Original Article Ginsenoside Rg3 exerts anticancer effects in lung cancer through metabolite Histon H3

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Abstract: Objectives: To investigate the effects of ginsenoside Rg3 on metabolites in lung cancer cells. Methods: A549 cells were inoculated into nude BALB/c mice. Ginsenoside Rg3 (0.2 mL) or normal saline was orally administered daily for 12 days. LC/MS-based metabolomics was performed to analyze the metabolite profiles across three groups. Results: In serum samples, 143 metabolites were significantly different between the model and ginsenoside Rg3 groups. In fecal samples, 44 metabolites differed significantly between the two groups. Levels of Lamin A/C and Histon H3 were upregulated in model tissues. Ginsenoside Rg3 treatment significantly inhibited the expression of Lamin A/C and Histon H3, suggesting inhibition of histidine metabolism activation in lung cancer. Furthermore, ginsenoside Rg3 or Lamin A knockdown inhibited histamine-induced proliferation, migration, invasion and epithelial-mesenchymal transition (EMT) in lung cancer cells. Conclusions: Ginsenoside Rg3 significantly altered the metabolic profile in lung cancer mice. Mechanistically, ginsenoside Rg3 downregulated Lamin A/C through histidine metabolic pathway and suppressed histamine-induced progression of lung cancer.

Keywords: Lung cancer, ginsenoside Rg3, LC-MS untargeted metabolomic, histidine, metabolites

Introduction

Ginsenoside Rg3, a bioactive compound derived from ginseng, has demonstrated a broad spectrum of pharmacological effects, including anti-inflammatory, anti-allergic, antiaging, and neuroprotective properties [1, 2]. In recent years, ginsenosides have attracted significant attention as potential anti-tumor agents, with extensive research highlighting their ability to combat cancer through various mechanisms [3, 4]. These mechanisms include inducing tumor cell apoptosis and differentiation, enhancing cell sensitivity to chemotherapy drugs, inhibiting angiogenesis, boosting antitumor immunity, and preventing tumor cell adhesion [5, 6]. In human lung cancer, Rg3 has been shown to inhibit tumor cell proliferation, metastasis and angiogenesis, while also improving chemotherapy sensitivity and immune response in patients [7-10].

Tumor progression is closely associated with metabolic reprogramming, as malignant cells require increased energy production and biosynthesis of critical molecules, such as nucleotides, lipids, and amino acids, to support rapid proliferation [11, 12]. Therefore, understanding the regulatory mechanisms underlying tumor metabolism during drug therapy is crucial for improving patient prognosis and guiding therapeutic strategies.

The aim of this study is to employ metabolomics sequencing to gualitatively and guantitatively analyze metabolic changes in a lung cancer mouse model treated with ginsenosides. By identifying key metabolites and metabolic pathways influenced by ginsenoside therapy, we seek to predict its therapeutic efficacy and uncover potential biomarkers for lung cancer treatment. This research not only provides insights into tumor metabolic regulation during drug therapy but also lays the foundation for developing personalized treatment strategies. Ultimately, this research holds promise for advancing the clinical application of ginsenosides in lung cancer therapy and improving patient outcomes.

Materials and methods

Cell culture

The human non-small cell lung cancer cell line A549 was purchased from Vitalriver (Beijing, China). Cells were cultured in A549-specific culture medium (Pricella, Wuhan, China), which consisted of Ham's F-12K supplemented with 10% fetal bovine serum, and incubated at 37°C with 5% CO₂. LaminA siRNAs were transfected into A549 cells using Lipofectamine 2000 according to the manufacturer's instructions. A549 cells were treated with 100 μ M Histamine for 24 h [12].

Animal experiments

BALB/c Nude mice (both male and female, 6-7 weeks old, weighing 16-22 g) from Vitalriver (Beijing, China) were used in this study. Eighteen mice were randomly divided into three groups: the control group (6 mice), model group (6 mice), and ginsenoside Rg3 group (6 mice). To establish tumor xenografts, A549 cells were subcutaneously inoculated into BALB/c nude mice. Once the tumor volume reached approximately 50 mm³, 0.2 mL ginsenoside Rg3 or normal saline was administered orally every day for 12 days. Feces and blood from the eye orbital were collected at the end of the treatment. The research was conducted in accordance with the ethical guidelines for animal research. The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Quanzhou First Hospital. At the end of the study, the mice were humanely euthanized using carbon dioxide asphyxiation, followed by cervical dislocation to ensure death. This method was chosen to minimize animal distress and pain, in compliance with the American Veterinary Medical Association (AVMA) guidelines for euthanasia.

Hematoxylin and Eosin (HE) staining

Tissue samples were fixed in 4% paraformaldehyde for 24 h at 4°C, and embedded in paraffin. For staining, slides were deparaffinized in xylene, rehydrated via graded ethanol. Sections were stained with Harris hematoxylin for 5 min, rinsed in tap water, differentiated in 1% acid ethanol. After washing, slides were counterstained in eosin Y for 1 min, dehydrated in ethanol, cleared in xylene, and cover slipped with neutral balsam. Stained sections were examined under a microscope.

Liquid chromatograph-mass spectrometer (LC/ MS)-based untargeted metabolomics

Fecal and serum metabolomics were performed by BIOTREE (Shanghai, China). Metabolites were extracted from fecal or serum samples using isotope-labeled extraction solutions. The target compounds were separated by chromatography using a Vanquish liquid chromatograph (ThermoFisher Scientific) and a Waters ACQUITY UPLC BEH Amide column (2.1 mm × 50 mm, 1.7 μ m). Data were collected using an Orbitrap Exploris 120 mass spectrometer (Xcalibur 4.4, Thermo Fisher Scientific). ProteoWizard software and the R package were used for data analysis and visualization.

Western blot analysis

Actin was used as an endogenous control for normalization. The protein levels of Lamin A, Lamin C, and Histone H3 were analyzed using western blot. After treatment with ginsenoside Rg3, cells were lysed using a RIPA buffer. Proteins were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), followed by transferring to a polyvinylidene fluoride (PVDF) membrane. Samples were incubated with primary antibodies at 4°C overnight, and then probed with secondary antibodies at room temperature for 1 h. The blots were developed using a chemiluminescent liquid (ECL) kit. Grayscale values were analyzed using ImageJ software. Lamin A (MA1-06101), Lamin C (MA5-47427), Histone H3 (PA5-16183), and actin (PA5-78715) antibodies were all purchased from ThermoFisher Scientific (Runcorn, Cheshire, UK); E-cadherin (20874-1-AP), N-cadherin (22056-1-AP), P53 (MA5-15448), and MMP-9 (MA5-15511) antibodies were purchased from Proteintech (Wuhan, China).

Cell counting kit-8 (CCK8)

Cell viability was assessed using CCK8 assay. A549 cells were seeded in a 96-well plate at a density of 1×10^4 to 5×10^4 cells per well after transection or treatment. Cells in each well were incubated with 10 µl of CCK8 solution for 2 h at 37°C. Then, the absorbance was measured at 450 nm using a microplate reader.



Figure 1. Pattern diagram of mouse model experiment. A549 cells were injected into BALB/c Nude mice. Oral administration of 0.2 mL ginsenoside Rg3 or normal saline was performed every day for 12 days. Tumor tissues were stained with HE. Untreated mouse lung tissue was used as a control. Serum and feces were extracted and preserved for metabolomics analysis. Micrographs were taken at 100×. M: model of lung cancer; G: ginsenoside Rg3.

Transwell assay

The Transwell assay was performed to assess cell invasion. After transfection or treatment, A549 cells were resuspended in serum-free medium at 5×10^4 to 1×10^5 cells/mL and placed in the upper chamber covered with Matrigel. Cells were incubated for 24 hours at 37°C. Then, cells were stained with 0.1% crystal violet for 20 min. The number of invasive cells were counted in randomly selected fields.

Wound healing assay

After transfection or treatment, A549 cells were incubated for 24 h at 37°C. A wound was created by scratching the monolayer with a 200 μ l pipette tip. Microscopic photos were taken at 0 and 24 hours post-scratching. Wound healing was analyzed using ImageJ software. The wound healing area was calculated as the percentage reduction in wound width over time, reflecting cell migration and wound closure efficiency.

Cell cycle detection

After transfection or treatment for 24 h, A549 cells were harvested at a density of 1×10^6 cells per sample and fixed with 70% ethanol overnight at 4°C. Following fixation, a detection solution was added into cells and incubated for 1 h at room temperature. The cells were then analyzed using a flow cytometer.

Statistical analysis

All data were presented as the mean \pm standard deviation (SD) and were analyzed using Statistical Product and Service Solutions 22.0 (SPSS, Illinois, USA). All results were based on at least three independent experiments. One-way analysis of variance (ANOVA) with Bonferroni post-hoc tests was used for comparison between groups. P < 0.05 was considered statistically significant.

Results

Screening of differential metabolites in serum samples

A549 cells were inoculated into BALB/c Nude mice to establish a mouse lung cancer model. After 12 days of treatment with ginsenoside Rg3, tumor tissue, serum, and feces were collected. The results of HE staining showed the tumor tissue in the model and ginsenoside Rg3 groups, as well as the normal tissue in the control group (**Figure 1**).

Then, metabolomics data from serum samples were obtained using LC/MS method. Principal component analysis (PCA) results showed that all samples were within a 95% confidence interval (Hotel's T-squared ellipse) and demonstrated clear separation between the groups (**Figure 2A**). Differentially expressed metabolites were identified using the VIP value of the first princi-



Figure 2. Screening of differential metabolites in serum samples. A. Scatter plot of PCA scores for all samples. B. Venn plot of differential metabolites among three groups. C. Heat map analysis of differential metabolites between model group and ginsenoside Rg3 group using normalized data. D. K-Means analysis for differential metabolites in all groups. The horizontal axis represents the sample group, the vertical axis represents the relative content of metabolites after standardization, and Cluster represents the set of metabolites with the same expression trend. M: model of lung cancer; G: ginsenoside Rg3. E. Scatter plot of differential metabolites in serum samples between model group and ginsenosides Rg3 group.

pal component of the OPLS-DA model (VIP > 1), combined with the P-value from the t-test (P < 0.05). A total of 157 differential metabolites were identified between control and model group, 143 differential metabolites between the model and ginsenoside Rg3 groups, and 268 differential metabolites between the control and ginsenoside Rg3 groups. The Venn diagram displays the overlapping regions of metabolite sets and their relationships across groups. The results showed that there was a total of 12 differential metabolites shared by the control, model and ginsenoside Rg3 groups (Figure 2B). A heat map (Figure 2C) was plotted for the 363 differential metabolites in serum samples between the control, model and ginsenoside Rg3 groups. To assess the relative changes in metabolite content across different groups, the relative abundance of all 363 differential metabolites was standardized using z-score, followed by K-means clustering analysis (Figure 2D).

Analysis of differential metabolites between model and ginsenoside Rg3 groups in serum samples

A volcano plot (Figure 2E) was generated to visualize the 143 differential metabolites between the model and ginsenoside Rg3 groups. Figure 3A lists the top 10 metabolites that were significantly upregulated (3,4-Dihydro-3-oxo-2H-(1,4)-benzoxazin-2-ylacetic acid, Apigenin 7-glucuronide, Cytidine, Wogonoside, Baicalin, 4-Hydroxycinnamic acid, 2-Hydroxycinnamic acid, 3-Hydroxycinnamic acid, Gentisic acid and 2,4-Dihydroxybenzoic acid) and significantly downregulated (N1-Methyl-2-pyridone-5-carboxamide, N1-Methyl-4-pyridone-3carboxamide, 21-Deoxycortisol, 1-O-Hexadecyl-2-O-(2E-butenoyl)-sn-glyceryl-3-phosphocholine, 3-(Uracil-1-yl)-L-alanine, 4-Imidazolone-5propanoate, N-(3-Piperidinyl) acetamide, 1-Methylnicotinamide, Biliverdin and 3-Methylcrotonylglycine) in the ginsenoside Rg3 group compared with the model group.

Pathway analysis and enrichment analysis of the 143 differential metabolites were performed based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (**Figure 3B**). The differential metabolites were significantly enriched in pathways related to nicotinate and nicotinamide metabolism, thiamine metabolism, amino sugar and nucleotide sugar metabolism, phenylalanine, arginine and proline metabolism, glutathione metabolism, porphyrin and chlorophyll metabolism, pyrimidine steroid hormone biosynthesis, and tyrosine metabolism.

Screening of differential metabolites in feces samples

Differential metabolites in fecal samples were obtained through metabolome sequencing. As shown in Figure 4A, all data from fecal samples fell within a 95% confidence interval, demonstrating an evident trend of separation between the groups. In total, 113 differential metabolites were identified across the fecal samples. Figure 4B shows the overlapping regions of metabolite sets and their relationships across the groups. There were 57 differential metabolites between the control and model group, 44 differential metabolites between the model and ginsenoside Rg3 groups, and 39 differential metabolites between the control and ginsenoside Rg3 groups. A heatmap was generated to visualize the 113 differential metabolites. showing a global overview of differential metabolic features across the three groups (Figure **4C**). Based on their relative content, the 113 differential metabolites were divided into seven clusters (Figure 4D).

Analysis of differential metabolites between model and ginsenoside Rg3 groups in feces samples

A total of 44 differential metabolites in fecal samples between the model and ginsenoside Rg3 groups are shown in the volcano plot (**Figure 4E**). The top 10 upregulated metabolites in the ginsenoside Rg3 group compared to the model group included arg-ala, piperazine-2-carbonitrile, betazole, histamine, val-his, docebenone, 11-dehydrocorticosterone, trp-arg, allysine, and crassicauline A. The top 8 downregulated metabolites in the ginsenoside Rg3 group compared to the model group were ethyl 2-methyl-4-oxo-6-pentylcyclohex-2-ene-carboxylate, M607T116, 7-Chloro-1-(4-fluorophenyl)heptan-1-one, [7-Hydroxy-7-methyl-6-oxo-3-[(E)-prop-1-enyl]-8,8a-dihydro-1H-isochromen-

Ginsenoside Rg3 in lung cancer



Figure 3. KEGG analysis for differential metabolites in serum samples between model and ginsenoside Rg3 groups. A. Matchstick analysis was plotted for top 10 upregulated and downregulated metabolites in ginsenoside Rg3 group compared with the model group. B. Network analysis for differential metabolites between model and ginsenoside Rg3 groups. *P < 0.05; **P < 0.01; ***P < 0.001.



Figure 4. Screening of differential metabolites in feces samples. A. Scatter plot of PCA scores for all samples. B. Venn plot of differential metabolites among three groups. C. Heat map analysis of differential metabolites between model group and ginsenoside Rg3 group using normalized data. D. K-Means analysis for differential metabolites in all groups. The horizontal axis represents the sample group, the vertical axis represents the relative content of metabolites after standardization, and Cluster represents the set of metabolites with the same expression trend. M: model of lung cancer; G: ginsenoside Rg3 group.



Figure 5. KEGG analysis for differential metabolites in feces samples between model and ginsenoside Rg3 groups. A. Matchstick analysis was plotted for top 10 upregulated and top 8 downregulated metabolites in ginsenoside Rg3 group compared with the model group. B. Network analysis for differential metabolites between model and ginsenoside Rg3 groups. *P < 0.05.

8-yl] 2,4-dihydroxy-6-methylbenzoate, (10E)-6,10-Dimethyl-3-methylidene-2,7-dioxo-2,3,3a, 4,5,6,7,11a-octahydro-6,9-epoxycyclodeca[b] furan-4-yl (2E)-4-(acetyloxy)-2-methylbut-2-enoate, M245T211, (10S)-Juvenile hormone III acid diol and Serotonin (**Figure 5A**). Pathway enrichment analysis of these 44 differential metabolites was performed based on the KEGG database (**Figure 5B**). The metabolites were significantly enriched in histidine metabolism, tryptophan metabolism, and steroid hormone biosynthesis (**Figure 5B**). Ginsenoside Rg3 inhibited an abnormally activated histidine metabolism pathway in lung cancer mice

In this study, we observed that histamine (Figure 5A, C00388) was significantly upregulated in the fecal model group compared with control group, and after treatment with ginsenoside Rg3, the level of histamine decreased to normal (Figure 4D, cluster 4). Meanwhile, differential metabolites were significantly enriched in the histidine metabolism pathway. Interestingly, histamine was also significantly downregulated by ginsenoside Rg3 in serum samples (Figure 2D, cluster 8).

Previous studies have shown that histamine contributes to lung cancer progression by enhancing Lamin A/C [13]. In this study, we collected tumor tissues from the three groups of mice and assessed key proteins in the histidine metabolism pathway using western blot (Figure 6A). The results showed that the levels of Lamin A/C and Histon H3 were significantly increased in the model tissue compared with the control group, while these levels in model tissue decreased to normal levels after treatment with ginsenoside Rg3 (Figure 6B). These results suggest that ginsenoside Rg3 inhibited the abnormally activated histidine metabolism pathway in lung cancer mice.

Ginsenoside Rg3 inhibited histamine induced proliferation in lung cancer

To investigate the metabolic pathway by which ginsenoside Rg3 inhibited lung cancer progression, ginsenoside Rg3 treatment or Lamin A-siRNA transfection was performed after histamine treatment (100 µM, 24 h) in 549 cells. As shown in Figure 6C, histamine significantly inhibited the viability of A549 cells compared to that of control cells. Importantly, Lamin A knockdown or ginsenoside Rg3 treatment obviously promoted the viability of histamine-treated A549 cells. Consistently, both Lamin A knockdown and ginsenoside Rg3 treatment significantly blocked the histamineinduced alterations in the cell cycle (Figure 6D). These data indicate that ginsenoside Rg3 inhibited histamine-induced proliferation of lung cancer cells.

Ginsenoside Rg3 inhibited histamine induced migration, invasion and epithelial to mesenchymal transition (EMT) in lung cancer

Migration and invasion were assessed using Transwell and Wound healing assays, respectively. As shown in Figure 7A and 7B, histamine inhibited the migration and invasion of A549 cells, whereas Lamin A knockdown or ginsenoside Rg3 treatment blocked histamineinduced migration and invasion, indicating that both Lamin A knockdown and ginsenoside Rg3 inhibited histamine-induced migration and invasion in lung cancer cells. Western blot showed that histamine increased E-cadherin expression and decreased N-cadherin, MMP9 and P53 levels. Moreover, Lamin A knockdown or ginsenoside Rg3 treatment significantly inhibited E-cadherin expression and promoted the expression of N-cadherin, MMP9 and P53 (Figure 7C-G). In brief, ginsenoside Rg3 or Lamin A knockdown reversed histamineinduced EMT in lung cancer cells.

Discussion

The anticancer effects of ginsenoside Rg3 in lung cancer have been extensively investigated. Previous studies have shown that Rg3 can enhance patient immunity, reduce PD-L1 expression, and restore T cell cytotoxicity against lung cancer cells [14]. Additionally, ginsenoside Rg3 has been shown to inhibit the proliferation of non-small cell lung cancer (NSCLC) cells by regulating DNA damage [15]. It can also enhance the anticancer activity of the chemotherapeutic drug gefitinib, increasing NSCLC cell sensitivity to gefitinib [16]. Ginsenoside Rg3 inhibits NF-kB-mediated EMT and cell stemness, thereby enhancing the sensitivity of hypoxic lung cancer cells to cisplatin [17]. However, the effect of ginsenoside Rg3 on the lung cancer metabolome remains unclear.

Tumor cells maintain high proliferation and migration abilities through the absorption or self-synthesis of a large number of essential biomolecules, such as amino acids, lipids, purines, and pyrimidines. In this study, the differential metabolites following ginsenoside Rg3 treatment mainly included Cytidine, N1-Methyl-2-pyridone-5-carboxamide, arg-ala, piperazine-2-carbonitrile, betazole, and histamine. Here, we focused on exploring the regula-

Ginsenoside Rg3 in lung cancer



Figure 6. Ginsenoside Rg3 inhibited histidine metabolism pathway in lung cancer. A. The protein levels of Lamin A, Lamin C and Histon H3 in tumor tissues were detected using western blot. Actin was used as an internal reference. B. The relative levels of Lamin A/C and Histon H3 were analyzed using ImageJ software. C. Effects of ginsenoside Rg3 treatment or Lamin A-siRNA transfection on cell viability of histamine-induced (100 μ M, 24 h) A549 cells. D. Effects of ginsenoside Rg3 treatment or Lamin A-siRNA transfection on cell viability of histamine-induced (100 μ M, 24 h) A549 cells. D. Effects of ginsenoside Rg3 treatment or Lamin A-siRNA transfection on cell cycle of histamine-induced (100 μ M, 24 h) A549 cells. All experiments were performed in triplicate to ensure reproducibility and reliability of the results. M: model of lung cancer; G: ginsenoside Rg3. *P < 0.05; **P < 0.01; ***P < 0.001.



Figure 7. Ginsenoside Rg3 inhibited histamine induced migration, invasion and EMT in lung cancer cells. A. The invasion was detected after 24 h of treatment or transfection using Transwell assay. Micrographs were taken at 400×. Scale bar, 20 μ m. B. Wound healing assay was used for the detection of cell migration. Micrographs were taken at 100×. Scale bar, 100 μ m. C-G. The protein levels of E-cadherin, N-cadherin, MMP9 and P53 were detected using western blot. Actin was used as an internal reference. All experiments were performed in triplicate to ensure reproducibility and reliability of the results. G: ginsenoside Rg3. **P < 0.01; ***P < 0.001.

tory effect of ginsenoside Rg3 on downstream signaling pathways via histamine. Recent studies have shown that histamine promotes the level of Lamin A/C in lung cancer cells by activating Calcium/Calmodulin dependent kinase II [13]. Our results also showed that the level of Lamin A/C in the tissues of lung cancer modeled mice was significantly higher compared to control mice. After treatment with ginsenoside Rg3, the level of Lamin A/C in tumor tissues significantly decreased. Histamine is an endogenous biogenic amine, widely distributed throughout the body, that promotes cell growth and plays a role in various physiological and pathological processes [18, 19]. In 3D spheroids within soft agar, Lamin A/C knockdown inhibits the growth and lung metastasis of melanoma and breast cancer cells [20]. However, the role of Lamin A/C in tumors remains controversial, and further validation is needed to determine whether ginsenoside Rg3 regulates lung cancer cell function through the histamine-Lamin A/C pathway.

Metabolic pathway analysis in this study showed that the differential metabolites after ginsenoside Rg3 treatment were mainly enriched in niacin and nicotinamide metabolism, steroid hormone biosynthesis, and various amino acid metabolism pathways. The efficacy of nicotinamide in treating skin, bladder, and head and neck cancers has been confirmed in a phase III clinical trial [21]. Several inhibitors targeting niacin and nicotinamide metabolism are considered to have anticancer or adjuvant therapeutic effects [22, 23]. Other differential metabolic pathways identified in this study are also closely associated with the regulation of tumor cell function, which will be the focus of our further research.

Moreover, differential metabolites were enriched in various amino acid metabolic pathways, including those involving allysine and arginine. Lysine is an essential amino acid in both humans and mammals. Lysine is catalyzed by lysyl oxidase (LOX) to generate allysine, which interacts with other lysine or active amino acid residues, thereby leading to collagen cross-linking [24, 25]. Collagen, as the main component of the ECM, plays a crucial role in tumor angiogenesis, immune escape, and metastasis. Research has shown that treatment therapy targeting LOX can interfere with ECM remodeling in renal cancer tissues [26]. This suggests that allysine metabolism may be involved in regulating tumor progression. Arginine, an important double-base amino acid, functions as a carrier for transporting and storing amino acids. In liver cancer cells, high levels of arginine bind to RNA-binding motif protein 39 (RBM39), influencing gene expression, driving metabolic reprogramming, and enabling tumor cells to acquire unlimited division ability. Furthermore, arginine can enhance competition between tumor cells and immune cells, thus promoting tumor progression [27].

Finally, we confirmed the effect of ginsenoside Rg3 or Lamin A knockdown on lung cancer cells *in vitro*. According to our results, histamine promoted the proliferation, migration and invasion, as well as the EMT process. Ginsenoside Rg3 or Lamin A knockdown inhibited these effects induced by histamine in lung cancer cells. These results suggest that ginsenoside Rg3 had a significant inhibitory effect on tumor progression caused by histamine. However, the interaction between ginsenoside Rg3 and Lamin A remains a topic for further research.

In conclusion, the present research constructed a lung cancer model and analyzed the metabolic profiles of serum and fecal samples from mice treated with ginsenoside Rg3. We identified differential metabolites between the treatment groups and explored the associated metabolic pathways. Notably, we demonstrated for the first time that ginsenoside Rg3 inhibited the expression of Lamin A/C in lung cancer tissues. This result suggests that ginsenoside Rg3 may exert its anti- cancer effect by downregulating histidine, Lamin A/C, and Histon H3 in the histidine metabolism pathway. Mechanistically, ginsenoside Rg3 suppressed histamine-induced progression of lung cancer by inhibiting processes such as cell proliferation, migration, invasion, and epithelial-mesenchymal transition (EMT). Future research is needed to determine the effect of the differential metabolites reported in this study.

Disclosure of conflict of interest

None.

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