(figure 3). Additionally, we provided evidence that PRDM1 acts as a novel negative regulator of the Type I interferon pathway (figure 3). Lastly, our research revealed a link between the presence of the risk allele T and a reduction in PRDM1 expression. This reduced expression appears to be due to the allele T's effect on the binding of the transcription factor SPI1 (figure 3).

Conclusion Our study leveraged advanced gene-editing tools to elucidate the landscape of functional SNPs in lupus, revealing their cell type-specific regulation of the Type I interferon pathway and their influence on key genes in the JAK-STAT pathway. Notably, we highlighted the significant role of SNP rs11152966 and its target gene PRDM1 in regulating the interferon pathway in lupus.

Genetics

705 EXAMINATION OF THE SHARED GENETIC ARCHITECTURE BETWEEN MULTIPLE SCLEROSIS AND SYSTEMIC LUPUS ERYTHEMATOSUS FACILITATES DISCOVERY OF NOVEL LUPUS RISK LOCI

[1,2]Sophia Kerns, [1,2]Katherine A Owen, [1,2]Amrie C Grammer, [1,2]Peter E Lipsky. [1]*AMPEL BioSolutions, LLC, Charlottesville, VA, USA*; [2]*The RILITE Research Institute, Charlottesville, VA, USA*

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Systemic Lupus Erythematosus (SLE) is an autoimmune disease with heterogeneous manifestations, including neurological and psychiatric symptoms. Genetic association studies in SLE have been hampered by insufficient sample size and limited power compared to many other diseases. Multiple Sclerosis (MS) is a chronic relapsing autoimmune disease of the central nervous system (CNS) sharing neurological features with SLE, especially neuropsychiatric SLE (NPSLE). Here, we identify a method of leveraging large-scale genome wide association studies (GWAS) in MS to identify novel genetic risk loci in SLE.

Statistical genetic comparison methods including linkage disequilibrium score regression (LDSC) and cross-phenotype association analysis (CPASSOC) to identify genetic overlap in disease pathophysiology, traditional 2-sample and novel PPI-based mendelian randomization to identify causal associations and Bayesian colocalization were applied to association studies conducted in MS to facilitate discovery in the smaller, more limited datasets available for SLE. Pathway analysis using SNP-to-gene mapping identified biological networks composed of molecular pathways with causal implications for CNS disease in SLE specifically, as well as pathways likely causal of both pathologies, providing key insights for therapeutic selection.

405 VISTA, A NOVEL REGULATOR OF TYPE I INTERFERON PRODUCTION IN THE SKIN

[1]Zachary Peters, [2]Lindsay Mendyka, [2]Sicong Shan, [2]Dorothea Barton, [2]Christopher Burns, [1]Randolph Noelle, [1,2]Sladjana Skopelja-Gardner. [1]*Geisel School of Medicine at Dartmouth, Lebanon NH, USA*; [2]*Dartmouth Hitchcock Medical Center, Lebanon NH USA*

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Background Persistent production of type I interferons (IFN-Is) is one of the hallmarks of lupus skin disease that is exacerbated by ultraviolet (UV) light. We previously showed IFN-I induction by UV occurs in a cGAS-STING-dependent manner, but the IFN-I signature returns to baseline levels in healthy skin, unlike in lupus. Here, we propose that the immune checkpoint VISTA is a regulator of skin IFN-I production in keratinocytes of therapeutic relevance to lupus.

Methods Skin biopsies from B6, B6.*Vsir*-/- (VISTA-deficient), B6.*Vsir*-/-*Sting*-/-, KRT14cre*Vsir*fl/fl (*Vsir*-/- in keratinocytes), and cre-*Vsir*fl/fl female mice (3 mo) were collected prior to, 3 and 24h after UVB (500mJ/cm2). Gene expression was quantified by RNA-seq (Rosalind). Skin infiltrating cells were quantified by flow cytometry. Human keratinocytes were isolated from healthy skin and *cultured in vitro*. Cells were treated with agonistic anti-VISTA (803) or isotype IgG2a (20ug/ml) prior to UVB (50mJ/cm2), in the presence or absence of IFNa (100U). Expression of IFN-Is and IFN-I stimulated genes (ISGs) were quantified by qPCR (4hr after UV) and IFN-I score derived.

Results At baseline, B6.*Vsir*-/- skin had increased IFN-k mRNA, IFN-b protein, as well as total STING protein levels. RNA-seq revealed increased expression of *Sting* and upstream cytosolic DNA sensors in VISTA-deficient mouse skin before and after UV. B6.*Vsir*-/- mice exhibited a 5- fold higher skin IFN-I score after UV compared to B6 mice. Higher baseline and UV-induced IFN- I response in VISTA-deficient skin was suppressed in the absence of STING (*Vsir*-/-*Sting*-/- mice). Moreover, fewer skin-infiltrating neutrophils and inflammatory monocytes were recruited to *Vsir*-/-*Sting*-/- vs. STING-sufficient *Vsir*-/- skin post UV. RNAseq also revealed decreased expression of DNA repair genes like *Ogg1, Xpd and Pole* in *B6. Vsir*-/- skin, which are essential for repair of UV-induced DNA damage. VISTA deficient mouse keratinocytes produced 2-fold higher IFN-k at baseline *ex vivo* and accumulated higher levels of oxidized DNA (8-OHdG) compared with B6 cells. Mice with a conditional VISTA deletion only in keratinocytes exhibited a 10-fold higher baseline IFN-I signature and increased IFN-b protein levels compared to controls. Expression of VISTA on human keratinocytes decreased 4 hr after UV, but increased 5-fold 24 hr after UV. Pre- treatment of human keratinocytes with an agonistic anti-VISTA antibody (803) suppressed UV- induced IFN-k, Stat1 phosphorylation and IFN-I score, even in keratinocytes with a pre-existing IFN-I signature.

Conclusion These studies identify VISTA as a suppressor of IFN-I production in keratinocytes and demonstrate STING-dependent IFN-I production in the absence of VISTA. As oxidized DNA is resistant to degradation in the cytosol where it can serve as a potent trigger of cGAS-STING, VISTA promotion of DNA repair may indirectly suppress STING signals. Antibody- mediated activation of VISTA in keratinocytes demonstrates its potential as a target to suppress IFN-I production in the context of photosensitivity and lupus.