A Graph-Theoretic-Approach Applied to Modular-Repertoire-Analysis Identifies Shared Gradual Whole Blood Interferon Signatures in Systemic Lupus Erythematosus and Primary Sjögren's Syndrome Patients and Reveals New Interferon-Related Modules in Disease Progression

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Ilya Korsunski[1], Noémie Jourde-Chiche[2], Peter Gregersen[3], Damien Chaussabel[4], Laurent Chiche[5] and **Naomi I. Maria**[6], [1]Center for Genomics and Human Genetics, Feinstein Institute for Medical Research, Manhasset, NY, [2]Nephrology, AP-HM, Department of Nephrology, CHU Conception, Marseille, France, [3]Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institute for Med Res, Manhasset, NY, [4]Translational Medicine, Sidra Medical and Research Center, Doha, Qatar, [5]Internal medicine, Hopital europeen, Marseille, France, [6]Center for Autoimmune and Musculoskeletal Diseases, Feinstein Institute for Medical Research, Manhasset, NY

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Background/Purpose: There is significant clinical and molecular heterogeneity among patients suffering from systemic autoimmune diseases, such as systemic lupus erythematosus (SLE) and primary Sjögren's Syndrome (pSS). Deciphering this heterogeneity could allow the molecular stratification of patients in terms of prognosis and therapeutic targets. Our previous work using a modular repertoire analysis (MRA) has demonstrated that the IFN signature observed in SLE patients is not restricted to a mere type I IFN signature, but involves the gradual activation of 3 distinct IFN modules driven by various IFN types including IFNγ. Although a type I IFN signature has been described in patients with pSS, a detailed MRA in pSS is still lacking. Here we aimed to refine MRA and discover new transcriptional signatures in SLE and pSS, by applying a novel graph-theoretic-approach (GTA) to reveal the progression of module activation patterns in these diseases.

Methods: Blood transcriptomic microarray datasets, including that of SLE patients (n=157 samples; LUPUCE cohort) fulfilling ACR-criteria and pSS patients (n=133; UKPSSR) fulfilling American European Consensus Group (AECG)-criteria, were analyzed using MRA followed by GTA. MRA was performed using a blood modular framework comprising 260 modules. A novel GTA, based on the Extended Suppes Bayes Causal Network (ESBCN), was used to generate an ordered, branching progression model of modular activation. Disease-specific causal graphs in selected datasets were built in order to generate hypotheses regarding disease progression for a particular disease. Significance to clinical characteristics was evaluated using Fisher's exact test and ANOVA, for categorical and continuous characteristics, respectively.

Results: The GTA-to-MRA analysis confirmed the previously described pattern of gradual activation of IFN modules in SLE patients: first M1.2 (81.5%), then M3.4 (67.5%) and finally M5.12 (22.3%). Interestingly, this gradual IFN signature was also observed in pSS patients who exhibited activation of *1* (64%), *2* (37%) or all *3* (8%) IFN modules. Additionally, GTA-to-MRA identified a dual mode of disease progression in SLE after the activation of the IFN modules M1.2 and M3.4: either completion of the IFN signature, to include the more IFNγ-related module M5.12 and with completion of a newly identified 4th IFN-related module M8.59, or the activation of a neutrophil module M5.15 associated with renal involvement. In

pSS, a dual mode of progression identified comparable completion of IFN signature to include M5.12, ending with the new IFN module M8.59, or activation of a 5th IFN-related module M8.95. Solely 6% of pSS patients portrayed a neutrophil signature, not linked to IFN progression, possibly identifying a relevant new pSS subgroup.

Conclusion: The application of GTA to blood MRA reveals for the first time the sharing of gradual activation of IFN modules between SLE and pSS, identifies new IFN-related modules through the observation of progression patterns, and discerns a pattern of progression involving a neutrophil signature associated with renal involvement in patients with SLE. Defining distinct molecular subgroups will aid in development of more tailored therapeutic regimens.