The possibility of urine microRNAs as a predictive biomarker for treating male LUTS/BPE with phosphodiesterase type 5 inhibitors

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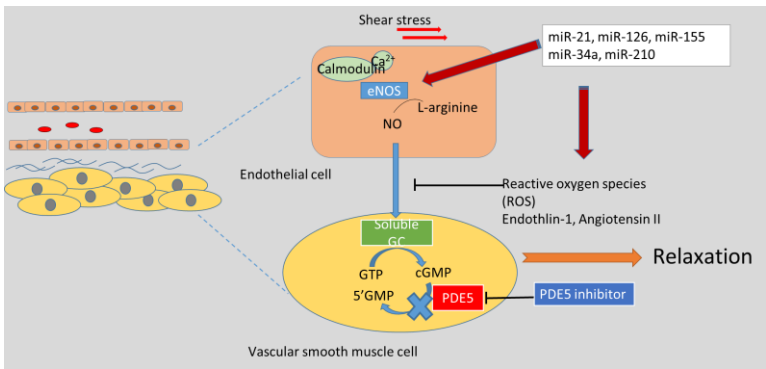
Hypothesis / aims of study

There are only a few reports about conveniently evaluating and predicting the effectiveness of PDE5 inhibitors from the viewpoint of these pathophysiological mechanisms. In this study, we focused on some urine microRNAs that possibly can regulate the function of endothelial cells via the control of several genes. We investigated whether the expression pattern of these urine microRNAs is associated with the clinical effects in the male LUTS/BPE patients treated with PDE5 inhibitors.

Study design, materials and methods

This clinical study protocol was approved by the institutional review board of Osaka City University. A total of 70 patients with male LUTS/BPE were enrolled to this study after the agreement with an informed consent. The patients received the administration of a PDE5 inhibitor, Tadalafil®, 5mg/ day for 12 weeks and their spot urine was used for measurement of the expression of microRNAs before and at 4 weeks after the treatment. Subjective urinary symptom score (I-PSS and OABSS), QOL and N-QOL index were estimated before and at 4, 8 and 12 weeks after administration of tadalafil. Objective urinary parameters (maximum urinary flow rate; Qmax and average urinary flow rate; Qave) in the uroflowmetry were measured before and at 12 weeks after the treatment. The clinically meaningful improvement (CMI) was defined as (1) ≥25% baseline-to-endpoint total IPSS improvement or (2) ≥2.5ml/s baseline-to-endpoint Qmax improvement. Finally, a total of 55 patients, except for the patients who discontinued the administration, was examined. The compartment of microRNA in each urine sample was collected by the purification kit and followed by the quantification real time RT-PCR using TaqMan Probe. We examined four microRNAs (miR-21, miR-126, miR-155-5p, miR-210-3p) associated with the function of endothelial cells.

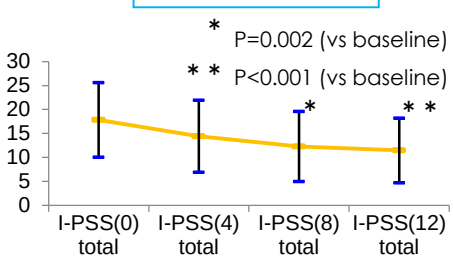
Crosstalk between endothelium and vascular smooth muscle possibly regulated by microRNAs



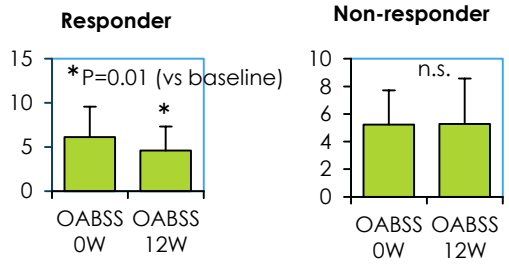
Patients' background

	Responder	Non-responder	P value
Patient No.	36	19	
Age	70(50-87)	73(52-82)	0.069
BMI	24.2(17.0-29.4)	24.1(19.8-30.8)	0.4
Prostate volume	22(10-110)	28.5(6.2-71.7)	0.43
I-PSS total	18(5-35)	16(5-29)	0.32
Storage symptoms	6(1-15)	7.5(1-12)	0.34
Voiding symptoms	10(1-20)	9(0-20)	0.48
QOL	5(2-6)	5(3-6)	0.41
OABSS	6(1-13)	4.5(1-9)	0.48
N-QOL index	13(1-38)	14(1-32)	0.82
BPH severity			
mild	7	3	
moderate	14	10	0.21
severe	15	6	
Add on other drugs			
no	15	8	0.75
yes	21	11	

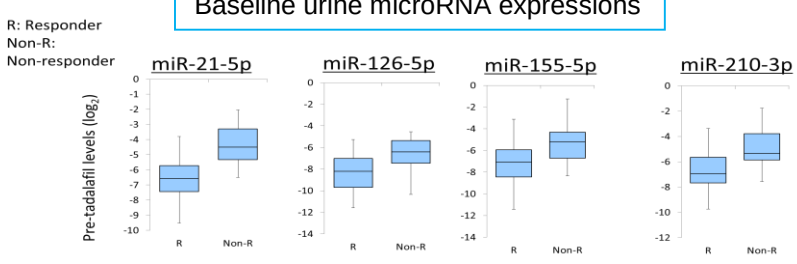
Change in I-PSS



Change in OABSS

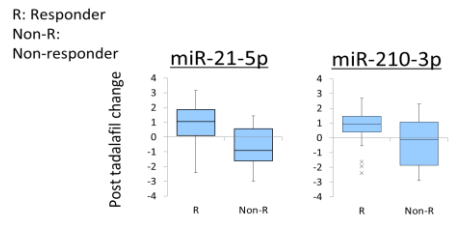


Baseline urine microRNA expressions



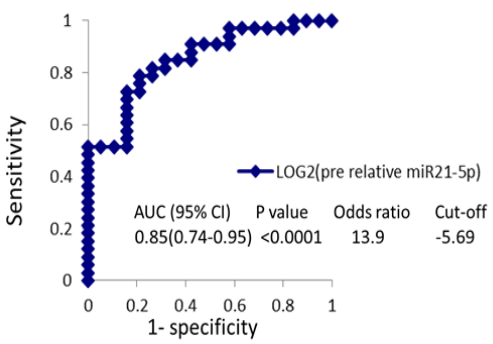
	miR-21-5p	miR-126-5p	miR-155-5p	miR-210-3p
Median Non-R/R (antilog)	0.68	0.78	0.73	0.77
P value	<0.001	0.01	0.006	0.002

Change between baseline-to-4 weeks in urine microRNA expressions



	miR-21-5p		miR-210-3p	
Median fold change (log: post/pre)	1.04	-0.91	0.94	-0.13
P value	<0.01		0.02	

ROC analysis



Results

In the multivariate regression analysis, the baseline urine miR-21 level (P=0.024, OR: 6.2, 95%CI; 0.24-3.4) was positively associated with the clinical response of tadalafil treatment for male LUTS/BPE. Furthermore, the ROC analysis assessing the association urine baseline urine miR-21 and response of tadalafil showed AUC of 0.85 (95% CI; 0.74-0.95).

Concluding message

Regulation of several endothelium-associated microRNAs expression possibly link to effects of PDE5 inhibitors through the proliferation and protection of endothelial cells. The urine endothelium-associated microRNA (e.g. miR-21) may be a biological predictor for the treatment with PDE5 inhibitors for male LUTS/BPE patients.

COI Disclosure Information

Tomoaki Tanaka

I have no financial relationships to disclosure