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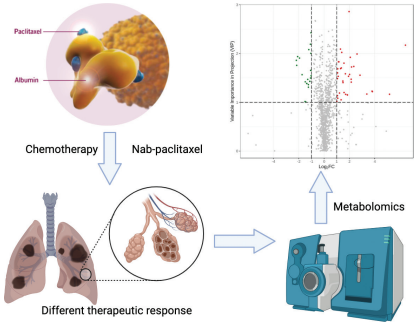
Short Communication

Baseline differences in metabolic profiles of patients with lung squamous cell carcinoma responding or not responding to treatment with nanoparticle albumin-bound paclitaxel (nab-paclitaxel)

Graphical abstract



Highlights

- A total of 1141 kinds of endogenous metabolites were detected in the serum of participants.
- Between the progressive disease (PD) vs partial response (PR), PD vs stable disease (SD), and SD vs PR groups, 61, 81, and 54 differential metabolites were identified, respectively.
- The PD vs SD, SD vs PR, and PD vs PR groups were well separated by the combination of cis-9,10-epoxystearic acid and octapentaenoic acid, salicyluric acid and DG (18:1/20:5/0:0), and D-glyceric acid and 9,12-octadecadienoic acid, respectively.

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In brief

In this study, 32 patients with lung squamous cell carcinoma (LUSC) who were treated with nab-paclitaxel were included to assess their chemotherapy response. Metabolomics studies identified 61, 81, and 54 different metabolites between patients with progressive disease (PD) and partial remission (PR), PD and stable disease (SD), and SD and PR groups, respectively

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Baseline differences in metabolic profiles of patients with lung squamous cell carcinoma responding or not responding to treatment with nanoparticle albumin-bound paclitaxel (nab-paclitaxel)

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ABSTRACT

Background: Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is a preparation widely used in chemotherapy for cancers. However, only some patients benefit from this treatment. Therefore, identifying which patients will respond to nab-paclitaxel therapy is crucial.

Methods: A cohort of 32 patients with lung squamous cell carcinoma (LUSC) treated with nab-paclitaxel were enrolled in this study. Plasma samples were collected before chemotherapy and used to perform metabolomic and lipidomic analyses. Tumor response to two cycles of chemotherapy was evaluated. Metabolites differentially present among populations were screened and analyzed.

Results: According to the RECIST criteria, one-third of patients had a significant response to nab-paclitaxel, whereas one-fifth showed no discernible benefit. According to the criteria of variable importance in projection >1 and fold change >2, we identified 61, 81 and 54 differential metabolites between the progressive disease (PD) vs partial response (PR), PD vs stable disease (SD), and SD vs PR groups, respectively. Moreover, we used three variation in logistic regression models and ROC diagnostic curves to identify optimal metabolites for stratifying patients with differing chemotherapeutic responses. The PD vs SD, SD vs PR, and PD vs PR groups were well separated on the basis of cis-9,10-epoxystearic acid/octapentaenoic acid (AUC 0.9330), salicyluric acid/DG (18:1/20:5/0:0) (AUC 1.0000) and D-glyceric acid/9,12-octadecadienoic acid (AUC 1.0000), respectively.

Conclusion: The baseline metabolic profiles significantly differed between responder and non-responder patients with LUSC treated with nab-paclitaxel. These differential metabolites have the potential to predict the outcomes of patients with LUSC before chemotherapy.

Keywords: lung cancer, paclitaxel, metabolomics, lipidomics, biomarkers

Short Communication

1. INTRODUCTION

Non-small cell lung cancer (NSCLC), accounting for 80% of diagnosed lung cancers, is among the most lethal cancers (5-year survival rate <10% for late stage NSCLC) [1, 2]. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is formed through binding of the classic chemotherapy agent paclitaxel to albumin, thus enabling the formation of nanoparticles. This form of paclitaxel is widely used in chemotherapy for lung cancer, breast cancer and other malignant tumors, because of its substantial efficacy, and low toxicity and adverse effects. In contrast to unbound, solvent-based paclitaxel, this treatment does not require anti-allergy treatment before administration [3, 4].

Previous studies have demonstrated that nab-paclitaxel combined with carboplatin elicits a better response than solvent-based paclitaxel with carboplatin in patients with lung squamous cell carcinoma (LUSC) [5, 6]. However, not all patients benefit from nab-paclitaxel treatment, and the clinical response to nab-paclitaxel is often unpredictable. Therefore, identifying whether patients are likely to respond to nab-paclitaxel is critical to facilitate more precise and targeted treatment regimes. In recent years, metabolomics has shown great potential in predicting individual differences in drug metabolism, efficacy and toxicity, and has been suggested to aid in providing individualized treatments for patients with various diseases [7, 8]. This approach has also been used for cancer therapy.

In this study, the utility of metabolomics was explored to discover biomarkers associated with the response to nab-paclitaxel chemotherapy in patients with NSCLC. To discover effective biomarkers for predicting and stratifying likely chemotherapy outcomes, we classified patients with differing responses and compared differences in their baseline metabolic characteristics.

2. METHODS

2.1 Study participants

From June 2019 to December 2019, 32 patients at the cancer center of Wuhan Union Hospital (Wuhan, Hubei, China) were initially enrolled, all of whom were confirmed to have LUSC and were being treated with nab-paclitaxel-based chemotherapy. Heparin anticoagulated plasma samples from each participant were collected before treatment and frozen at –80°C until metabolic analysis. Seven patients were excluded from this study because of a lack of efficacy of nab-paclitaxel treatment.

The tumor response to chemotherapy after two cycles of treatment was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines and classified into progressive disease (PD), partial response (PR) or stable disease (SD). The study protocol was approved by the Ethics Committee of the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, and written informed consent was obtained from all participants.

2.2 Targeted metabolic/lipidomic detection and statistical analysis

Metabolomic testing and subsequent statistical analysis were performed as previously reported [9]. In brief, two aliquots of plasma collected before chemotherapy were pre-treated with two methods to extract either hydrophilic or hydrophobic compounds. The metabolomes and lipidomes of these treated samples were then analyzed through ultra-performance liquid chromatography-tandem mass spectrometry by using a database of more than 3000 endogenous molecules. The results were analyzed with multivariate statistical methods, pathway enrichment analysis and Spearman correlation analysis. The orthogonal partial least squares discriminant analysis (OPLS-DA) model was used to predict the efficacy of nab-paclitaxel, on the basis of metabolic data. Detailed information is provided in the **Supplementary File**.

3. RESULTS

3.1 Baseline data for the study population

The clinical characteristics of the study participants are displayed in **Table 1**. The average age of these individuals was approximately 63 years. Most patients were men (84%). Four-fifths of the participants were smokers or ex-smokers. More than half had advanced-stage lung cancer. One in five participants did not respond to nab-paclitaxel chemotherapy (PD), 32% showed a significant decrease in tumor volume (PR), and 48% showed minimal changes (SD) according to the RECIST criteria.

3.2 Identification of differential metabolites among chemotherapy response groups

We used a comprehensive platform to determine metabolomes and lipidomes. The platform's database contains more than 3000 characteristic compounds, 1141 of which were detected in the present study, including 332 types of endogenous metabolites and 809 types of lipids (**Table 2** and **Supplementary File 1**).

Table 1 | Characteristics of enrolled patients with LUSC.

Patient characteristics	
Age, years	63.1±5.9
Sex (male/female)	21:4
Smoking history (smoking/former smoking/never smoking)	16:4:5
BMI	21.1±2.9
TNM stage (III: IV)	10:15
RECIST 2.0 (PD:PR:SD)	5:8:12

Footnotes: Age and BMI are expressed as mean±S.D.

Table 2 | Compound database and detected compounds.

	Category	Database	Detected	Differential metabolites		
				PD vs PR	PD vs SD	SD vs PR
Metabolomics	Amino acids	220+	97	6	5	2
	Alcohols and amines	100+	9	/	/	/
	Aldehydes/ketones/esters	120+	4	/	1	/
	Benzene and substituted derivatives	150+	26	/	1	1
	Bile acids (BA)	35+	14	6	5	1
	Carboxylic acids and derivatives	80+	26	3	3	/
	Heterocyclic compounds	50+	24	/	1	/
	Hormones and related compounds	40+	7	/	/	/
	Nucleotides	150+	39	2	6	3
	Organic acids and derivatives	250+	68	10	6	4
	Tryptamines/cholines/pigments	15+	5	/	/	/
	Coenzymes and vitamins	50+	11	/	/	1
	Other	50+	2	/	/	/
Lipidomics	Cholesteryl esters (CE)	20+	15	/	/	/
	Ceramides (Cer)	80+	20	/	/	/
	Sphingomyelin (SM)		30	/	1	/
	Coenzyme Q10	2	1	/	/	/
	Eicosanoids	150+	6	/	/	1
	Free fatty acids (FFA)		22	1	/	/
	Carnitines (CAR)		38	/	/	/
	Lysophosphatidic acids (LPA)	560+	2	/	/	/
	Lysophosphatidylcholines (LPC)		26	1	/	1
	Lysophosphatidylethanolamine (LPE)		17	1	/	2
	LPG/LPI/LPS		3	/	2	/
	Phosphatidic acid (PA)		3	/	/	/
	Phosphatidylcholine (PC)		109	2	1	3
	Phosphatidylethanolamine (PE)		63	/	5	6
	Other phosphatidyl compounds		24	/	/	/
	Monoglycerides (MG)	370+	2	/	/	/
	Diglycerides (DG)		52	1	7	6
	Triglycerides (TG)		199	17	34	18
	Other lipids	350+	177	11	3	5
	Total	**3000+**	**1141**	**61**	**81**	**54**

The characteristics of metabolites potentially associated with chemotherapy response were determined with the OPLS-DA score map. On the basis of the 1141 detected compounds, the OPLS-DA score plot indicated a clear separation of the PD vs PR, PD vs SD, and SD vs PR groups (Figure 1a). We constructed volcano plots of all compounds detected in all groups (Figure 1b), in which the ordinate indicates the variable importance

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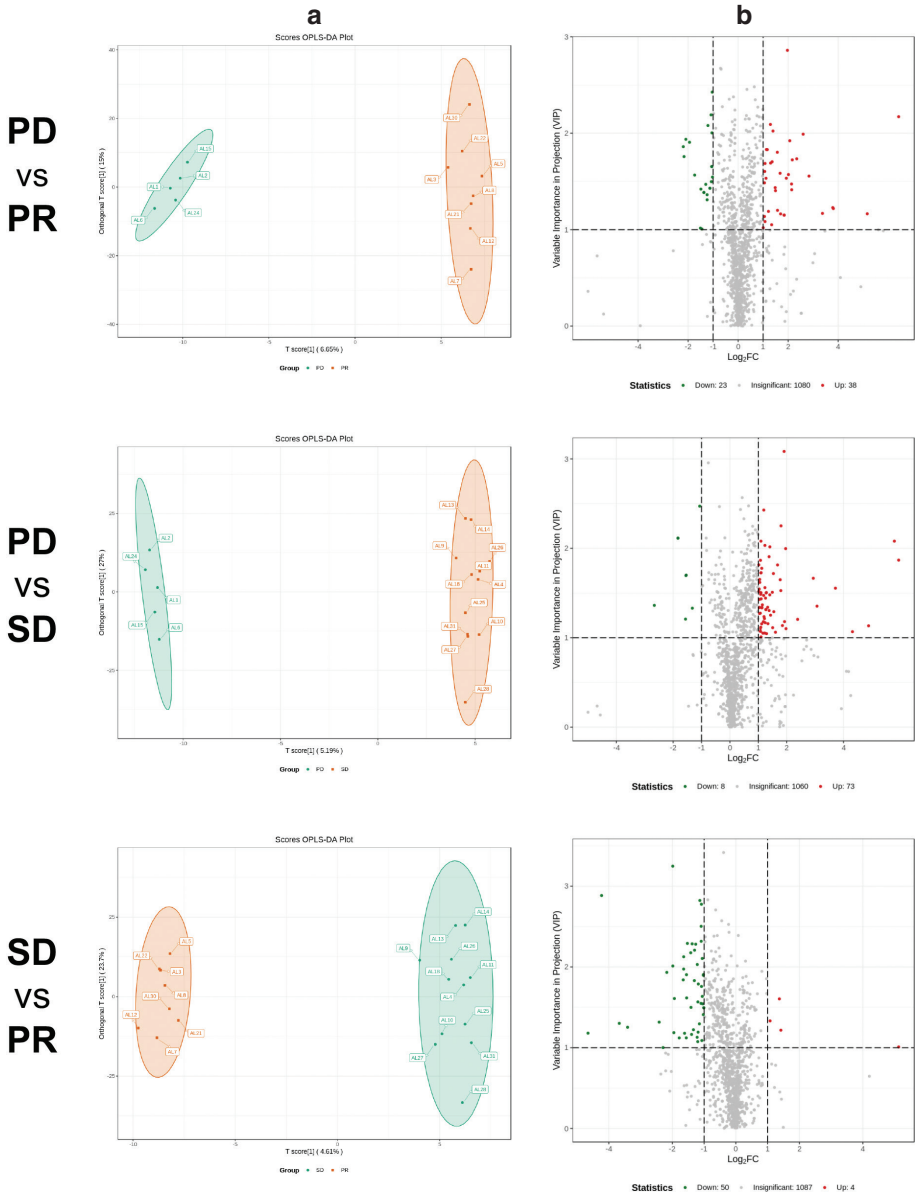

Figure 1 | (a) OPLS-DA score map. (b) Volcano plot.

in the projection value of the OPLS-DA score chart, and the abscissa indicates the logarithmic transformation of the fold change. On the basis of the criteria of variable importance in the projection >1 and fold change >2, we identified 61, 81 and 54 differential metabolites between the PD vs PR, PD vs SD, and SD vs PR groups, respectively. Red dots indicate up-regulation of metabolites, and green dots indicate down-regulation. A list of all differential metabolites among groups is shown in **Supplementary File 2**.

The differential metabolites were displayed in three heatmaps (**Supplementary Figures 1-3**). Notably, lipids accounted for a considerable proportion of the detected metabolites. Specifically, we identified 34, 53 and 41 differential lipid types (such as triglycerides [TG], diglycerides [DG], and phosphatidylcholine or phosphatidylethanolamine), which accounted for 56%, 65% and 76% of all differential metabolites between the PD vs PR, PD vs SD, and SD vs PR groups, respectively. In addition, various forms of TG were detected according to their chain lengths (**Supplementary File 2**) and accounted for approximately half the differential lipids. For example, 17 TG in the PR group were up-regulated an average of 3.2 fold that in the PD group. Similarly, 34 types of TG were up-regulated in the SD group vs the PD group (average 2.5 fold difference). These data

suggested that patients with lower TG levels may be more likely to respond poorly to nab-paclitaxel chemotherapy. However, this result must be validated by larger-scale metabolomic studies.

3.3 KEGG pathway analysis of the chemotherapy response groups

The KEGG database, the predominant public database for integrated metabolic pathways, helps researchers contextualize studies on genes, protein expression and metabolite concentrations, and provides a powerful tool for in vivo metabolism analysis and metabolic network research. We analyzed three differential metabolite comparison groups: PD vs PR, PD vs SD, and SD vs PR. The annotation results of the significant differential metabolites were classified according to KEGG pathways (**Figure 2a-c**). Among organismal system pathways, vitamin digestion and absorption, thermogenesis, regulation of lipolysis in adipocytes, fat digestion and absorption and cholesterol metabolism were important pathways differing among the three comparison groups in KEGG functional enrichment analysis. The proportions of annotated metabolites to total metabolites all exceeded 40%. This analysis clearly showed that differential lipids played key roles in these enriched pathways.

Nearly all differential metabolites could be classified into metabolic pathways (annotation proportion >87%). In particular, glycerolipid metabolism was identified as an important metabolic pathway differing among groups, and the insulin resistance pathway was enriched in all comparisons between groups. The between-group differences in the above enrichment pathways were statistically significant (**Figure 2d-f**).

3.4 Identification of predictive efficacy of differential metabolites

As described above, we identified 61, 81 and 54 differential metabolites between the PD vs PR, PD vs SD, and SD vs PR groups, respectively. A Venn diagram was constructed to demonstrate the relationships among groups of differential metabolites (**Figure 3a**). The intersection of the diagram indicated that the organic acid 3,4,5-trimethoxycinnamic acid was present in three groups of differential metabolites.

On the basis of the differential metabolites, we used a logistic regression model and ROC diagnostic curve to identify the optimal metabolites for stratification of patients with differing chemotherapeutic responses. The Akaike information criterion was used to screen the best metabolite combination, with lower values indicating better model fit. The PD vs SD, SD vs PR, and PD vs PR groups were well separated by cis-9,10-epoxystearic acid/octapentaenoic acid (AUC 0.9330), salicyluric acid/DG (18:1/20:5/0:0) (AUC 1.0000) and D-glyceric acid/9,12-octadecadienoic acid (AUC 1.0000), respectively (**Figure 3b**). Specifically, cis-9,10-epoxystearic acid and octapentaenoic acid were up-regulated in the PD group vs the SD group ($p<0.05$). Similarly, salicyluric acid/DG (18:1/20:5/0:0) was up-regulated in the SD group vs the PR group ($p<0.05$). D-glyceric acid levels were significantly higher in the PR group than the PD group ($p<0.01$); however 9,12-octadecadienoic acid levels were non-significantly lower in the PR group (**Figure 3c**).

4. DISCUSSION

Albumin-bound chemotherapeutic agents, a class of drugs used to treat cancer, have many advantages such as higher efficacy and lower toxicity than their solvent-based counterparts [10, 11]. Nab-paclitaxel, a nanoparticle conjugate of paclitaxel and human albumin, was the first clinically successful albumin-bound chemotherapeutic agent. Nab-paclitaxel has shown efficacy in lung cancer, pancreatic cancer and breast cancer [10, 12, 13]. Langer has found that nab-paclitaxel combined with carboplatin, as a first-line treatment for advanced NSCLC, is superior to the traditional solvent-based paclitaxel combined with carboplatin, and has higher safety [14]. These findings might be explained by higher administration concentrations of nab-paclitaxel and higher serum concentrations of free paclitaxel enhancing anti-tumor activity [15, 16]. However, not all patients respond to nab-paclitaxel, and biomarkers predicting which patients benefit most from its this treatment remain lacking [17].

Personalized medicine is the selection of medicines for subgroups of patients or individual patients, with the aim of maximizing treatment efficacy and minimizing toxicity [18, 19]. Metabolomics is a method of analyzing the levels of metabolites in biological fluids or tissues, to predict the benefits and toxicity of drug interventions [20]. In past decades, metabolomics was used primarily for early screening and diagnosis of cancer [21]. However, studies are increasingly using metabolomics to analyze chemotherapy efficacy in patients with cancer [20, 22, 23]. For example, lipids and high-sensitivity C-reactive protein have been shown to be important predictive biomarkers of lung cancer risk [22, 24]. Moreover, glycodeoxycholic acid and glycocholic acid have been found to have excellent sensitivity and specificity in predicting the efficacy of anlotinib in patients with lung cancer. Targeted metabolomic analysis has also identified NG-dimethylarginine as the most promising biomarker for the prediction of proteinuria occurrence after anlotinib treatment [20]. Additionally, a study has demonstrated that metabolites in the citric acid cycle, glutamate metabolism and amino acid metabolism can be used to predict the efficacy of platinum-based chemotherapy in patients with NSCLC, with high sensitivity and specificity [23].

Although metabolic alternations are recognized as typical hallmarks of cancer, changes in lipid metabolism remain poorly understood. Lipids are a class of molecules with various types of structures, including TG, DG, cholesterol, phospholipids, fatty acids and

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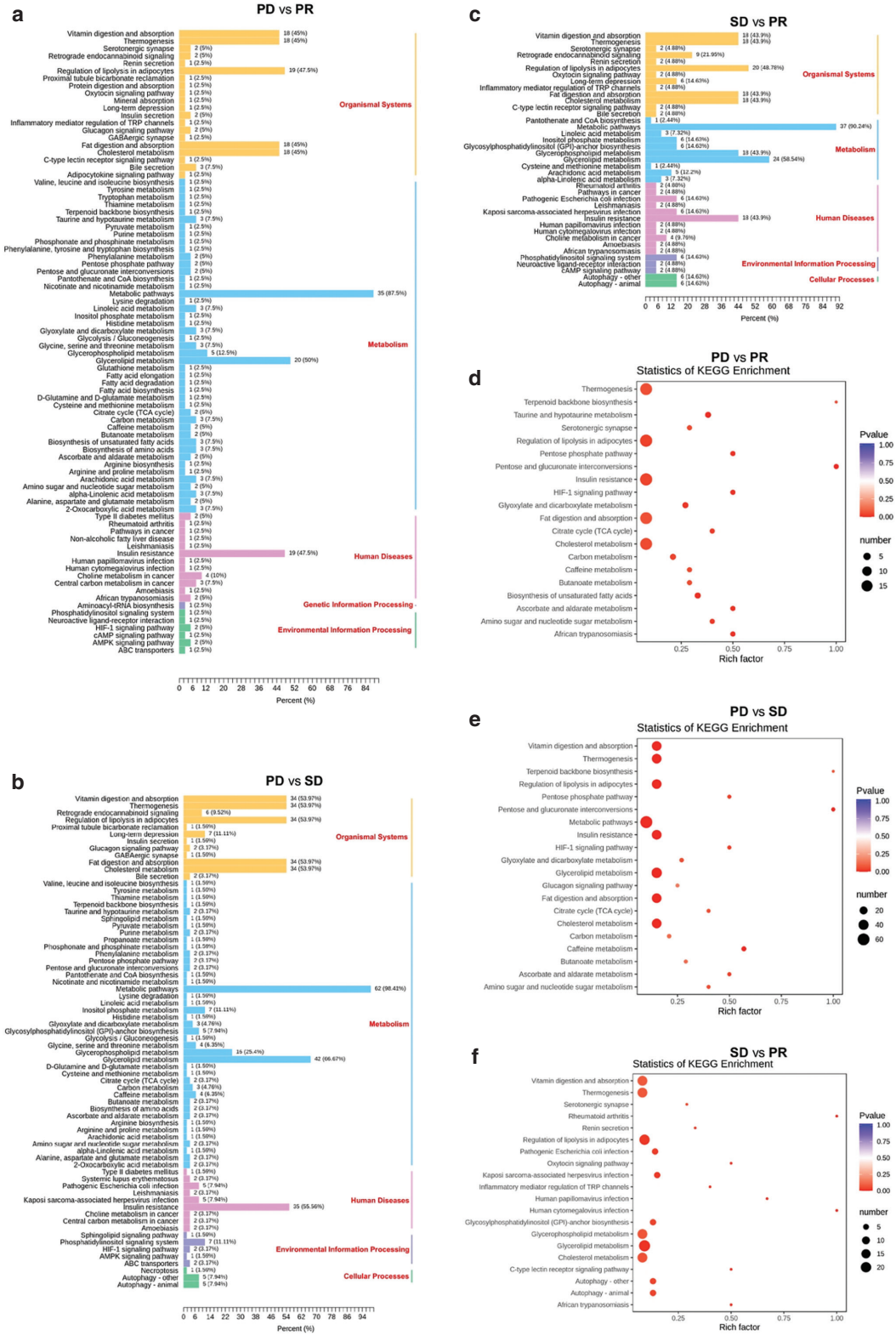
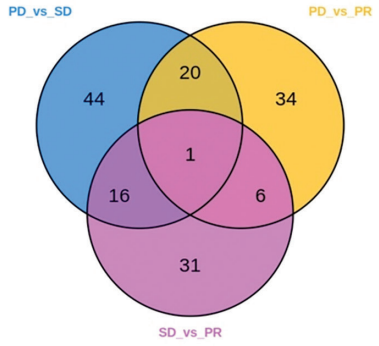


Figure 2 | KEGG enrichment analysis of patients with NSCLC.
(a-c) Differential metabolites classified in biological pathways (the ordinate shows the name of the KEGG metabolic pathway, and the abscissa shows the number of metabolites annotated with the pathway and proportion with respect to the total number of metabolites annotated). (d-f) Statistics of KEGG pathways (bubble color represents adjusted p values, and bubble size represents counts).

a



b

The model parameters of optimal metabolite combination between groups.

Group	Compounds	coefficient	AUC	Sensitivity	Specificity
PD vs SD	Cis-9,10-epoxystearic acid	-2.87	0.9330	1.0000	0.8000
	Octapentaenoic acid	-1.16			
	Intercept	59.52			
SD vs PR	Salicyluric acid	-1290.6	1.0000	1.0000	1.0000
	DG (18:1/20:5/0:0)	-906.29			
	Intercept	31277.98			
PD vs PR	D-Glyceric Acid	272.71	1.0000	1.0000	1.0000
	9,12-octadecadienoic acid	-95.13			
	Intercept	-2022.03			

c

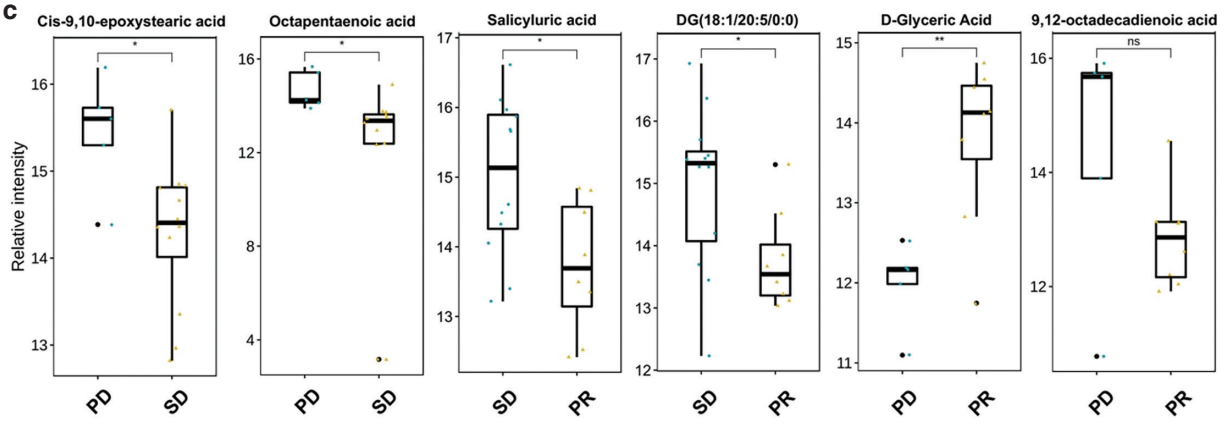


Figure 3 | Differential metabolites among groups.

sphingolipids. These lipids are widely distributed in organelles and play key roles in the construction of all membranes [25]. In addition, lipids act as second messengers that transduce signals in various organelles. Moreover, lipids serve as important energy sources when nutrients are limited [26]. Dysregulation and reprogramming of lipid metabolism have been shown to lead to the progression of malignancy, and targeting the regulation of lipid metabolism has emerged as a novel anti-cancer strategy [27].

Herein, we used both metabolic and lipidomic analysis to comprehensively screen for differential metabolites among patients with LUSC with differing treatment responses. The baseline levels of some amino acid, bile acid, nucleotide and organic acid compounds differed among patient groups with differing responses. Our lipidomic analysis indicated that certain types of plasma lipids, particularly TG and phosphatidylethanolamine, differ among PD, SD and PR populations. Interestingly, the levels of various TG species were markedly higher in in responders than non-responders. A recent clinical case report has indicated a close association between paclitaxel and serum TG levels [28]. Specifically, the patients developed severe hypertriglyceridemia after being administered paclitaxel and carboplatin, but their TG levels returned to normal after a change to gemcitabine and carboplatin. Paclitaxel is believed to induce high serum TG levels. Moreover, Wang et al. have reported that paclitaxel-based chemotherapy results in transient hypertriglyceridemia in patients with lung cancer and have suggested that serum TG must be monitored during paclitaxel-based chemotherapy [29]. Inci et al. have demonstrated that paclitaxel leads to hepatic steatosis in patients with cancer [30]. Therefore, paclitaxel-induced hypertriglyceridemia is frequently seen in clinical settings. However a systematic study of this phenomenon remains lacking. On the basis of our findings, we suggest that elevated serum TG may be a temporary response in patients with good therapeutic effects. Elevated TG levels might be necessary to provide energy for organisms to inhibit tumor growth. However, more detailed exploration is required to confirm this hypothesis.

In the enriched pathway analysis, terpenoid backbone biosynthesis (pyruvate) and pentose and glucuronate interconversions (2-oxoglutarate and pyruvate) were found to significantly differ between responders and non-responders. Pyruvate, an antioxidant, attenuates paclitaxel-mediated DNA damage and sub-G1

cells [31]. Pyruvate metabolism is closely associated with cancer therapy, and inhibition of pyruvate dehydrogenase kinase has been shown to be a therapeutic anti-cancer strategy [32]. Aleshin et al. have found that the metabolism of 2-oxoglutarate affects chemotherapeutic efficiency in lung cancer via the p53/p21 axis and the tricarboxylic acid cycle [33]. In this study, we observed potential effects of 2-oxoglutarate and pyruvate on paclitaxel chemotherapy; however, their molecular mechanisms must be further verified and elucidated.

This study has several limitations. First, this was an exploratory experiment in a small group of participants; consequently, further verification in larger cohorts is required. Second, additional experiments are required to explore potential mechanisms that may explain our findings. Finally, tissue metabolomics will be an essential future direction to identify potential biomarkers derived from tumor tissue secretions.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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