

Circulating miRNAs profile and risk of end-stage renal disease in type 1 diabetes.

Eiichiro Satake¹, Marcus G. Pezzolesi², Adam M. Smiles¹, Monika Niewczas¹, Andrzej S. Krolewski¹

¹*Joslin Diabetes Center, Boston, MA*

²*University of Utah, Salt Lake City, UT*

Background: MicroRNAs (miRNAs) are short endogenous, non-coding RNA molecules which are expressed in a variety of human biofluids. These molecules are involved in gene regulation and play important roles in the pathogenesis of various renal diseases including diabetic nephropathy. However, miRNA signatures associated with diabetic nephropathy in Type 1 diabetes (T1D) has not been fully established. The objective of this study was to determine the circulating miRNA signature that is associated with risk of end-stage renal disease (ESRD) in T1D patients with chronic kidney disease (CKD).

Methods: The expression levels of 2,083 miRNAs from the human miRNA genome were measured in baseline plasma samples from 196 T1D patients with CKD3. We applied a new technology, HTG Molecular Diagnostics EdgeSeq platform for miRNA sequencing and quantitation. Data were normalized by quantile normalization with sample weights.

Results: Among 196 patients, there were 90 patients who progressed to ESRD within 10 years follow-up. After filtering out miRNAs with low expression level, a total of 988 miRNAs were detectable in plasma samples from these study participants. To identify miRNAs associated with risk of ESRD, we performed fold change analysis and Cox model analysis. In total, there were 28 miRNAs significantly correlated to risk of ESRD (p-value <10⁻⁴). For these candidate miRNAs, we divided them into 5 groups according to the Cox model analysis, and selected 5 representative miRNAs (exemplars) from each group. Multivariate Cox analysis showed that 4 of them were still associated with risk of ESRD after adjusting for baseline ACR and eGFR. Pathway analysis revealed that 3 exemplars were associated with insulin signaling pathway and/or the TGF- β pathway.

Conclusion: We discovered a profile of circulating miRNAs that is a very strong predictor/determinant of progression to ESRD in patients with T1D. This profile is represented by exemplar miRNAs which can be used to develop a multi-miRNA prognostic biomarker to predict time to onset of ESRD. Furthermore, some of these miRNAs can be used as therapeutic targets to prevent or treat progressive renal decline that leads to ESRD in diabetes.

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