low CVR Group-2. Patients in Group-3 displayed an intermediate CVR but a pro-inflammatory immune cell profile. This metabolomic patient stratification was validated in a separate JSLE cohort. Importantly ApoB:A1 ratio was identified as a highly predictive biomarker (ROC area under the curve>0.99) distinguishing between JSLE patients in Group-1 and 2, indicating high and low CVR respectively. Finally, longitudinal analysis revealed that the ApoB:A1 ratio biomarker remained stable over time.

Conclusion: ApoB:A1 ratio and metabolomic lipoprotein signatures could be new biomarkers to predict CVR in JSLE patients. Patient stratification using these biomarkers could provide an opportunity for tailored disease treatments using lipid modification therapy and/or diet/lifestyle interventions.

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OP0149

CD4+ T CELLS FROM CHILDREN WITH ACTIVE JUVENILE IDIOPATHIC ARTHRITIS SHOW ABERRANT CHROMATIN ORGANIZATION AND CTCF LOCALIZATION ASSOCIATED WITH TRANSCRIPTIONAL ABNORMALITIES

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Background: Our group and others have shown that peripheral blood cells of children with juvenile idiopathic arthritis (JIA) display numerous transcriptional abnormalities. However, most of these studies have been performed on mixed cell types (peripheral blood mononuclear cells, whole blood). Little cell type specific data is available, making mechanistic inferences and links to disease pathogenesis difficult.

Objectives: To define transcriptional patterns in CD4+ T cells from children with polyarticular JIA and query mechanisms underlying transcriptional abnormalities.

Methods: We studied CD4+ T cells obtained from children with active polyarticular onset JIA and sought to identify epigenetic features associated with altered gene expression. We performed RNA-seq and ATAC-seq on a cohort of patients who had the active disease and were under treatment with methotrexate and etanercept (ADT), patients who fit criteria for clinical remission on medication (CRM), and healthy control children (HC). We used standard used the common dispersion protocol in EdgeR to identify differential gene expression. We used our recently developed and validated Hidden Markov Modeler for ATAC-seq software to identify differentially accessible regions, comparing ADT, CRM, and HC samples. We integrated ATACseq and RNAseq data using the BETA software package. After preliminary analysis revealed a potential role for the transcriptional regulator, CCCTC binding factor (CTCF) in the observed transcriptional patterns, we performed ChIPseq and HiChIP studies on an independent group of JIA CD4+ T cell samples.

Results: We found widespread transcriptomic differences between ADT and either HC or CRM patients. We identified 4,062 genes that showed differential expression between ADT and HC samples. Gene expression patterns from CRM samples were nearly identical to healthy controls, suggesting that remission largely results in normalization of CD4+ T cell transcriptomes. We performed transcription factor motif analysis on the ATAC-seq identified accessible regions that were associated with differentially expressed genes. We identified the motif for the CCCTC-binding factor (CTCF) as being enriched within these accessible regions, compared to accessible regions associated with non-differentially expressed genes. We performed CTCF ChIP-seq and HiChIP on a second cohort

of ADT and HC patients and were able to identify differential binding events, mediated by genetic alterations that interacted with differentially expressed genes.

Conclusion: Transcriptional abnormalities in CD4+ T cells of children with polyarticular JIA are associated with aberrant chromatin organization compared to healthy children. Some of this organization is due to aberrant localization of the transcriptional regulator CTCF, which is due, in some patients, to genetic variance.

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OP0150

MONOCYTE AND MACROPHAGE TRANSCRIPTIONAL PHENOTYPES IN SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS REVEAL TRIM8 AS A MEDIATOR OF IFNGAMMA HYPERRESPONSIVENESS AND RISK FOR MACROPHAGE ACTIVATION SYNDROME

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Background: Systemic juvenile idiopathic arthritis (SJIA) is a severe and distinct subtype of childhood arthritis. Children with SJIA are at risk for macrophage activation syndrome (MAS), a life-threatening episode of hyperinflammation driven by interferon-gamma (IFN γ). Previous work has suggested that monocytes in SJIA display hypersponsiveness to IFN γ , but the molecular basis of this remains unclear.

Objectives: Utilize transcriptional profiling of monocytes and macrophages in SJIA to identify polarization phenotypes including features of interferon response

Methods: Bulk RNA-sequencing (RNA-seq) was performed on purified monocytes from 26 patients with SJIA without over MAS. In addition, single-cell RNA-seq was performed on isolated bone marrow macrophages from control patients and patients with SJIA and MAS. THP-1 monocytic cells and primary human monocyte-derived macrophages (MDM) were transfected with TRIM8-specific or negative control small-interfering RNA prior to stimulation with IFN γ .

Results: RNA-seq of purified SJIA monocytes revealed marked transcriptional changes between cells from patients with high vs low serum ferritin levels. Pathway analysis demonstrated enriched upregulated gene ontology pathways including Response to External Stimulus ($p=2.73 \times 10^{-17}$), Defense Response ($p=2.66 \times 10^{-14}$) and Inflammatory Response ($p=1.95 \times 10^{-11}$). When comparing the SJIA monocyte signature to well-characterized polarization phenotypes, we identified substantial overlap with multiple polarization states, most notably M1 and M2b, but little evidence of IFN γ -induced signature. Among the most highly upregulated genes in SJIA monocytes was tripartite motif containing 8 (TRIM8), an E3 ubiquitin-ligase involved in activation of IFN γ through promoting degradation of the suppressor of cytokine signaling 1 (SOCS1). Elevated TRIM8 expression was found in monocytes from both active and inactive SJIA patients, with the highest levels in those with subclinical MAS features ($n=3$). Furthermore, we utilized single cell RNA-seq to determine gene expression profiles of bone marrow macrophages from a patient with subclinical MAS. This identified a distinct subpopulation of bone marrow macrophages which exhibited markedly altered transcriptional profiles, with alterations in gene pathways predicted for hemophagocytes in MAS, including cellular response to interferon gamma ($p=1.35 \times 10^{-14}$), endocytic vesicle membranes ($p=8.44 \times 10^{-14}$), and phagosome ($p=2.98 \times 10^{-9}$). These bone marrow macrophage also showed significantly increased TRIM8 expression (6.4-fold increase, $p=0.02$). To confirm the role of TRIM8 in augmenting macrophage responses to IFN γ , RNA interference was used to knock-down TRIM8 expression in THP-1 cells and MDM. TRIM8 knock-down macrophages showed significant reductions in both early (4 hour) and late (24-48 hours) response to IFN γ , as determined by production of CXCL9, a biomarker for MAS activity in both humans and animal models.

Conclusion: Peripheral blood monocytes in SJIA display markers of multiple polarization states, while during MAS tissue macrophages demonstrate a clear IFN γ response phenotype. TRIM8 is highly expressed in both monocytes and macrophages in SJIA, and in vitro knockdown of TRIM8 impairs IFN γ responses in macrophages. Together these data provide a molecular mechanism for monocyte hyperresponsiveness to IFN γ in SJIA, as well as a novel therapeutic target for MAS.

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