THU0014

COMPARATIVE TRANSCRIPTOME ANALYSES ACROSS TISSUES AND SPECIES IDENTIFY TARGETABLE GENES FOR HUMAN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND LUPUS NEPHRITIS (LN)

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Background: Systemic Lupus Erythematosus (SLE) is a complex disease associated with the dysfunction of multiple tissues and cells. The causal tissue for each disease phenotype is not known a priori. Despite improvements in diagnosis and treatment, major organ involvement (such as the kidneys) contributes significantly to morbidity and mortality that still remain increased. There is an unmet need for timely targeted therapy.

Objectives: RNA-sequencing was performed to investigate the patterns of transcription variation across tissues between healthy and lupus-prone mice at different stages of lupus, and how these patterns associate with human Systemic Lupus Erythematosus (SLE).

Methods: NZB/W-F1 lupus prone mice were sacrificed at the pre-puberty, pre-autoimmunity and nephritic stage. Age-matched C57BL/6 were used as controls. An "effector" tissue (spleen) and "end-organs" (kidneys, brain) were collected. Total RNA was isolated, and mRNA-sequencing was performed. A time-series analysis was developed and differentially expressed genes (DEGs) were analyzed with DESeq. Hierarchical clustering and functional enrichment analysis were performed with gProfiler. Human orthologs of mouse tissue DEGs were identified in the whole-blood RNA-sequencing dataset comprised of 55 lupus-nephritis (LN), 65 non-LN SLE patients and 58 healthy individuals (HI). Human orthologs were compared to human DEGs. Using machine learning, human orthologs identified in the mouse dataset were used to predict kidney involvement in the human dataset, which was split in training and validation sets.

Results: Lupus susceptibility and progression signatures at different tissues and different stages of the disease were identified. Tissue-specific signatures and a common cross-tissue signature were also described. Previously described and novel biological processes and pathways were revealed. The comparative murine-human transcriptome analysis identified human orthologs from the mouse spleen-signature (including CCL5, IFIT and HLA genes) that are involved in systemic autoimmunity. It also identified human orthologs from the kidney- and brain-signature (including FCGR2A, C1Q, JAK1 and APOA2) that are involved in major "end-organ" damage and response mechanisms. Using a neural network model, 193 human orthologs accurately predicted LN patients vs HI (accuracy=0.86, sensitivity=0.82, specificity=0.91 in the validation set). Using a support vector machine model, 30 human orthologs and age and gender were the best predictors of LN vs non-LN SLE patients (accuracy=0.71, sensitivity=0.73, specificity=0.69 in the validation set).

Conclusion: Murine tissue gene signatures identified by RNA-sequencing analysis revealed biological processes and pathways that could be potentially used as biomarkers or therapeutic targets in human SLE. Comparison of the murine tissue-transcriptome with the whole-blood human-transcriptome revealed common gene signatures, demonstrating similar biological processes and pathways. Machine learning identified a murine kidney lupus signature that can accurately predict kidney involvement in human SLE. Validation in other datasets is ongoing.

References:

[1] Panousis NI, et al. Ann Rheum Dis 2019;78:1079

Acknowledgments: This work was supported by FOREUM, SYSCID and ERC -Advanced Grant

Disclosure of Interests: Eleni Frangou: None declared, Panayiotis Garantziotis: None declared, Maria Grigoriou: None declared, Aggelos Banos: None declared, Nikolaos Panousis: None declared, Emmanouil Dermizakis: None declared,

Table 2. Baseline characteristics and predictors of progression

	PROGRESSORS N= 17	NON-PROGRESSORS N=19	UNIVARIABLE OR (95% CI)	MULTIVARIABLE OR (95% CI)
Mean age y.o.(SD)	50.12 (10.01)	52.53 (9.22)	0.97 (0.91-1.04) p=0.446	-
Female (%)	11 (64.7)	14 (73.7)	1.52 (0.37-6.35) p=0.560	-
RF titre, mean (SD)	77.18 (99.93)	36.58 (53.39)	1.01 (0.99-1.02) p=0.162	1.01 (1.01-1.03) p=0.035
ACPA titre, mean (SD)	123.44 (109.44)	103.77 (116.18)	1.00 (0.99-1.01) p=0.594	0.99 (0.98-1.00) p=0.283
ANA+ (%)	2 (11.8)	5 (26.3)	2.68 (0.45-16.11) p=0.282	-
CRP, mean (SD)	5.41 (5.31)	2.97 (1.96)	1.21 (0.96-1.52) p=0.104	1.31 (0.99-1.73) p=0.055
ESR, mean (SD)	12.24 (11.97)	12.16 (8.44)	1.00 (0.94-1.07) p=0.981	-
Shared epitope (%)	8 (47.1)	10 (52.6)	1.25 (0.34-4.63) p=0.739	-
IFN-Score-A (-ΔCt), mean (SD)	-5.81 (1.07)	-6.23 (1.08)	1.45 (0.76-2.77) p=0.253	1.97 (0.83-4.66) 0.124
IFN-Score-B (-ΔCt), mean (SD)	-4.21 (0.56)	-4.52 (0.45)	3.53 (0.83-14.97) p=0.087	8.82 (1.02-76.38) p=0.048

George Bertias Grant/research support from: GSK, Consultant of: Novartis, Dimitrios Boumpas: None declared, Anastasia Filia: None declared

DOI: 10.1136/annrheumdis-2020-eular.4102

THU0015

TYPE I INTERFERON SIGNATURE PREDICTS PROGRESSION TO INFLAMMATORY ARTHRITIS IN ACPA+ AT-RISK INDIVIDUALS WITHOUT CLINICAL SYNOVITIS

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Background: Interferon (IFN) is known to play a role in the pathogenesis of many autoimmune diseases, among them, rheumatoid arthritis (RA). A study showed that two interferon-stimulated gene expression scores (IFN-Score-A and IFN-Score-B) can be used to predict progression to connective tissue disease (CTD) in at-risk individuals, positive for anti-nuclear antibodies (ANA+) [1]. This validated score could potentially be applied to individuals at-risk of RA.

Objectives: To investigate the role of type I IFN in patients at-risk of RA and assess its potential role as a biomarker to predict progression to inflammatory arthritis (IA).

Methods: PBMC samples were taken from 36 at-risk individuals positive for anti-citrullinated protein antibodies (ACPA+), with a non-specific musculoskeletal complaint but no clinical synovitis and a normal ultrasound scan at baseline (BL). 17 of them developed IA later on, and had a second sample taken at the moment of progression. The other 19 did not progress and had a second sample taken after 1 year. Expression of IFN stimulated genes was assessed using TaqMan. T-test was used to compare the expression of the genes at the two time points of each individual. Binary logistic regression was used to assess BL predictors of progression. Multivariable analysis was adjusted for confounders such as C-reactive protein (CRP) rheumatoid factor (RF) and ACPA titre.

Results: Table 1 shows the list of tested genes. There were no differences in the gene expression of progressors at BL and at the moment of IA diagnosis. Similarly, no differences were found between the non-progressors at BL and after 1 year. Comparing BL samples from progressors and non-progressors, there was a trend to higher expression of IFN-score-B in the progressors (Mann Whitney p=0.055), whereas IFN-score-A was similarly expressed in both groups. This is similar to the results found in a cohort of ANA+ individuals at risk of progressing to CTD [1]. Multivariable analysis showed that IFN-score-B and RF titre were predictive for IA progression with an odds ratio (OR) of 2.18 (p=0.048) and OR 1.01 (p=0.035).

Table 1. Interferon stimulated genes and scores A and B

GENE	IFN score	GENE	IFN score
CCL8	A	BST2	B
CEACAM1		IFI16	
CXCL10		IFIH1	
GBP1		LAMP3	
IFI27		NT5C3B	
IFI44		PHF11	
IFI44L		SERPING1	
IFIT1		SOC31	
IRF7		SP100	
ISG15		STAT1	
RSAD2		TAP1	
XAF1		TRIM38	
		UBE2L6	
		UNC93B1	

Conclusion: These exploratory results suggest that IFN changes in IA progressors precede subclinical inflammation on ultrasound. A preliminary risk model shows that IFN-score-B could be useful to predict progression to IA in at-risk of RA individuals; however, these results require validation in a larger at-risk cohort.