THU0243

HSA_CIRC_0123190 FUNCTIONS AS A COMPETITIVE ENDOGENOUS RNA TO REGULATE APLNR EXPRESSION BY SPONGING HSA-MIR-483-3P IN LUPUS NEPHRITIS

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Background: Lupus nephritis (LN) is one of the most severe complications of systemic lupus erythematosus (SLE). Circular RNAs (circRNAs) can act as competitive endogenous RNAs (ceRNAs) to regulate gene transcription, which is involved in mechanism of many diseases, such as, autoimmunity diseases. However, the role of circRNA in lupus nephritis has been rarely reported.

Objectives: In this study, we aim to investigate the clinical value of circRNAs and explore the mechanism of circRNA involvement in the pathogenesis of LN.

Methods: Renal tissues from three untreated LN patients and three normal controls (NCs) were used to identify differently expressed circRNAs by RNA sequencing (RNA-seq). Validated assays were used by quantitative reverse transcription polymerase chain reaction (qRT-PCR). Correlation analysis and receiver operating characteristic (ROC) curve were used to reveal the clinical value of selected circRNA, miRNA and mRNA. The interactions between circRNA and miRNA, or miRNA and mRNA were further determined by luciferase reporter assay. The degrees of renal fibrosis between the two groups were compared by Masson-trichrome staining and immunohistochemistry staining.

Results: 159 circRNAs were significantly dysregulated in LN patients compared with NC group. The expression of hsa_circ_0123190 was significantly decreased in renal tissues of patients with LN ($p=0.014$), as same as the sequencing results. The area under the ROC curve of hsa_circ_0123190 in renal tissues was 0.820. Bio-informatic analysis and luciferase reporter assay illustrated that hsa_circ_0123190 can act as a sponge for hsa-miR-483-3p which was also validated to interact with APLNR mRNA. APLNR mRNA expression was positively related with chronicity index (CI) of LN ($R^2=0.452$, $p=0.033$). Finally, the factors of renal fibrosis, especially TGF- β ($p=0.018$), were more pronounced in the LN group.

Conclusion: Hsa_circ_0123190 could function as a ceRNA to regulate APLNR expression involved in renal fibrosis by sponging hsa-miR-483-3p in LN

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THURSDAY, 04 JUNE 2020

SLE, Sjögren's and APS - clinical aspects (other than treatment)

THU0244

3 YEAR FOLLOW UP OF AN AT-RISK CONNECTIVE TISSUE DISEASE COHORT: ANALYSIS OF CLINICAL, GENE EXPRESSION AND FLOW CYTOMETRIC BIOMARKERS

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Background: We previously reported results from the first 118 "At-Risk" of autoimmune connective tissue disease (AI-CTD) individuals (i.e. ANA positivity, non-specific symptoms of ≤ 1 year and treatment naïve). At 1 year, 16% progressed to meet classification criteria for an AI-CTD. This was predicted by high baseline interferon (IFN) Score B and family history of RMD[1].

However, some may have progressed at later time points, or had clinically significant disease despite not meeting diagnostic criteria. Longer term outcomes, baseline and follow up flow cytometry biomarkers were never reported.

Objectives:

- (i) Describe detailed analysis of 3-year follow-up data of the At-Risk cohort
- (ii) Evaluate flow cytometric biomarkers as predictors of these outcomes
- (iii) Analyse follow up biomarkers

Methods: We conducted a prospective observational longitudinal study of At-Risk individuals in Leeds ($n=150$). Patients were assessed at baseline, then annually for 3 years. Depending on diagnostic criteria and need for therapy, patients were grouped as follows:

1. Absolute non-progressors (no clinical diagnostic criteria)
2. Undifferentiated CTD (U-CTD) (≥ 1 clinical criteria at baseline persisting at follow-up but not meeting criteria). This group was subdivided into those who required treatment with an immunosuppressant (IS) excluding antimalarials and those who did not
3. Year 1 progressors (meeting criteria for an RMD by 1 year)
4. Late progressors (meeting criteria for AI-CTD beyond 1 year follow-up).

Bloods were analysed at baseline and 1 year for two IFN-stimulated gene expression scores previously described[2], monocytes and subsets of B and T cells using flow cytometry. Association between clinical criteria, biomarkers at baseline and long term outcomes were tested using ANOVA.

Results: 3 year follow up data was available in 147/150 patients. Outcomes were: Absolute non-progressors: 63/147 (43%); U-CTD: 54/147 (37%); Year 1 progressors: 21/147 (14%) [SLE=18; pSS=3]; Late progressors (in years 1-2): 9/147 (6%) [SLE=7; pSS=2]. None progressed or required IS initiation beyond the first 2 years of follow-up. In U-CTD group, 7/54 (13%) were prescribed an IS. This work describes a larger group of 36/147 (24%) At-Risk individuals who developed clinically significant disease (CSD: progressors or need for IS) versus clinically non-significant disease (CNSD: absolute non-progressors or UCTD not needing IS). Analysis of baseline biomarkers between CSD and CNSD confirmed a significant difference in IFN Score B (mean difference -0.74, $p = 0.027$), but not IFN Score A (mean difference -0.68, $p = 0.15$). In flow cytometry analysis, there was also a significant difference in percentage monocytes (mean difference -4.09, $p = 0.004$) but no other subset. Absence of clinical criteria at baseline did not predict clinical outcome, and no one clinical criterion had greater predictive value.

In follow up samples we noted a significant reduction in expression of IFN Score B in both groups, regardless of whether they received antimalarials or IS therapy.

Conclusion: Here we report findings of a larger group of 24% At-Risk individuals who developed CSD (progressors and patients who did not meet criteria but needed IS therapy). These results provide a more complex picture of IFN activity in the initiation of SLE than previously suspected. First, we confirm that a specific subset of ISGs rather than a classic IFN signature predicts progression. Second, the reduction in IFN-Score-B in both groups suggests that IFN Score B activity is a transient phenomenon, playing a greater role in disease initiation than in disease maintenance.

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THU0245

PENALIZED REGRESSION ANALYSIS IDENTIFIES CRITERIA AND NON-CRITERIA FEATURES THAT MAY INCREASE THE ACCURACY OF EXISTING SETS OF CRITERIA FOR CLASSIFYING SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Background: The ACR-1997, SLICC-2012 and EULAR/ACR-2019 classification criteria have high sensitivity and specificity for SLE, yet they classify non-overlapping groups of patients suggesting that they can be supplemented with additional features to improve their diagnostic performance.

Objectives: To identify criteria and non-criteria manifestations that are significantly associated with SLE in clinical practice and can be used to complement the existing sets of classification criteria.

Methods: Individual items from all three classification criteria (ACR-1997, SLICC-2012, EULAR/ACR-2019) and non-criteria features were analyzed in a randomly selected sample of 800 adults diagnosed with SLE or control rheumatologic diseases (1:1 ratio). The classification performance of each set of criteria was analyzed in combination with complementary features; multivariable least absolute shrinkage and selection operator (LASSO) logistic regression was performed for feature selection. We calculated the diagnostic odds ratio (DOR) of the criteria and the additional features retained in each model.

Results: The EULAR/ACR-2019 and SLICC-2012 criteria have increased accuracy for SLE classification as compared to the ACR-1997 criteria (univariate DOR: 243.2 and 157.3 versus 78.8, respectively). In multivariable regression based on the ACR-1997 criteria, inclusion of additional features such as maculopapular rash, alopecia and hypocomplementemia significantly enhanced the model predictive capacity (area under the curve [AUC]: 0.95 versus 0.87 of the ACR-1997 criteria alone). Similar analysis based on the SLICC-2012 and EULAR/ACR-2019 criteria identified photosensitivity as an additional criterion significantly associated with SLE (multivariable DOR: 5.4 and 9.4, respectively). Accordingly, models including photosensitivity had superior predictive capacity over the criteria-only models (AUC: 0.94 versus 0.91 for SLICC-2012, 0.96 versus 0.91 for EULAR/ACR-2019). Furthermore, non-criteria features including Raynaud's/livedo reticularis, anti-RNP antibodies, splenomegaly and myocarditis were independently associated with SLE thus enhancing further the predictive capacity of criteria-based models.

Conclusion: We identified a number of criteria and non-criteria features which can be used in combination with the existing sets of criteria to increase classification of SLE patients in clinical practice. Photosensitivity could be considered as an additional feature to improve sensitivity of the recent classification criteria.

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THU0246

DIAGNOSTIC CLUSTER PROFILING OF PATIENTS IN A REAL-WORLD DATA SET WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Previous systemic lupus erythematosus (SLE) studies have identified potential clusters of SLE clinical manifestations post diagnosis.

Objectives: To describe the presentation of SLE at diagnosis across different cohorts of patients and describe management and outcomes after diagnosis within clusters.

Methods: Cross-sectional study of 263 rheumatologists in the US and EU5. Data were collected from the Adelphi Real World 2015 Lupus Disease Specific Programme. Rheumatologists completed patient record forms (PRFs) for the next 5 prospectively consulting SLE patients; these patients completed patient self-completion (PSC) forms describing how SLE affected them. PRF data includes patient's characteristics and management history. PSCs focused on similar data collection, including patient reported outcome measures on the humanistic burden. Age at diagnosis, symptoms at diagnosis, organ involvement at diagnosis, and severity at diagnosis were used as covariates in a latent cluster analysis.

Results: Data were extracted from 1376 PRFs. Cluster analysis resulted in up to 6 clusters, and disease understanding led to the selection of a 4-cluster solution. Cluster 1 displayed the mildest disease, characterised by joint involvement, while cluster 2 displayed more skin involvement in conjunction with joint. Cluster 3 were characterised by renal involvement and cluster 4 had skin and joint involvement, but also high constitutional and haematological involvement at diagnosis (Table 1).

Table 1 Cluster analysis

Organ involvement at diagnosis, n (%)	Clusters					p-value
	Overall (n=1304)	1 (n=210)	2 (n=493)	3 (n=162)	4 (n=439)	
Musculoskeletal	1145 (87.8)	174 (82.9)	444 (90.1)	134 (82.7)	393 (89.5)	0.0065
Mucocutaneous	898 (68.9)	5 (2.4)	397 (80.5)	95 (58.6)	401 (91.3)	<0.0001
Neuropsychiatric	87 (6.7)	19 (9.0)	9 (1.8)	16 (9.9)	43 (9.8)	<0.0001
Cardiorespiratory	176 (13.5)	36 (17.1)	14 (2.8)	22 (13.6)	104 (23.7)	<0.0001
Gastrointestinal	44 (3.4)	8 (3.0)	14 (2.8)	8 (4.9)	14 (3.2)	0.6115
Ophthalmic	47 (3.6)	0	20 (4.1)	10 (6.2)	17 (3.9)	0.0102
Renal	213 (16.6)	15 (7.1)	9 (1.8)	162 (100)	27 (6.2)	<0.0001
Constitutional	425 (32.6)	45 (21.4)	89 (18.1)	55 (34.0)	236 (53.8)	<0.0001
Haematological	452 (34.7)	64 (30.5)	22 (4.5)	80 (49.4)	286 (65.1)	<0.0001
Severity at diagnosis, n (%)						
Mild	209 (16.0)	55 (26.2)	99 (20.1)	1 (0.6)	54 (12.3)	<0.0001
Moderate	806 (61.8)	122 (58.1)	324 (65.7)	75 (46.3)	285 (64.9)	
Severe	289 (22.2)	33 (15.7)	70 (14.2)	86 (53.1)	100 (22.8)	

Significant between-cluster differences were observed when comparing outcomes; cluster 4 have been diagnosed longest (mean weeks diagnosed 354.6 v. 1: 232.6, 2: 228.7, 3: 338.2, p<0.0001). Cluster 3 consulted more in the last 12 months (mean number of visits 7.9 vs. 1: 5.7, 2: 6.3, 4: 7.6).

Significant differences were also observed between clusters in relation to current treatment proportions: corticosteroid (highest cluster 3: 78.4%), immunosuppressant (highest cluster 3: 75.3%), biologic DMARD (highest cluster 4: 17.8%) and antidepressant (highest cluster 4: 4.1%).

Conclusion: This study demonstrates the heterogeneity of SLE at diagnosis and highlights four distinct presentations of the disease at diagnosis. Significant proportions of patients present with advanced disease, these clusters go on to present the greatest burden demonstrating the need for better diagnostic tools and novel earlier intervention.

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THU0247

FREQUENCY AND PREDICTORS OF THE LUPUS LOW DISEASE ACTIVITY STATE IN CHINESE PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: AN OBSERVATIONAL COHORT STUDY

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Background: As a consensus-based definition of minimally acceptable disease activity in systemic lupus erythematosus (SLE), Lupus Low Disease Activity State (LLDAS) has been well-validated and widely accepted. However, no data about the time to LLDAS in Asian ethnicity has been reported so far.

Objectives: To estimate the time to LLDAS and the predictors of time to LLDAS in our prospective observational cohort of Chinese patients with SLE.

Methods: Patients were from Peking University First Hospital SLE cohort and those having not fulfilled LLDAS at enrolment were included in this study. The time to LLDAS and annual cumulative probabilities of LLDAS achievement were estimated by the Kaplan-Meier approach. The predictors of time to LLDAS were identified by univariate and multivariable Cox proportional hazards.

Results: A total of 574 patients with SLE were included and 435 (75.8%) of them achieved LLDAS during a median 4.2 years of follow-up. The median time to LLDAS was 19.0 months and the cumulative probabilities at 1, 2, 3, 5 and 10 years were 19.8%, 57.6%, 72.0%, 85.1% and 98.0%, respectively. In multivariable Cox models, older age at disease onset, treatment-naïve and hydroxychloroquine prescription were found to be independent predictors of shorter time to LLDAS, after adjusted by daily prednisone dose, SLE Disease Activity Index 2000 and physician's global assessment. Finally, we developed a matrix model based on the identified independent predictors to present the time to LLDAS in patients with respective characteristics.

Conclusion: Our study proved that LLDAS is attainable as an early treatment target for SLE in Chinese patients. The older age at disease onset, treatment-naïve and hydroxychloroquine prescription were independent predictors of shorter time to LLDAS.