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GENE EXPRESSION PATTERN OF TRANSIENT RECEPTOR POTENTIAL C IN BLADDER TISSUE OF INTERSTITIAL CYSTITIS

Hypothesis / aims of study

The pathogenesis of interstitial cystitis (IC) is still unknown. A previous study demonstrated increased expression of genes involved in pronociceptive inflammatory reactions including TRPM2, TRPV1, TRPV2, TRPV4, ASIC1, NGF in Hunner type IC and different expression patterns in non-Hunner type IC (1). Recently, a specific increase in the expression of TRPC1 and TRPC4 in bladder-innervating sensory neurons and the sprouting of sensory fibers in the bladder mucosa was demonstrated in a rat cystitis model induced by repeated cyclophosphamide injections (2). However, few studies investigated expression of TRPC in human IC sample. In this study, the difference of mRNA expression of TRPC was assayed and compared among bladder tissue of control, Hunner type IC and non-Hunner type IC.

Study design, materials and methods

Patients with IC scheduled for hydrodistension or those with non-invasive bladder cancer undergoing transurethral resection (as controls) were enrolled. Diagnosis of IC was based on the clinical guidelines for IC and hypersensitive bladder (3). Bladder biopsy specimens of 1) non-Hunner type IC, 2) non-Hunner's lesion of Hunner type IC, 3) Hunner's lesion of Hunner type IC, and 4) non-cancerous portions of bladder cancer (control), were placed immediately in ice-cold RNAlater and subjected to quantitative real-time reverse-transcription polymerase chain reaction. The mRNA expressions of TRPC channels in IC specimens were compared with those in the controls. Symptom severity at patients' enrolment was assessed by O'Leary and Sant's symptom index (OSSI), problem index (OSPI), and visual analogue scale for pain (VAS). For each sample, gene expression levels were normalized to that of GAPDH and calculated as fold expression relative to the median of the control group. Level of gene expression was analyzed by the Wilcoxon rank sum test, and its relation with symptom severity was evaluated by Pearson product-moment correlation coefficient, with $p < 0.05$ considered statistically significant. R version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analysis.

Results

A total of 50 subjects (non-Hunner type IC, 17; Hunner type IC, 22; control, 11) were enrolled and all the IC patients were compatible with NIDDK criteria (Table 1). Compared with control samples, the mRNA expression of TRPC1 significantly increased in non-Hunner type IC (Table 2). In Hunner type IC, non-Hunner lesions demonstrated a significant increase in expression of TRPC1, TRPC3, TRPC4 and TRPC5, and Hunner's lesions showed an increase for TRPC4 alone. The increased expression of TRPC4 at Hunner's lesions was most pronounced (4.02 fold) followed by TRPC5 at non-Hunner lesions of Hunner type IC (3.03). Correlation between symptom severity and mRNA expression of TRPCs was ambiguous; in non-Hunner type IC, TRPC1 and TRPC3 expressions were related to OSSI and OSPI, respectively, whereas in Hunner type IC, TRPC1 and TRPC5 expressions of non-Hunner lesions and TRPC6 expression of Hunner's lesions were related to OSSI.

Table 1: Patients' backgrounds

Variables	BC (Control)	Non-Hunner type IC	Hunner type IC
Patients (male /female)	11 (8/3)	17 (6/11)	22 (2/20)
Age at diagnosis (Range)	69.7±12.3 (48-82)	56.1±18.5 (20-73)	70.6±10.6 (36-83)
O'Leary & Sant's symptom index	2.73±1.01	13.1±3.15*	14.1±4.06*
O'Leary & Sant's problem index	2.73±1.27	11.5±3.37*	12.4±3.24*
Visual analogue scale for pain (0-10)	0.55±0.69	5.25±2.77*	7.55±1.85*

BC: bladder cancer, IC: interstitial cystitis, *: p <0.05 versus control

Table 2: mRNA expression of TRPC family in the bladder tissue of interstitial cystitis

Gene symbol	**Non-Hunner type IC**		**Hunner type IC**			
			non-Hunner's lesions		**Hunner's lesions**	
	Fold change	**p-value (n=17)**	**Fold change**	**p-value (n=22)**	**Fold change**	**p-value (n=22)**
TRPC1	1.48	0.0369*	1.99	0.0213*	1.11	0.807
TRPC3	1.70	0.0659	1.82	0.0325*	1.05	0.8657
TRPC4	1.22	0.8897	1.88	0.0213*	4.02	0.0007***
TRPC5	1.65	0.2255	3.03	0.0011**	2.16	0.0822
TRPC6	1.22	0.4869	1.38	0.1053	1.23	0.5344

*p<0.05, **p<0.01, ***p<0.001 versus control

Table 3： Correlations between symptom severity and mRNA expression of TRPCs

	OSSI		OSPI		VAS	
Gene symbol	**r**	**p value**	**r**	**p value**	**r**	**p value**
TRPC1	-0.878	0.021*	0.165	0.754	0.040	0.940
	-0.463	0.040*	0.044	0.855	0.129	0.587
	-0.253	0.282	0.024	0.920	-0.210	0.374
TRPC3	0.327	0.527	-0.921	0.011*	--0.293	0.574
	-0.137	0.566	0.182	0.443	0.183	0.439
	0.149	0.531	0.368	0.111	-0.021	0.929
TRPC4	-0.621	0.189	0.146	0.783	-0.422	0.404
	-0.121	0.612	-0.149	0.532	-0.489	0.029*
	-0.132	0.580	-0.298	0.202	0.006	0.981
TRPC5	-0.519	0.291	-0.271	0.680	0.314	0.544
	-0.532	0.016*	-0.039	0.869	0.125	0.600
	-0.366	0.113	-0.189	0.426	-0.241	0.305
TRPC6	-0.706	0.117	0.678	0.139	0.230	0.662
	-0.408	0.074	0.029	0.902	0.255	0.278
	-0.520	0.019*	-0.399	0.081	-0.220	0.352

r: Pearson's correlation coefficient, *: $p<0.05$, **: $p<0.01$

The values of the upper, middle and lower panels represent r between symptom score and mRNA expression in non-Hunner type IC, non-Hunner's lesions of Hunner type IC and Hunner's lesions of Hunner type IC, respectively.

Interpretation of results

The present study demonstrated a different pattern of increased expression of TRPC genes among subtypes of IC. TRPC1 and TRPC3 expressions may link to the symptom severity in non-Hunner type IC, whereas in Hunner type IC, TRPC1, TRPC5 and TRPC6 expressions may do so.

Concluding message

The results of this study support the hypothesis that TRPC family has some roles in pathogenesis of IC as well as other TRP families. Further researches are required to elucidate the function of TRPC family in the bladder.

References

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