Gene expression profile of spinal cord and dorsal root ganglion in a rat model of cisplatin-induced peripheral neuropathic pain

Myung Ha Yoon^{1,2}, Keun Suk Park¹, Jeong Il Choi¹, Hyung Gon Lee¹, Yeo Ok Kim¹

¹Department of Anesthesiology and Pain Medicine, Chonnam National University, Medical School, Gwangju, Korea.
²Center for Creative Biomedical Scientists at Chonnam National University, Gwangju, Korea.

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a major side effect of anti-cancer drugs. However, the underlying mechanisms remain poorly understood.

Microarray gene analyses of nervous system tissues hold great promise for the identification and development of novel targets for persistent pain modulation.

This study aimed to analyze the genes associated with pain in CIPN rats and identify novel therapeutic targets for treating CIPN.

MATERIALS & METHODS

Animal Preparation

- Male Sprague-Dawley rats weighing 130-150 g were used in the present study.
- Chemotherapy-induced peripheral neuropathy (CIPN)**
:CIPN was induced by intraperitoneal injection of cisplatin (2 mg/kg) once a day during four days

Behavioral Pain Testing

- Assessment of mechanical allodynia**

The extent of pain was evaluated by measurement of the paw withdrawal threshold to mechanical stimulation delivered using von Frey filaments. Only rats exhibiting marked allodynia (a withdrawal threshold < 5 g) after cisplatin injection.

Gene expression profiling in CIPN rats

- Microarray analysis**
: GeneChip® Rat Gene 2.0 ST Array

At 5 and 14 days after CIPN development extracted lumbar spinal cord dorsal horn and L5 DRG. And then, we used microarray analysis to examine gene expression, and was validated by real-time PCR

RESULTS

Fig. 1. Hindpaw withdrawal responses to von Frey filaments were measured after administration of different doses of cisplatin or vehicle. Each line represents mean $\pm$ SEM. B: baseline withdrawal threshold before administration of cisplatin or vehicle. *P < 0.001.

Fig. 2. Count of differentially expressed probes at 5 and 14 days after CIPN development. : fold change ≥ 1.5 & 2, p < 0.05

Gene Symbol	G3/G1.fc	G3/G1.adj.pval	Gene Symbol	G4/G2.fc	G4/G2.adj.pval	Gene Symbol	G5/G1.fc	G5/G1.adj.pval	Gene Symbol	G6/G2.fc	G6/G2.adj.pval
LOC689064	-5.899631	8.34E-17	Abcb1b	3.947795	0	LOC689064	-4.933718	3.92E-14	Eda2r	3.153604	2.03E-09
Hbb	-5.387068	3.07E-29	Cdkn1a	3.457452	2.51E-09	Sgk1	3.326972	3.32E-07	Abcb1b	2.63821	1.34E-05
Hba1	-4.176073	4.08E-21	Omd	3.098452	0	Hbb	-3.197892	1.14E-14	Cdkn1a	2.635017	1.04E-05
	3.836463	0	LOC102551941	2.905105	1.16E-12	Chodl	3.18282	0	Ckap2	2.172719	3.24E-05
Sgk1	3.977624	0	Eda2r	2.863513	2.58E-09	Hba1	-3.038579	1.82E-09	Rrm2	2.11952	0.02566905
	2.746947	0.004798283	Ephx1	2.476667	0		2.771578	0.004213818	Mslal2	-2.09923	0.016025894
Abcg2	2.672018	0	Fabp7	-2.45174	9.26E-21		-2.709362	2.26E-12	Ephx1	2.099113	3.80E-07
LOC100910745	-2.54009	5.84E-13	Slc7a11	2.258406	2.07E-08	LOC100233206	2.657852	0.002312680			
	2.448435	0.000262547	Bcan	-2.22899	0.000305527	LOC100910765	-2.640877	6.05E-12			
Pdk4	2.333299	2.53E-07				Prph	2.271701	6.31E-09			
LOC287187	-2.293488	1.13E-06	Sult1a1	2.214154	0	Slc18a3	2.202122	0.002090414			
Gpd1	2.226292	2.46E-09	Npy	2.184733	0.046343895	Spp1	2.157801	1.87E-10			
Mtln	2.13594	0.000132138	Cd80	2.120369	7.76E-05	LOC287167	-2.094573	5.72E-06			
Chodl	2.118005	6.74E-08		2.068963	9.44E-05	Mit219-2	-2.047282	1.87E-10			
Sult1a1	2.049864	0.011974918	Osr1	2.031545	7.25E-06						
Slc19a3	2.037175	5.48E-05	Fmo2	2.025232	1.99E-06						
Cd74	-2.008462	1.45E-05									

Table 1. Analysis of differentially expressed genes at 5 and 14 days after CIPN development. : fold change ≥ 2 , p < 0.05

Fig. 3. Validation results of Wnt related genes by real-time PCR. ND: no detection

CONCLUSION

These findings indicate a crucial gene underlying the etiology of chemotherapy-induced peripheral neuropathy and suggest that targeting the Wnt signaling may be an effective approach for treating CIPN.