(CD68+CD163-) (23.7%, 21.6 – 31.7), M2 Macrophages (CD68+CD163+) (35.9%, 26.4 – 40.7), and CD16+ cells (25.7%, 20.4 – 29.5) (figure 3). Further verification using a Z-axis overlay of intracellular markers on tSNE plots of immune cell clusters identified by CyTOF confirmed low expression of IFN-1and the interferogenic pathway, phosphorylated stimulator of interferon genes (pSTING), in the pDCs (figure 2B).

Conclusions Taken together, these findings suggest pDCs may not play the central role in CLE as major IFN-1 producers and myeloid cells are larger contributors of IFN-1 in numbers and as a percent. pDCs may have a pathogenic role in CLE through IFN-1-independent mechanisms.

901 SYMPOSIUM: MOLECULAR BIOLOGY AND IMMUNOLOGY OF PAIN

Stephen G Waxman. *Depts. of Neurology, Neuroscience and Pharmacology, Yale Medical School and VAMC West Haven CT Chasing Men on Fire: Genes regulating pain sensibility in humans*

10.1136/lupus-2022-lupus21century.52

Given the need for more effective treatments, there is a pressing need for a better understanding of chronic pain, including pain in SLE. Discovery of peripheral sodium channels (Nav1.7, Nav1.8, Nav1.9) and of pain resilience genes (KCNQ2, KCNQ3) opens up the possibility of targeting peripheral generators of pain (primary sensory neurons) without affecting the heart or CNS, thus enabling new and more effective pain therapies devoid of CNS side effects or addictive potential.

In this lecture I will review several lines of recent progress. Molecular genetics has validated peripheral sodium channels Nav1.7, 1.8 and 1.9 as strong drivers of firing of peripheral pain-signaling neurons and thus of human pain. Building upon this, recent studies have begun to provide proof of concept that Nav1.7-specific blockers can reduce pain. In parallel, genomically-guided pharmacogenomic approaches indicate that the goal of patient-specific, personalized pain therapy is an achievable objective.

Molecular genetics has also begun to identify pain resilience genes, pointing toward another set of molecular targets for pain therapy.

While there is still a lot of work to do, the goal of more effective, non-addictive treatments for chronic pain appears to be in sight.

Lay summary We are beginning to understand, in exciting detail, the molecular drivers of human pain. This new knowledge is bringing us closer to the goal of more effective, non-addictive treatments for chronic pain.

Molecular Biology of Lupus

902 LOSS-OF-FUNCTION VARIANTS IN *SAT1* CAUSE X-LINKED CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

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Objectives Families that contain multiple siblings affected with childhood-onset of systemic lupus erythematosus (SLE) likely have strong genetic predispositions. We performed whole-exome sequencing (WES) to identify familial rare risk variants and to assess their effects in lupus.

Methods Sanger sequencing validated the two ultra-rare, predicted pathogenic risk variants discovered by WES and identified additional variants in 562 additional SLE patients. Effects of a splice site variant and a frameshift variant were assessed using a Minigene assay and CRISPR/Cas9-mediated knock-in (KI) mice, respectively.

Results The two familial ultra-rare, predicted loss-of-function (LOF) *SAT1* variants exhibited X-linked recessive Mendelian inheritance in two unrelated African-American families. Each LOF variant was transmitted from the heterozygous unaffected mother to her two sons with childhood-onset SLE. The p. Asp40Tyr variant affected a splice donor site causing deleterious transcripts. The young hemizygous male and homozygous female *Sat1*p.Glu92Leufs*6 KI mice spontaneously developed splenomegaly, enlarged glomeruli with leukocyte infiltration, proteinuria and elevated expression of type I interferon inducible genes. *SAT1* is highly expressed in neutrophils and

encodes spermidine/spermine-N1-acetyltransferase 1 (SSAT1), a rate-limiting enzyme in polyamine catabolism. Young male KI mice exhibited neutrophil defects and decreased proportions of Foxp3+CD4+ T-cell subsets. Circulating neutrophil counts and proportions of Foxp3+CD4+ T cells correlated with decreased plasma levels of spermine in treatment naïve, incipient SLE patients.

Conclusions We identified two novel *SAT1* loss-of-function variants, showed the ability of the frameshift variant to confer murine lupus, highlighted the pathogenic role of dysregulated polyamine catabolism, and identified *SAT1* LOF variants as new monogenic causes for SLE.

Genetics

903 DECODING GENOME-WIDE ASSOCIATION STUDY (GWAS) HITS FOR LUPUS USING MASSIVELY PARALLEL REPORTER ASSAYS

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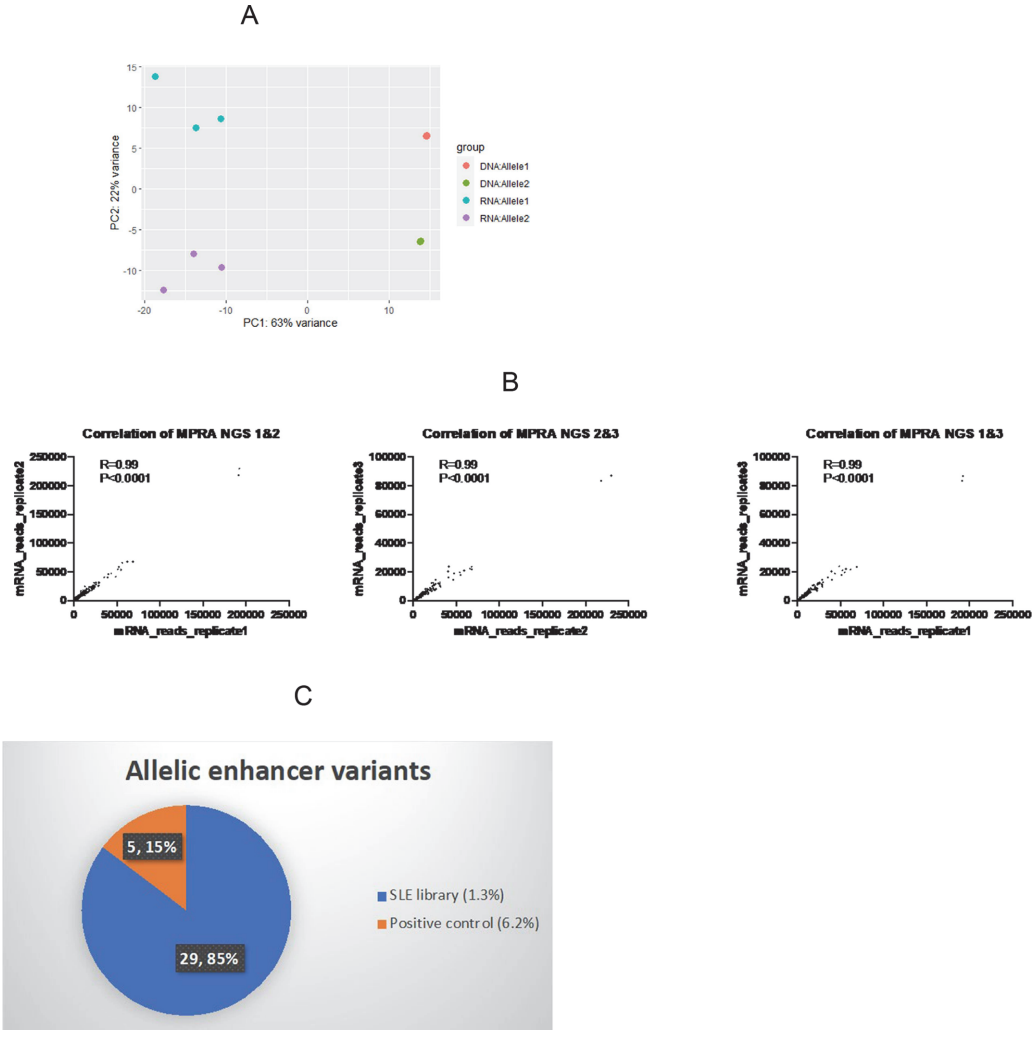
Background Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a strong genetic component (Block, Winfield et al. 1975, Deapen, Escalante et al. 1992, Alarcon-Segovia, Alarcon-Riquelme et al. 2005) and most of the genes involved have modest impact, complicates genetic dissection of disease etiology (Eberle, Ng et al. 2007, Stahl, Wegmann et al. 2012). To overcome this, a sensitive approach to identify risk alleles with small gene effects called genome-wide association studies (GWAS) has been applied for SLE studies and more than one hundred loci have been linked with disease risk (Gateva, Sandling et al. 2009, Bentham, Morris et al. 2015, Morris, Sheng et al. 2016, Langefeld, Ainsworth et al. 2017, Zhang, Zhang et al. 2018). Therefore, decoding GWAS is a promising strategy to identify novel drug targets in SLE. However, translating GWAS hits into disease pathogenic mechanisms has proven difficult as most of the identified disease-associated hits are noncoding single-nucleotide polymorphisms (SNPs), suggesting a regulatory role, and cannot be distinguished from others that reside incidentally within risk loci due to Linkage Disequilibrium (LD), which significantly increase the number of SNPs need to be investigated. A high-throughput screen method is therefore ideal for this task. Massively parallel reporter assays (MPRAs) that test the translational impact of candidate SNPs have been applied for



Abstract 903 Figure 1