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Full-length article

Effects of navelbine and docetaxel on gene expression in lung cancer cell strains[1]

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Key words

cDNA macroarray; lung neoplasms; navelbine; docetaxel

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Abstract

Aim: To search genes sensitivity to the anti-cancer drugs navelbine (NVB) and docetaxel (DOC) in small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) cell strains. **Methods:** The sensitivity of 4 strains of SCLC and 6 strains of NSCLC to NVB and DOC was evaluated using the MTT assay. The expression of 1291 sensitive-related genes to the anti-cancer drugs in 10 lung cancer cell strains was measured using cDNA macroarrays and the relationship was analyzed. **Results:** In total, there were 56 ($r \geq 0.4$) genes sensitive to NVB and DOC. For NVB: 36 genes were sensitive to NVB, 20 co-expressed genes between the SCLC+NSCLC set and the NSCLC set; 27 expressed genes and 7 specially expressed genes in the SCLC+NSCLC set; and 29 expressed genes and 9 specially expressed genes in the NSCLC set. For DOC, 50 genes were sensitive to DOC, 12 co-expressed genes between the SCLC+NSCLC set and the NSCLC set; 24 expressed genes and 12 specially expressed genes in the SCLC+NSCLC set; and 38 expressed genes and 26 specially expressed genes in the NSCLC set. The genes sensitive to NVB and DOC in lung-cancer cell stains were mainly divided into the following 4 categories: signal transduction molecules, cell factors, transcription factors and metabolism-related enzymes and inhibitors. **Conclusions:** There were obvious differences in genes related to NVB and DOC between SCLC and NSCLC cell strains, but the same as categories of function.

Introduction

Chemotherapy failure in lung cancer is usually caused by multidrug resistance. Discovering ways to overcome resistance to chemotherapeutic drugs is the main problem to be resolved. There are different mechanisms of resistance to different drugs, while various mechanisms can produce resistance to the same drug. Many of these mechanisms, such as drug transition protein (CABC and lung cancer resistant protein), change the molecular target, the state of detoxifying enzymes, the obstruction of apoptosis, the repairing ability of DNA or the activity of oncogenes. Much work has been reported on the function of drug resistant genes in lung cancer using calcium antagonists and the MTT assay, as well as other methods, but there are few reports about the relationship between anticancer drug sensitivity and related genes.

Gene chip technology has provided a powerful tool to study the expression profile of genes and their related genes, providing much better data than the previous gene-monitoring techniques. The cDNA gene chip techniques can be divided into 2 types according to the different density of hybridized genes: (i) macroarrays[1]; and (ii) microarrays[2]. Macroarrays are better than microarrays in that they are economical, have a high level of repeatability and therefore accuracy, and they do not require special instruments. We therefore used macroarrays to measure the gene expression profiles of 10 lung cancer cell strains. We also measured drug sensitivity to navelbine (NVB) and docetaxel (DOC) in 10 lung cancer cell strains using the MTT assay, and analyzed the relationship between them. The precision of our results was then confirmed by reverse transcription–polymerase chain reaction (RT-PCR). This outcome has significance for clinical therapy.

Materials and methods

Cell strains There were 11 cell strains used in the experiments, of which 6 were NSCLC strains (LK-2, PC-7, PC-9, PC-14, A549 and Lu65) and 4 were SCLC strains (H69, N231, Lu135 and SBC-3); BET2A was used as a control. All cell strains were cultured in RPMI 1640 supplemented with 5% fetal bovine serum at 37 ºC in humidified air containing 5% CO_2.

Concentration adjustment of anticancer drugs The concentration of NVB was adjusted to within the range 0.005 μg/mL–10 μg/mL using RPMI 1640, and DOC was adjusted to within the range 0.005 μg/mL–50 μg/mL using dimethylsulphoxide (DMSO).

Measurement of cell sensitivity to anticancer drugs Sensitivity to the anticancer drugs was assessed using the MTT assay[3]. The IC_{50} was calculated using the Reed-Muench method[4], while the index of sensitivity was calculated as: IC_{50}/peak plasma concentration (PPC).

Anticancer drug sensitivity-related genes Genes related to anticancer drug sensitivity were assessed using cDNA macroarray.

Isolation of mRNA from total RNA Total RNA was isolated from 1×10^8 cells, which were grown in suspension, at A_{260}/A_{280} ratio$\in$[1.8, 2.0]. mRNA was isolated by incubation with oligo-dT-magentic beads (Toyobo Co, Osaka, Japan), followed by washing to remove non-specific binding.

Reverse transcription-polymerase chain reaction and labeling of the mRNA polyA$^+$RNA 0.8 μg was picked and RT-PCR was carried out using the RT, Rever TraAce (Toyobo Co, Osaka, Japan). The probes were labeled with biotin by incorporation of biotin-16-dUTP during the synthesis of cDNA.

Making the filters Gene Navigator cDNA Array System-Cancer Selected (Geneticlab, Sapporo Co, Osaka, Japan) was used. Anti-cancer drug-sensitivity genes (1291 species) were spotted onto the filter in duplicate. There were 280 non-mammalian genes and 49 housekeeping genes as negative controls[5]. A list of the set of genes on the filter is shown on the web site(http: //www.toyobo.co.jp/seihin/xr/product/genenavi/genenavigator.html).

cDNA array hybridization Filters were preincubated in 30 mL Perfect Hyb (Toyobo Co, Osaka,Japan) at 68 ºC for 30 min. Biotin-labeled probes (100 μL) were denatured at 100 ºC for 5 min before being added to the prehybridization solution. The filters were incubated in the hybridization mixture at 68 ºC for 20 h, then the filters were washed 3 times at 68 ºC for 10 min using 30 mL 2×SSC/0.1% sodium dodecylsulfate (SDS) and 0.1×SSC/0.1% SDS.

Signal measuring After washing the filters, specific signals on the filters were detected using the Imaging High Chemifluorescence Detection Kit (Toyobo Co, Osaka,Japan). Vistra ECF substrate (AttoPhos) (Amersham Pharmacia Biotech,Uppsala,Sweden)was used as the chemifluorescence substrate. Substrate images were acquired by Fluorimager (Amersham Pharmacia Biotech,Uppsala, Sweden).

Measuring gene expression The drugs were clustered on the basis of Pearson correlation coefficients relating their patterns across the 10 cell strains to the expression patterns of genes. These correlation coefficients were calculated for each combination of gene and drug by taking the level of expression of the gene in each cell line, enhancing it by the corresponding sensitivity of the cell to the drug, summing the results over all of the cell strains and renormalizing. This produced 1291 correlation coefficients (1 for each gene and target) for each of the 2 drugs. We then clustered the 2 drugs on the basis of these correlation coefficients.

Computer soft analysis "A" was designed as a drug active model (the drug sensitivity of 10 lung cancer cell strains to NVB and DOC-IC_{50}), Tr was the related data model of the level of mRNA expression (the expression of 1291 genes from 10 lung cell strains), and gene expression data included the rate of expression intensity of measuring gene and BET2A cells.

Statistical analysis The AT-clustered image map (CIM; Figure 1 and Figure 2) summarizes the relationship between drug activity and gene expression by means of the clustering method. In this CIM, drugs were together with related genes, and genes were also together with related drugs. Each color reflects the connection of one gene and one drug. For example, a red point (high positive Pearson correlation coefficient) indicates that cell strains with more expressed genes tend to be more sensitive to the agent; a blue point (high negative Pearson correlation coefficient) indicates the opposite; a yellow point and a green point indicate a lower correlation.

Expression of clusterin, galectin-1 mRNA Following RT-PCR, Generunner software was used to design specific primers (Table 1), and the specificity of the primer was proved through the BLAST(Basic Local Alignment Search Tool) internet database. Total RNA was extracted from LK-2 and A549 cell lines according to methods described previously and the first chain was finished through RT-PCR. b-Actin was used as an internal control.

The PCR amplification products were visualized by bromide-ethyl pastille following sodium dodecyl sulphate-polyacrylamide gel electrophoresis with the DL-2000 molecular weight standard (Generunner).

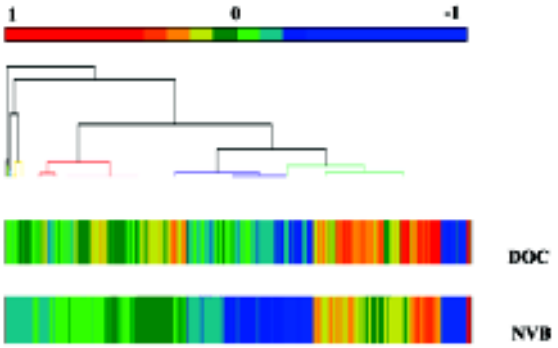

Figure 1. Comparison of the effects of docetaxel (DOC) and navelbine (NVB) on the clustered image map in 10 lung cancer cell strains.

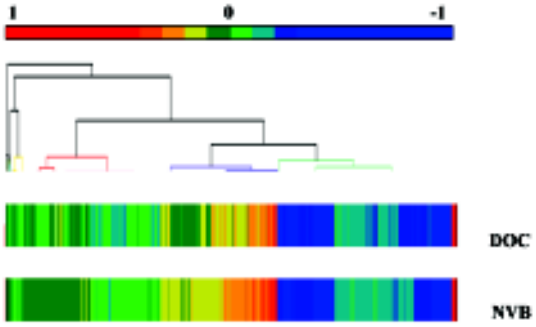

Figure 2. Comparison of the effects of docetaxel (DOC) and navelbine (NVB) on the clustered image map in NSCLC. Gene expression analysis for genes sensitive to DOC and NVB in lung cancer cell strains is detailed in Table 3 and Table 4.

Table 1. Length of reverse transcription-polymerase chain reaction primers and products.

Sample	Sequence of primer (5'-3')	Product size (bp)
Clusterin		469
Forward	GGAGTGTGCAATGAGACCATGATGG	
Reverse	GCTGAGCCTCGTGTATCATCTCAAGG	
Galectin		422
Forward	AATCATGGCTTGTGGTCTGGTC	
Reverse	CTGGCTGATTTCAGTCAAAGGC	
β-Actin		501
Forward	AGCGCAAGTACTCCGTGTG	
Reverse	AAGCAATGCTATCACCTCC	

Results

Comparison of the sensitivity of the lung cancer cell strains to navelbine and docetaxel The anti-cancer drug sensitivity of the lung cancer cell strains to NVB was greater than that to DOC (Table 2).

Comparing the clustered image map of the drugs with the clustered image map of genes The study related the 1291 gene expression profiles from the CIM of the lung cancer cell strains to NVB and DOC (Figure 1 and Figure 2). In the 10 lung cancer cell strains, there were more genes positively correlated to DOC than to NVB, but there were more genes negatively related to NVB than to DOC. Of the 6 NSCLC cell strains, there were more genes that expressed either positive or negative correlations to DOC than to NVB.

Table 2. Comparison of the anticancer sensitivity of lung cancer cell strains to navelbine (NVB) and docetaxel (DOC)*.

Cell stains	IC_{50}/μg·mL^{-1}		IC_{50}/PPC	
	NVB	Doc	NVB	Doc
N231	0.006±0.004	6.035±2.685	0.057±0.038	3.018±1.342
Lu135	0.022±0.016	0.529±0.189	0.223±0.116	0.265±0.095
H69	0.020±0.016	4.716±1.801	0.200±0.165	2.342±0.875
SBC-3	0.508±0.104	>50	5.080±1.044	>25.00
Lu65	0.064±0.030	3.606±1.388	0.637±0.301	1.803±0.694
LK-2	0.025±0.014	26.312±3.329	0.247±0.142	13.140±1.679
PC-9	1.430±0.436	21.336±5.380	14.303±4.365	13.970±8.235
PC-7	2.642±0.960	2.456±1.223	26.423±9.599	1.229±0.612
PC14	>10	20.381±1.816	>100	10.019±0.181
A549	>10	21.308±2.114	>100	9.989±0.509

*The peak plasma concentration (PPC) of NVB is 0.1 μg/mL; the PPC of DOC is 2 μg/mL.

In total, there were 51 genes sensitive to NVB and DOC in the 10 lung cancer cell strains, 3.95% of all the genes in the experiment. There were 24 genes sensitive to DOC (11 positive Pearson correlation coefficients, 13 negative Pearson correlation coefficients), and 27 genes sensitive to NVB (3 positive Pearson correlation coefficients, 24 negative Pearson correlation coefficients, Table 3).

Table 3. Analysis of drug sensitivity-related genes in lung cancer cell strains to docetaxel (DOC) and navelbine (NVB).

Pearson correlation coefficient	DOC			NVB		
	Negative	Positive	Total	Negativ	Positive	Total
≥0.4	8	10	18	13	2	15
≥0.5	4	1	5	4	1	5
≥0.6	1	0	1	5	0	5
≥0.7	0	0	0	2	0	2
Total	13	11	24	24	3	27

In total, there were 67 genes sensitive to DOC and NVB in 6 NSCLC cell strains. They made up 5.19% of all the experimental genes. Thirty-eight genes were sensitive to DOC and 29 genes were sensitive to NVB. There were more genes negatively related to NVB and DOC than positively related (Table 4).

Table 4. Analysis of drug sensitivity-related genes in NSCLC cell strains to docetaxel (DOC) and navelbine (NVB)

Pearson correlation coefficient	DOC			NVB		
	Negative	Positive	Total	Negative	Positive	Total
≥0.4	20	4	24	10	4	14
≥0.5	9	0	9	10	0	10
≥0.6	4	0	4	3	0	3
≥0.7	1	0	1	2	0	2
Total	34	4	38	25	4	29

* NSCLC (PC7, PC14, PC9, A549, LK-2, LU65)

Analysis of gene sensitivity to navelbine and docetaxel In total, there were 56 genes related significantly to NVB and DOC ($r \geq \pm 0.4$; Table 5 and Table 6). They can be divided into 11 types:

1 11 genes negatively related to DOC and NVB in the SCLC and NSCLC. They were *metallothinein, cathepsin B, TNF-R1, cathepsin L, TGFb-induced* 68 kDa, TIMP1, PAI-1, IGFBP4, UPAR, CD13 and Jagged.

2 7 genes negatively related to NVB in the SCLC and NSCLC. Genes negatively related to DOC were only in the NSCLC. They were *Galectin-1, Annexin 11, aA-AR, EphA2, Rho C, GATA-6 and Fibromodulin.*

3 6 genes negatively related to DOC and NVB in the NSCLC. They were *APC, Clusterin, FGFR-2, thrombospondin 1, HSC70*, and *HSP32*, but the *TPA* gene was a positively related gene.

4 The procoagulant gene was positively related to NVB in the SCLC and NSCLC. The *midkine* gene was positively related to DOC.

Table 5. Drug sensitivity-related genes co-expressed in SCLC and NSCLC.

Entering serial number	Gene name	NVB		DOC	
		SCLC + NSCLC	NSCLCS	CLC + NSCLC	NSCLC
X64177	Metallothinein	-0.715	-0.721	-0.683	-0.713
L16510	Cathepsin B	-0.712	-0.707	-0.552	-0.682
X55313	TNF-R1	-0.668	-0.605	-0.521	-0.608
X12451	Cathepsin L	-0.617	-0.540	-0.544	-0.511
*	TGFβ-induced, 68 kDa	-0.648	-0.572	-0.573	-0.543
X03124	TIMP1	-0.684	-0.688	-0.481	-0.689
M16006	PAI-1	-0.541	-0.478	-0.454	-0.509
M63403	IGFBP4	-0.521	-0.558	-0.435	-0.561
X51675	UPAR	-0.510	-0.477	-0.462	-0.476
X13276	CD13	-0.482	-0.426	-0.435	-0.477
U61276	Jagged	-0.491	-0.408	-0.421	-0.409

*Non-entering serial number;
serial number of function (see Table 7); DOC, docetaxel; NVB, navelbine.
NSCLC (PC7, PC14, PC9, A549, LK-2, LU65)

Table 6. Specific expression of the drug sensitivity-related genes in SCLC and NSCLC.

Entering serial number	Gene name	NVB		DOC	
		SCLC + NSCLC	NSCLC	SCLC + NSCLC	NSCLC
J04456	Galectin-1	-0.621	-0.687	—	-0.654
*	Annexin ll	-0.569	-0.521	—	-0.422
U03864	Alphal A-AR	-0.483	-0.569	—	-0.580
M59371	Eph A2 (Eck)	-0.468	-0.501	—	-0.545
L25081	Rho C	-0.413	-0.468	—	-0.426
U66075	GATA-6	-0.456	-0.419	—	-0.440
*	Fibromodulin	-0.425	-0.418	—	-0.414
M64722	Clusterin	—	-0.599	—	-0.586
M87770	FGRF-2	—	-0.528	—	-0.547
X14787	Thrombospondin 1	—	-0.505	—	-0.513
Y00371	HSC70	—	-0.528	—	-0.481
M74088	APC	—	-0.411	—	-0.404
X06985	HSP32	—	-0.432	—	-0.434
M15518	TPA	—	0.431	—	0.408
M14113	Procoagulant	0.516	0.484	—	—
Z12020	MDM2	0.423	0.484	0.475	—
AF101264	CaMKK	—	0.432	0.526	—
L33801	GSK-3 beta	-0.424	—	-0.401	—
L15409	VHL	-0.471	—	-0.494	—
AB002409	SLC	-0.416	—	—	-0.400
Z11887	MMP-7	-0.459	—	—	—
L47345	Elongin A	-0.437	—	—	—
AB006780	Galectin-3	-0.419	—	—	—
U16957	AT2	0.429	—	—	—
*	Lactate	—	-0.416	—	—
M69148	Midkine	—	—	0.430	0.455
X13247	IFNg	—	—	0.402	—
*	Phospholipase D	—	—	0.403	—
X78686	ENA-78	—	—	0.416	—
X79389	GSTT1	—	—	0.430	—
*	Id4	—	—	0.430	—
M12828	CD8a	—	—	0.445	—
U81234	GCP-2	—	—	0.450	—
U10990	TAK1	—	—	0.418	—
U22322	Rak	—	—	—	-0.452
U39487	XO	—	—	—	-0.428
U01877	P300	—	—	—	-0.427
X61615	LIFR	—	—	—	-0.425
U20240	C/EBPγ	—	—	—	-0.418
J03817	GSTM1B	—	—	—	-0.408
U44378	Smad4	—	—	—	-0.407
*	Thymosin b	—	—	—	-0.404
X07979	CD29	—	—	—	-0.411
X15606	ICAM-2	—	—	—	0.403
*	Ataxia Telangiectasia Group D-Associated Protein	—	—	—	0.427

*Non-entering serial number;
serial number of function (see Table 7); DOC, docetaxel; NVB, navelbine.
NSCLC (PC7, PC14, PC9, A549, LK-2, LU65)

Table 7. Classification of gene sensitivity to navelbine (NVB) and docetaxel (DOC) in lung cancer cell strains.

Serial number of function	Classification	NVB				DOC			
		SCLC	NSCLC	Co-expressed	Total	SCLC	NSCLC	Co-expressed	Total
1	Signal transduction molecule	7	9	7	9	7	13	4	16
2	Growth factor receptor	0	1	0	1	0	1	0	1
3	Growth factor	0	0	0	0	1	1	1	1
4	Apoptosis related	1	1	1	1	0	1	0	1
5	Cell factor	5	1	1	5	5	3	1	7
6	Cyclin protein	1	1	1	1	1	0	0	1
7	Transcription factor	2	1	1	2	2	2	0	4
8	Metabolism-related enzymes and inhibitors	5	6	4	7	4	8	4	8
9	Proteolysis	1	1	1	1	2	2	2	2
10	Molecular chaperone	0	1	0	1	0	1	0	1
11	Other*	4	6	2	8	3	6	1	8
Total		26	28	19	36	25	38	13	50

*Refers to non-classified genes.
NSCLC (PC7, PC14, PC9, A549, LK-2, LU65)
SCLC (Lu135, N231, H69, SBC-3)

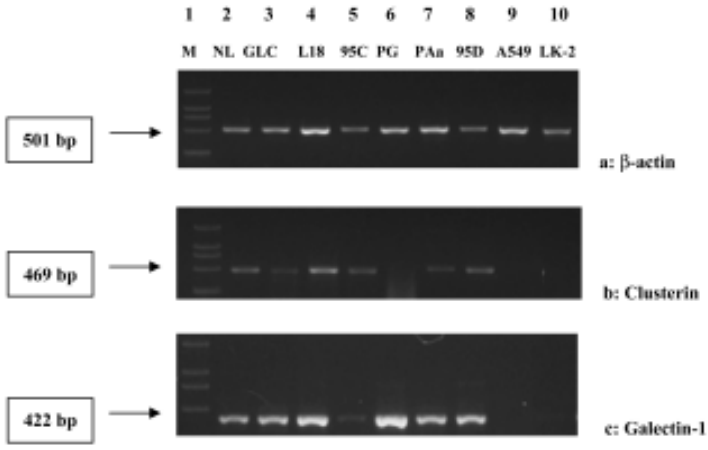

Figure 3. Gene expression of *Clusterin, Galectin-1, TIMP-1* and *metallothionein* in NSCLC (PC7, PC14, PC9, A549, LK-2, LU65) cell lines were verified by reverse transcription polymerase chain reaction. 1, PCR marker, M; 2, normal lung, NL; 3–10, NSCLC. (A) PCR product of β-actin. Reaction conditions: 94 °C, 3 min; 94 °C, 20 s; 56 °C, 30 s; 72 °C, 50 s; 72 °C, 10 min for extension. After 23 cycles, expression could be seen in NL and 8 NSCLC. (B–E) PCR products of *TIMP-1, Clusterin, Galectin-1* and *metallothionein*, with β-actin as an internal control. Reaction conditions: 94 °C, 3 min; 94 °C, 40 s; 60 °C, 40 s; 72 °C, 40 s, 72 °C, 10 min for extension. 22, 26, 26 and 32 cycles, respectively. (B) *Clusterin* was not expressed in the A549 and LK-2 cell lines, but was expressed weakly in the GLC and PG cell lines. (C) *Galectin-1* was not expressed in the A549 and LK-2 cell lines, but was expressed weakly in the 95C cell line.

5 The *MDM2* gene was positively related to NVB in the NSCLC and SCLC. The *CaMKK* gene was positively related to NVB only in the NSCLC, *MDM2* and *CaMKK* were both positively related to DOC in the SCLC.

6 GSK-*3β* and *VHL2* were both negatively related to NVB and DOC in the SCLC.

7 *Elongin A*, *MMP-7* and *Galectin-3* were negatively related to NVB in the SCLC. *Elongin A*, *MMP-7*, *Galectin-3* were negatively related to DOC in the NSCLC, but the *AT2* gene was positively related to NVB in the SCLC.

8 8 genes positively related to DOC in the SCLC. They were *TAK1*, *IFN-γ*, *Phospholipase D* ,*ENA-78*, *GSTT1*, *Id4*, *CD8α* and *GCP-2*.

9 9 genes negatively related to DOC in the NSCLC. They were *Rak*, *XO*, *P300*, *LIFR*, *C/EBPγ*, *GSTMIB*, *Smad4*, *Thymosin b* and *CD29*.

10 *ICAM-2* and *Ataxia Telangiectasia Group D-Associated Protein* were positively related to DOC in the NSCLC.

11 *ICAM-2* and *Ataxia Telangiectasia Group D Associated Protein* and NSCLC were positively related to DOC.

The classification of gene sensitivity to NVB and DOC in lung cancer cell strains is shown in Table 7. They were divided into 4 types: signal transduction molecules, cell factors, transcription factors, and metabolism-related enzymes and inhibitors.

Verification In order to verify the reliability of hybridization, GLC, L18, 95C, PG, PAa, 95D, A549 and LK-2 cell lines were chosen. cDNA of *Galectin-1*,and *Clusterin*, which were downregulated in expression and selected with cDNA macroarray, was used in semi-quantitative RT-PCR. The results are shown in Figure 3A–3C.

Discussion

The morbidity of lung cancer is higher now than in the past, and lung cancer therapy is less sensitive to chemotherapy than other kinds of cancer. Because most patients are in the middle or late stages when cancer is found, the rate of surgical success is low. Therefore, chemotherapy is a commonly integrated treatment for lung cancer patients. NVB and Doc are both new anticancer drugs act on microtubules[6–9]. NVB can inhibit the assembly of tubulin and act on the mid-stage of mitosis, leading to stasis of cancer cell growth. Because of its special anticancer function, in December 1994 the FDA (Food and Drug Administration) approved NVB in combination with CDDP for use as a first-line therapy for advanced NSCLC patients[10]. As for DOC, its mechanism is to promote the aggregation of tubulin and to inhibit its disassembly, preventing cells from entering into the growth phase. It is widely used in cancer treatments, mainly for lung cancer and breast cancer in advanced stages[11].

In clinical cases there are usually different sensitivities to anticancer drugs. The same chemotherapeutic medicine is often used for patients with different types of cancer cells, even for different individuals with the same type of cancer cells. This is due to such factors as the different biological characters of tumors, different patients and different drug responses.

There are many methods to determine sensitivity to anticancer drugs by analyzing gene expression. Only 1 gene at a time can be tested through northern blotting, which has an obvious disadvantage in automation. Other methods include differential display, cDNA sequence analysis and SAGE, but they also have many disadvantages. For any organism, we can analyze many different drug responses by means of DNA gene chip technology, and obtain more reliable results than with other methods. We conclude that other single element methods are less advantageous than the DNA gene chip technique[12–15].

A recent study showed that drug sensitivity to DOC is concerned with P-GP(P Glucose protein), and changes in target molecules, changes in signal transduction system, cell-control factors and apoptosis-related factors. In addition, the metabolism of DOC in the body is primarily through the sub-family of CYP3A proteins. The activity of enzyme in this family varies greatly among individuals, and the factors sensitive to NVB have not yet been reported.

We have examined the genes sensitive to DOC and NVB in 10 lung cancer cell strains using cDNA macroarrays. The results showed that there were 56 genes significantly related to NVB and DOC ($r \geq \pm 0.4$). Among them, 36 were related to NVB, 20 were co-expressed in the NSCLC set and the NSCLC+SCLC set; 27 were related in the NSCLC+SCLC set and 7 were specifically related genes; 29 were related genes in the NSCLC set, and 9 were specifically related genes. There was a total of 50 genes related to DOC and 12 co-expressed genes related in the NSCLC and NSCLC+SCLC sets; 24 related genes in the NSCLC+SCLC set and 12 specifically related genes. In the NSCLC set there were 38 related genes and 26 specifically related genes.

The genes described above are mainly signal transduction molecules, metabolism-related enzymes and inhibitors, cell factors and transcription factors. At the same time, *Clusterin* and *Galectin-1* genes, which were downregulated in expression in LK-2, were tested using RT-PCR. The results were in agreement with those obtained through cDNA macroarray. However, with the A549 cell line, the cDNA macroarray did not show the same downregulated expression as with RT-PCR. Genes screened by cDNA macroarray therefore need to be further tested using other methods.

In this study, we identified the relationship among the gene expression profiles of 10 lung cancer cell strains, which focused on 1291 genes and drug sensitivity to DOC and NVB. This study may help to explain the mechanisms of action of NVB and DOC, provide theoretical evidence in the search for new ways to overcome drug resistance, discover new anticancer drugs by providing new targets, and facilitate individualized therapy regimens and increased response

rates. The aim of our future work is to identify and analyze these new genes screened for drug sensitivity, especially those not known to us previously.

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