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Figure.

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OP0019 **DEFINING SYSTEMIC LUPUS ERYTHEMATOSUS MOLECULAR TAXONOMY THROUGH DATA-DRIVEN RESTRATIFICATION AND IDENTIFICATION OF CLUSTER-TAILORED DRUGS FOR A PERSONALIZED MEDICINE APPROACH**

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Background: Systemic Lupus Erythematosus (SLE) is characterized by lack of treatment diversity, largely empirical treatment decisions, and paucity of novel compound development.

Objectives: We sought to stratify SLE patients based on their molecular phenotype and predict personalized therapeutic compounds, tailored to the molecular fingerprint of each subgroup.

Methods: We performed a co-expression analysis using our publicly available whole blood RNA-seq data of 120 SLE patients. Modules of commonly regulated genes were established and used to re-stratify patients through hierarchical clustering, in a data-driven, clinically independent, manner. Next, we established an in silico, subgroup signature-based, drug prediction pipeline. Investigated drugs included both those currently in practice and those who have been tested in

SLE clinical trials and are listed in the iLINCS prediction databases. Finally, drug repurposing analysis was performed, to identify novel perturbagens that counteract group-specific SLE signatures.

Results: Molecular taxonomy identified five distinct lupus molecular endotypes, each characterized by a unique gene module enrichment pattern. A group defined by strong neutrophilic signature encompassed almost exclusively patients with active nephritis, while a B-cell expression group included patients with severe lupus phenotype. Metabolic processes enrichment defined a group of patients with disease of moderate severity and serologic activity. Finally, patients with mild lupus features were distributed in two groups, which demonstrated enhanced basic cellular functions, myelopoiesis, and autophagy. The ability of different compounds to reverse the transcriptomic aberrancies observed in each patient group was examined. Bortezomib efficiently reversed disturbances in the "neutrophilic" cluster. Azathioprine and ixazomib might be a reasonable option for patients of the "B-cell" cluster, whereas fostamatinib appeared efficacious for the "Metabolism" patient subgroup.

Conclusion: The clinical spectrum of SLE encompasses distinct molecular endotypes, each defined by unique pathophysiologic aberrancies, which can be utilized to guide personalized care and direct novel compound development.

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OP0020 **HOMEBOX D TRANSCRIPTION FACTORS SHAPE DIFFERENTIAL JOINT ENVIRONMENT BETWEEN ANTERIOR FINGER JOINTS AND THUMB**

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Background: The expression of embryonic Homeobox (HOX) genes is tightly regulated based on anatomic location in human adult dermal and synovial fibroblasts. Previously, we showed that HOX-D10, -D11 and -D13 are higher expressed in synovial fibroblasts from small distal joints from the hands and feet, in particular in digits II-V and wrists compared to thumb and that this expression pattern is epigenetically imprinted¹. The consequences of the tightly restricted expression of these transcription factors are largely unknown.

Objectives: To elucidate the function of HOXD10, -D11 and -D13 in synovial fibroblasts.

Methods: Synovial tissues were isolated from paws of naïve C57BL/6 mice (n=8), from patients with rheumatoid arthritis (RA), osteoarthritis (OA) and from healthy controls. Synovial fibroblasts were cultured and transfected with GapmeR to silence HOXD10, -D11, and -D13, respectively or with control GapmeR. RNA sequencing was performed on the NovaSeq platform and pathway analysis was done using R packages and web-based tools (GSEA, EnrichR, Cytoscape). HOXD target gene expression was measured by qPCR (n=3-6).

Results: To confirm and further analyze the distinctive expression pattern of HOXD genes, we measured their expression in healthy synovial tissues of different joints of human feet and mouse paws. Similar to what we had found in hands, HOXD10, -D11 and -D13 were less abundant in the joints of the first digit of human feet compared to digits II-V (n=3-4 in each joint). Measurements in joints of mouse paws showed lower expression of HoxD10, -D11 and -D13 in distal interphalangeal joints compared to proximal interphalangeal joints and metacarpophalangeal (MCP) joints, respectively. Silencing of HOXD10, -D11 and -D13, affected the expression of 5333, 2217 and 7347 genes, respectively, in cultured RA synovial fibroblasts from human wrists (n=3).

There were more transcripts equally regulated by HOXD10 and -D13 (40% of all HOXD10 and 31% of all HOXD13 regulated transcripts), than by HOXD11 and either -D10 or -D13 (18% of all HOXD10 regulated genes and 16% of all HOXD13 regulated genes), suggesting most redundancy between HOXD10 and -D13 (Figure 1). Among genes differentially expressed in SF isolated from MCP II-V versus thumb joints, 19%, 4% and 33% were regulated by HOXD10, -D11 or -D13, respectively, supporting a role for HOXD13 in particular in shaping the joint specific environment. All three HOXD transcription factors regulated genes involved in cell cycle progression, demonstrating dependence of synovial fibroblasts on these HOX genes for cell division. Other enriched pathways were Toll-like receptor and integrin signaling pathways, regulation of unsaturated fatty acid synthesis and autophagy and extra-cellular matrix protein organization. We could