

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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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.4025

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:

- Describe detailed analysis of 3-year follow-up data of the At-Risk cohort
- Evaluate flow cytometric biomarkers as predictors of these outcomes
- 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:

- Absolute non-progressors (no clinical diagnostic criteria)
- 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
- Year 1 progressors (meeting criteria for an RMD by 1 year)
- 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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Disclosure of Interests: Sabih-UI Hassan: None declared, Zoe Wigston: None declared, Antonios Psarras: None declared, Katie Dutton: None declared, Md Yuzaiful Md Yusof: None declared, Edward Vital Grant/research support from: AstraZeneca, Roche/Genentech, and Sandoz, Consultant of: AstraZeneca, GSK, Roche/Genentech, and Sandoz, Speakers bureau: Becton Dickinson and GSK

DOI: 10.1136/annrheumdis-2020-eular.3661

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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