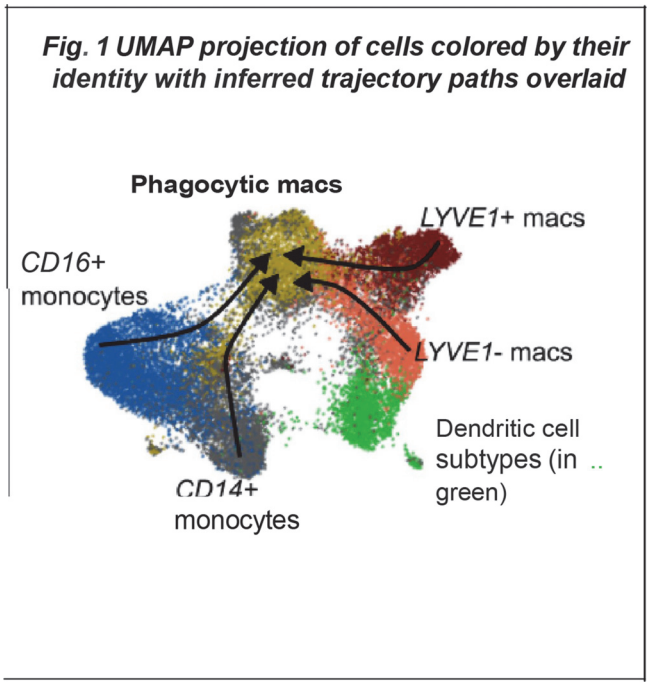
Results Assessing differences in metabolic programing between monocytes isolated from healthy volunteers or SLE patients, we observed that SLE monocytes exhibit enhanced rates of glycolysis and oxidative phosphorylation, accompanied by an increase in isocitrate dehydrogenase (IDH2) and its product, α-KG. 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.



Abstract 2002 Figure 1 Singlle-cell RNA sequencing identifies myelloid subsets in kidney biopsies from patiients with act1ive lupus nephritis. ~22,000 intrarenal monocytes and macrophages from 155 lupus nephritis patient biopsies were collected for single cell RNA-seq that enabled celllular identification (colored clusters). Trajectory analysis (black arrows) reveals that phagocytic macrophagies were derived from 4 distinct populatiions of infilltrating and residentia'l macrophagies (from bottom clockwiise: infiltrating *CD14*+ & *CD16*+ monocytes, residential *LYVE1*+ and *LYVE1* macrophages).

2002 DISTINCT INTRARENAL MONOCYTE AND MACROPHAGE POPULATIONS DIFFERENTIATE INTO A COMMON PHAGOCYTIC STATE THAT IS ASSOCIATED WITH HISTOPATHOLOGIC KIDNEY INJURY IN HUMAN LUPUS NEPHRITIS

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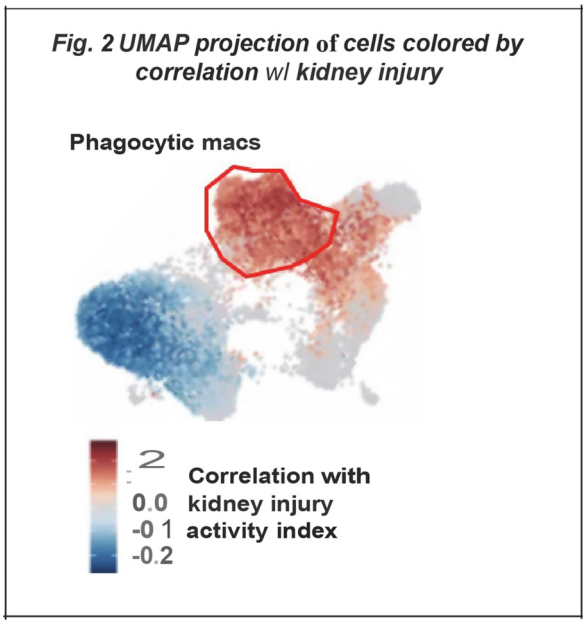
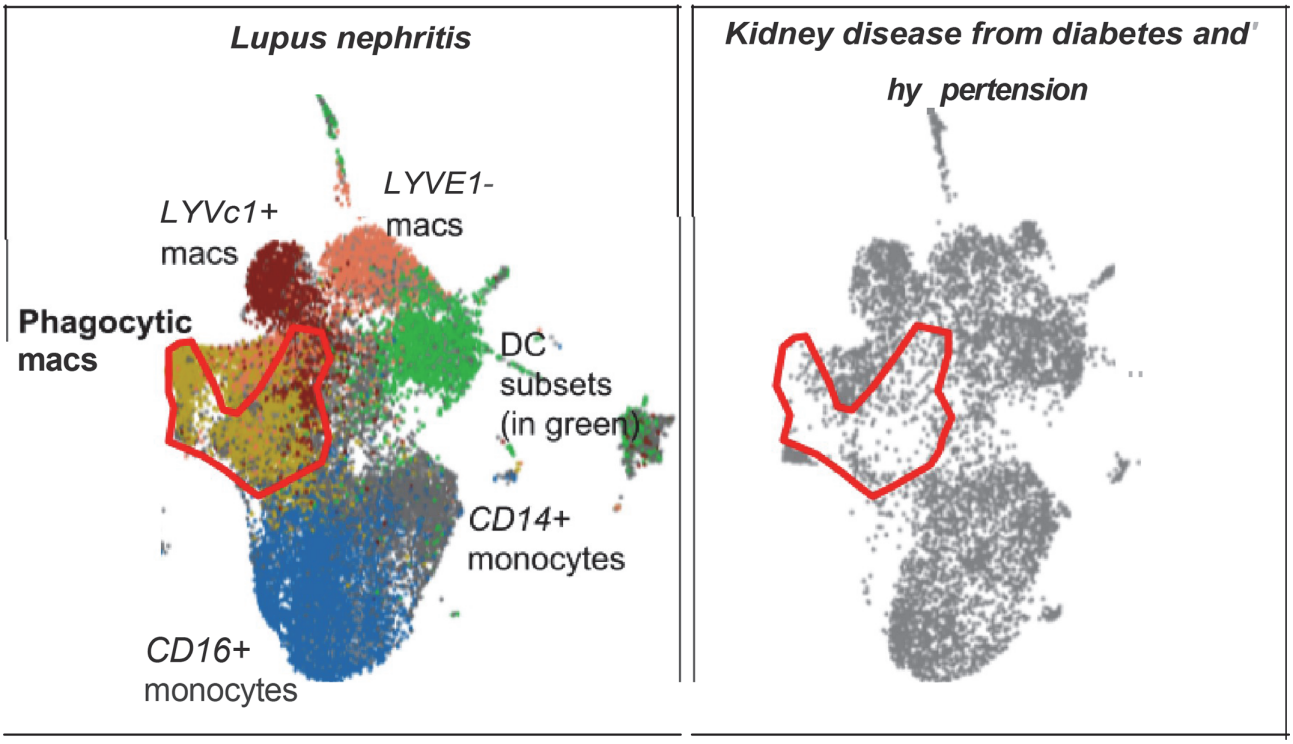
The presence of monocytes and macrophages in kidney biopsies has been associated with kidney injury and poor prognosis in lupus nephritis. Infiltrating and residential subtypes may acquire specialized functions in response to kidney damage that drive homeostatic or aberrant tissue remodeling. The functions 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



Abstract 2002 Figure 2 Phagocytiic 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 popullations in singl e ce'll RNA-seq and clinical data.



Abstract 2002 Figure 3 Phagocytic macmphages in lupus nephritis are infrequent in diabetic and hypertensive kidney disease.
Fig. 3 Phagocytic macrophages (red outlines) and a small subset of *LYVE1*+ macrophages in lupus nephritis are infrequent iin kidney biopsies from patients with diabetes and hypertension. Intrarenal myeloiidlcells from 155 lupus neplhriitis and 45 chronic kidney disease patients were integrated.

populations of CD16+ and CD14+ monocytes, and residential *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 non-autoimmune kidney disease from hypertension and diabetes (figure 3). Together, our findings suggest that phagocytic macrophages may play an important role in kidney remodeling and that these cells originated from distinct infiltrating and residential populations in response to kidney lesions found in lupus nephritis.

2003 TISSUE-RESIDENT, EXTRAVASCULAR MONOCYTIC LIKE CELL IS CRITICAL FOR INFLAMMATION IN THE SYNOVIUM PERLMAN, HARRIS

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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.

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

2101 GENE EXPRESSION PROFILING OF KEY IMMUNE/INFLAMMATORY PATHWAYS REVEALS MOLECULAR ENDOTYPES OF SLE WITH CLINICAL IMPLICATIONS

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