RENAL TISSUE EXPRESSION OF microRNAs IN ANCA-ASSOCIATED VASCULITIS

Matic Bošnjak [1], Emanuela Boštjančič [1], Željka Večerić-Haler [2,3], Maja Frelih [1] and Nika Kojc [1]

[1] Institute of Pathology, Faculty of Medicine, University of Ljubljana, Korytkova ulica 2, 1000 Ljubljana, Slovenia ; [2] Clinical Department of Nephrology, University Clinical Center Ljubljana, Zaloška 7, 1000 Ljubljana; [3] Faculty of Medicine, University of Ljubljana, Vrazov trg 2, 1000 Ljubljana, Slovenia.

OUTLINE & AIM

In ANCA-associated vasculitis (AAV), the accurate characterization of disease-specific microRNAs (miRNAs) is lacking despite mounting evidence of their implication in the pathogenesis of AAV.

Renal tissue miRNA expression profile in AAV has not been comprehensively studied, especially compared to both healthy adults and patients with various glomerulonephrites other than AAV. To identify a potential AAV-specific miRNA expression profile, we have compared pooled tissue samples of treatment-naive AAV to both healthy controls and controls with other glomerulonephrites.

Disease- and tissue-specific alterations of miRNAs thus characterized could serve as non-invasive biomarkers of disease activity and of the underlying AAV-related renal inflammatory involvement. Additionally, this knowledge could contribute to better understanding of the multifactorial etiopathogenesis of AAV by addressing its epigenetic aspect.

METHODS

Pooled RNA isolates from formalin-fixed, paraffin-embedded renal biopsy material of 26 treatment-naive MPO^+ and $PR3^+$ AAV patients with florid renal involvement and 26 control patients (10 without pathohistological change on light microscopy, ie. CTRL and 16 with various glomerulonephrites other than AAV, ie. GN) were included for the comprehensive miRNA expression profiling of the 752 panel-included miRNAs by qPCR.

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Differences in individual miRNA expression values ($\Delta\Delta$Ct), normalized to global mean average, were tested for statistical significance between the pooled samples.

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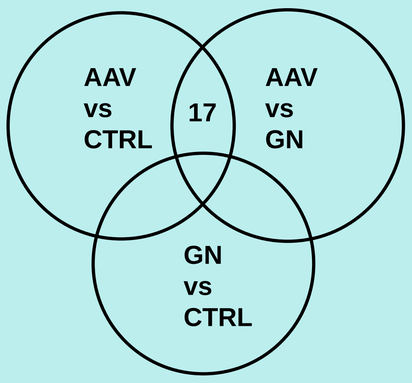
The miRNAs demonstrating statistical significance in expression difference between AAV and control group pools were then annotated to signalling pathways and to their targets.

Age, gender, eGFR, daily proteinuria values and the degree of interstitial fibrosis/tubular atrophy at kidney biopsy were recorded for each included case and every effort was made to match AAV patients and controls by age, gender, and IF/TA to the maximum extent possible.

RESULTS

17 individual miRNAs differentiated AAV from control pools with statistical significance.
A considerable subset were implicated in processes considered important in AAV pathogenesis such as monocyte and macrophage polarization, T-cell activation/differentiation, renal fibrogenesis, endothelial injury and in cytokines such as IL-6 and B-cell activating factor.



The screening process also identified 7 miRNAs that have not yet been affiliated with the pathogenesis of any non-neoplastic renal disease.

MicroRNA	MicroRNA FAMILY	KNOWN IMPLICATIONS
hsa-miR-21-3p	no	TGF-β/Smad3 signaling (fibrosis)
hsa-miR-24-2-5p	miR-24	/
hsa-miR-30a-3p	miR-30	BAFF, Notch1, p53 signalling (podocyte injury)
hsa-miR-30b-5p	miR-30	IFN-α signalling (mesangial proliferation in LN), Notch1, p53 signalling (podocyte injury)
hsa-miR-30c-5p	miR-30	Notch1, p53 signaling (podocyte injury)
hsa-miR-96-5p	no	/
hsa-miR-130b-5p	miR-130b	/
hsa-miR-142-5p	no	SOCS1/STAT6 signalling (macrophage polarization)
hsa-miR-150-5p	no	PU.1 transcription factor (macrophage polarization)
hsa-miR-181a-5p	no	SHP2/STAT3 signalling (macrophage polarization)
hsa-miR-204-5p	miR-204/211	IL-6 receptor (chemokine generation in renal tubular epithelium)
hsa-miR-376a-5p	miR-376	/
hsa-miR-508-3p	miR-606	/
hsa-miR-542-5p	no	TGF-β signaling (Th17 and T_{reg} differentiation)
hsa-miR-582-5p	no	FOXO1 (monocyte apoptosis)
hsa-miR-769-5p	no	/
hsa-let-7a-5p	let-7	CD11b signaling (macrophage polarization)

CONCLUSION

Altered expression of miRNAs in AAV-affected renal tissue and their (potential) tissue-serum concordance could and should form the basis for determining AAV-related renal involvement noninvasively. The fact that a substatial proportion of hitherto identified miRNAs relate to established biological processes that are considered to be important in AAV pathogenesis lends credence to the results. However, a validation study of these candidate differentiatially expressed miRNAs in an independent and larger cohort is mandatory to establish their diagnostic and/or prognostic utility.

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