Results Assessing differences in metabolic programing 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 IFNa/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.
populations of CD16+ and CD14+ monocytes, and resident LYVE1+ and LYVE1- macrophages (figure 1).

Interestingly each infiltrating and residential cellular subset appeared to differentiate into these phagocytic macrophages in our trajectory analysis, suggesting that distinct cellular subsets converged on this common phagocytic state (figure 1). These phagocytic macrophages were infrequent in kidney biopsies collected from patients with diabetes and hypertension. Intarnal myeloid cells from 155 lupus nephritis and 45 chronic kidney disease patients were integrated.

Methods We utilized functional genomic analysis of murine and human synovium including single cell-CITE and ATAC seq.

Results Here, we identify and characterize intravascular (i.v.) and extravascular (e.v.) synovial monocyte populations (Syn Ly6c- cells) which are distinct in surface marker expression and transcriptional profile from circulating monocytes, dendritic cells and tissue macrophages, and are conserved in in patients with rheumatoid arthritis. e.v. Syn Ly6c- cells are independent of NR4A1 and CCR2, long-lived and embryonically derived while the i.v. Syn Ly6c- cells are dependent on NR4A1, short lived and derived from circulating monocytes. e.v. Syn Ly6c- cells undergo increased proliferation and reverse diapedesis dependent on LFA1 in response to arthrogenic stimuli and are required for the development of inflammatory arthritis.

Conclusions These findings uncover a new facet of mononuclear cell biology and are imperative to understanding tissue-resident myeloid cell function in the synovium.

Transcriptomics

TISSUE-RESIDENT, EXTRAVASCULAR MONOCYTIC LIKE CELL IS CRITICAL FOR INFLAMMATION IN THE SYNOVIUM PERLMAN, HARRIS

Background In recent years, our understanding of the mononuclear phagocyte system has expanded, highlighting previously unknown complexities in cell origin and function. However, to date few studies have examined a role for monocytes in tissues, with the majority of studies centered on circulating monocytes, or monocyte-derived macrophages. While transcriptional studies have exposed critical gene signatures for classical monocytes (CM) and non-classical monocytes (NCM) in the bone marrow and circulation, no such studies examined heterogeneity and function at the tissue level.