scores. Numerically more CB-CAPS positive patients had SLE-DAI rash and met SLEDAI renal criteria. There was no difference in medication use or features of polysymptomatic distress such as widespread pain, fatigue, or depression (table 1).

Serologic activity emerged as a hallmark of CB-CAPS positivity. CB-CAPS positive patients were more likely to have positive ANA, anti-5m, anti-U1RNP, anti-RNP70, anti-C1q and anti-phospholipid antibodies than those who were CB-CAPS negative (table 2). Serologic markers of disease activity including elevated levels of anti-dsDNA and decreased C3 or C4 also tracked with CB-CAPS positivity (table 2).

Conclusion Narrowing the heterogenous clinical and immunologic features of SLE into endotype subgroups is a crucial step toward precision medicine and personalized care in SLE. CB-CAPS positive patients represent an important subset of patients who are characterized by greater serologic activity and internal organ pathology. Moreover, the cumulative burden of SLE activity is greater in those with CB-CAPS positivity, as measured by the ACR/EULAR criteria score. CB-CAPS positivity could provide both diagnostic and prognostic information with implications for improved disease monitoring. Further studies are needed to assess the effects of targeted therapeutics and the long-term outcomes of the CB-CAPS positive endotype.

Acknowledgements None.

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THE TOLEROGENIC EFFECTS OF IL-2 ON T REGULATORY CELLS (TREGS) ARE TGF-β DEPENDENT

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10.1136/lupus-2022-lupus21century.105

Background We and others have previously shown that IL-2 is essential for TGF-β to allow conversion of naïve CD4+CD25− T cells into CD4+CD25+Foxp3+ Tregs. To further those studies, we recently used IL-2- loaded nanoparticles (NPs) coated with anti-CD2 antibody (Ab) to target both T cells and NK cells in lupus mice, identifying a key role of a population of TGF-β-producing NK cells in the induction of the CD4+ and CD8+ Foxp3+ Tregs that prevented disease.

Methods Anti-CD2 Ab-coated NPs made of poly(lactic-co-glycolic acid (PLGA) and encapsulating IL-2 or IL-2/TGF-β were used to inhibit a lupus-like disease characterized by a human anti-mouse graft versus host disease (GVHD) that develops after transfer of human PBMCs into immunodeficient NOD SCID mice.

Research NPs containing only IL-2 protected mice from autoimmune disease similarly to NPs containing both IL-2 and TGF-β. Remarkably, the blockade of TGF-β signaling with an ALK-V inhibitor not only abolished the protective effects of the NPs but also reduced the survival of the diseased mice.

Conclusions In the absence of TGF-β, IL-2 induces pathogenic T effector cells instead of promoting the induction of protective Tregs. This key role of TGF-β in the induction of Tregs has relevance for the ongoing clinical trials that employ low-dose IL-2 or IL-2 muteins in SLE and other autoimmune diseases to expand functional Tregs. Since lymphocyte production of TGF-β is decreased in SLE, our study suggests that in the immunotherapeutic management of SLE, one needs to correct the deficits of both IL-2 and TGF-β to optimally induce and expand functional Tregs.

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α-KETOGLutarate-Dependent KDM6 Histone Demethylases Epigenetically Regulate Interferon Stimulated Gene Expression in Lupus

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10.1136/lupus-2022-lupus21century.106

The authors have declared that no conflict of interest exists.

Objective To investigate the hypothesis that interferon (IFN) stimulated gene (ISG) expression in systemic lupus erythematosus (SLE) monocytes is linked to changes in metabolic reprogramming and epigenetic regulation of ISG expression.

Methods Monocytes from healthy volunteers and SLE patients at baseline or following IFNα treatment were analyzed by extracellular flux analysis, proteomics, metabolomics, chromatin immunoprecipitation and gene expression.

Treatment of SLE monocytes or pristane-treated C57BL/6 mice with GSK44 assessed the effects of histone demethylases KDM6A/B on ISG expression.
**Results** Assessing differences in metabolic programming between monocytes isolated from healthy volunteers or SLE patients, we observed that SLE monocytes exhibit enhanced rates of glycolysis and oxidative phosphorylation, accompanied by an increase in isocitrate dehydrogenase (IDH2) and its product, α-KG. As IDH2 levels correlate with IFN-stimulated genes (ISG) expression, we hypothesized that IFNα priming of monocytes may be driving epigenetic changes at ISG promoters via increased α-KG. We observe decreased H3K27 trimethylation (repressive) and increased H3K4 trimethylation (permissive) at the promoters of ISGs, in keeping with the role α-KG plays as an obligate cofactor for histone demethylases KDM6A and KDM6B, which enhance gene expression by removing H3K27me3 marks at promoters.

Inhibition of KDM6A/B resulted in decreased ISG expression both in SLE patient monocytes and in a mouse model of IFN-driven lupus.

**Conclusion** Our study demonstrates the first link suggesting chronic IFNα/β exposure alters epigenetic regulation of ISG expression in SLE monocytes via changes in immunometabolism, a mechanism reflecting innate immune memory or trained immunity to type I IFN. Importantly, it opens the possibility that drugs targeting histone modifying enzymes such as KDM6A/B may be effective in restoring homeostasis to the IFN network in SLE.

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**Abstract 2002 Figure 1** Single-cell RNA sequencing identifies myeloid subsets in kidney biopsies from patients with active lupus nephritis. ~22,000 intrarenal monocytes and macrophages from 155 lupus nephritis patient biopsies were collected for single cell RNA-seq that enabled cellular identification (colored clusters). Trajectory analysis (black arrows) reveals that phagocytic macrophages were derived from 4 distinct populations of infiltrating and residentiaI macrophages (from bottom clockwise: infiltrating CD14+ & CD16+ monocytes, resident LYVE1+ and LYVE1- macrophages).

**Abstract 2002 Figure 2** Phagocytic macrophages (and smaller subsets of LYVE1+ and LYVE1- cells) were associated with the activity index in covarying neighborhood analysis, an unbiased method to identify associations between cell populations in single cell RNA-seq and clinical data.

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The presence of monocytes and macrophages in kidney biopsies has been associated with kidney injury and poor prognosis in lupus nephritis. Infiltrating and resident subtypes may acquire specialized functions in response to kidney damage that drive homeostatic or aberrant tissue remodeling. The functions and cellular differentiation of monocytes and macrophages in kidneys have been difficult to study due to the inability to collect immune cells from small human kidney biopsies as well as technical limitations to deeply phenotype cells. We previously reported on the characterization of 466 kidney monocytes and macrophages collected from the kidney biopsies of 24 patients with lupus nephritis using plate-based single cell RNA seq. Here, we have characterized ~22,000 kidney monocytes and macrophages collected from 155 lupus nephritis patient biopsies with droplet-based single cell RNA seq. Our analysis of this comprehensive data set has revealed deep new insights into the cellular identities and the potential roles of monocyte and macrophage subsets in lupus nephritis (figure 1). Critically, we identified phagocytic macrophages that were positively associated with the histopathologic activity index suggesting an important role for these cells and their functional gene programs that regulate cellular debris clearance and lipid metabolism (figure 2). We also identified infiltrating...