGs in the blood and spleen of *Trim21*^{-/-} mice. *Trim21*^{-/-} mice also demonstrated enhanced total IgG levels in serum, significantly increased deposition of IgG in the skin and increased ISG expression in the kidneys, all suggesting that loss of TRIM21 in mice results in enhanced IFN-driven responses systemically. Enhanced basal, UVB- and cGAMP-dependent IFN β expression was observed in *Trim21*^{-/-} BMDMs and MDFs which was restored in BMDMs from *Trim21*^{-/-}/Sting^{-/-}, suggesting the cGAS-STING pathway was inappropriately regulated in these absence of TRIM21. As TRIM21 is an E3 ligase and known to regulate protein stability, we assessed levels of cGAS, DDX41 (a DNA sensor and regulator of STING signaling) and STING itself. Mechanistically, we found only DDX41 protein levels were stabilized in *Trim21*^{-/-} MDFs or BMDMs, respectively, suggesting it to be a target on this pathway.

Conclusions Taken together our results indicate that TRIM21 protects against IFN induction both at a local and systemic level in response to DNA sensing. Understanding the role of TRIM21 in preventing systemic disease will have important understandings of its role in driving increased disease activity and flare in SLE.

Acknowledgements Supported by Leon Fine Award in Translational Science and Center for Research in Women's Health and Sex Differences, Cedars Sinai Medical Center.

402

GENETIC DISSECTION OF TLR9 REVEALS COMPLEX REGULATORY AND CRYPTIC PRO-INFLAMMATORY ROLES

Claire Leibler¹, Shinu John¹, Kayla Thomas¹, Shuchi Smita¹, Rachael Gordon¹, Jeremy Tilstra², Sebastien Gingras¹, Sheldon Bastacky³, Kevin Nickerson¹, Mark J Shlomchik*¹. ¹Department of Immunology; ²Department of Medicine; ³Department of Pathology, School of Medicine, University of Pittsburgh

10.1136/lupus-2021-lupus21century.15

Background Toll like receptors (TLR) 7 and 9, endosomal sensors for ssRNA and dsDNA, are key mediators of lupus auto-reactivity. Although considered homologous, they have opposing effects on lupus severity: TLR7 exacerbates disease while TLR9 protects. One theory is that TLR9 induces protection by competing with TLR7 for endosomal trafficking, thus restraining TLR7 expression and signaling. However, since both TLR9 and TLR7 ligands are available in lupus, and both TLRs are supposed to signal via MyD88, this theory doesn't explain the differential effects of the two TLRs on disease. To reconcile this, we hypothesized that TLR9 could induce counter-regulatory signaling and/or regulate TLR7 via a ligand- or signaling-independent mechanism.

Methods and Results To differentiate between these hypotheses, we created mutants of TLR9 that prevent ligand binding (TLR9^{K51E}) or MyD88 signaling (TLR9^{P915H}) in the TLR9 locus of MRL/lpr mice. Mutant mice were assessed for dermatitis, nephritis, immune dysregulation, and auto-antibodies.

TLR9^{K51E/K51E} mice had increased survival and decreased kidney pathology compared to TLR9^{-/-} mice, indicating that