Abstract. Lung cancer causes thousands of deaths worldwide every year, and present therapeutics show little benefit for advanced-stage patients. Researchers do not know why and how lung cancer begins. Lactamase β (LACTB) is a tumor-suppressor in some cancers. However, its role in lung cancer is unknown. By analyzing the TCGA database and Kaplan-Meier Plotter database, LACTB was found to be downregulated in lung cancer tissues but the methylation level was increased. Patients with high LACTB expression exhibited improved survival. Then, in vitro assays demonstrated that LACTB overexpression inhibited cell migration and invasion, and induced apoptosis in H1299 and H1975 cells. Knockdown of LACTB caused the reverse effects. Moreover, a much higher apoptotic rate and more potent inhibitory effects on H1299 and H1975 cells were obtained when LACTB was combined with docetaxel. In addition, members of the epithelial-mesenchymal transition (EMT) signaling pathway were assessed using western blot analysis. The expression of E-cadherin was decreased while levels of N-cadherin and vimentin were increased after knockdown of LACTB in lung cancer cells. By contrast, overexpression of LACTB increased the level of E-cadherin but decreased N-cadherin and vimentin. Therefore, LACTB is a tumor suppressor in lung cancer that inhibits cell migration and invasion and induces cell apoptosis. Meanwhile, LACTB was found to strengthen the anticancer role of docetaxel and to suppress the EMT pathway in lung cancer.

Introduction

Lung cancer is the most lethal malignancy in the world and causes approximately 132 thousand deaths each year. A total of 235,700 patients are diagnosed each year according to the newest cancer statistical report by the American Cancer Society (ACS) (1). In China, the data were astonishing due to the large population. The average incidence was 733,300 and the number of deaths was 610,200 (2). At present, the main strategy for lung cancer is still surgical resection followed by drug chemotherapy and/or radiation therapy (3). However, the majority of patients do not benefit from traditional therapy. Approximately 57% of the patients diagnosed with lung cancer have distant metastasis while 17% have a localized distribution (1). The patient's survival is dependent on their cancer stage. The five-year survival rate of patients with distant metastasis is only 6% (1). There is little time left for us to identify more potent weapons to fight lung cancer.

Lung cancer tends to metastasize due to its high genetic heterogeneity (4). From the emergence of second-generation sequencing technology, a list of genetic factors including mRNAs, long non-coding (lnc)RNAs, and microRNAs (miRNAs) have been detected that take part in the progression or metastasis of lung cancer. For example, miR-196b was reported to inhibit cell metastasis of lung cancer (5). Loss of E-cadherin was found to promote cell metastasis in lung cancer (6). However, in a cohort of lung cancer patients, the dominant genetic factors are always different, which suggests that it is a long journey to determine the deep underlying mechanisms of lung cancer.

Lactamase β (LACTB) is a gene mapped to chromosome 15q22.2. It is a gene that encodes a mitochondrial locally localized β-lactamase. It is reported to play suppressor roles in the metastasis and progression of various type of cancer. For example, LACTB was found to suppress the migration and invasion of melanoma and to block the lung metastasis of melanoma cells (7). In glioma, LACTB inhibited the proliferation, invasion and angiogenesis of tumor cells (8). Tumor angiogenesis is a well-known pathway that mediates the
distant metastasis of cancer cells (9). Zeng et al demonstrated that LACTB attenuated p53 ubiquitination and inhibited the progression of colorectal cancer (10). However, in contrast, LACTB was found to contribute to cancer metastasis and to correlate with the poor prognosis of nasopharyngeal and pancreatic cancer (11,12). These data suggest that the role of LACTB differs in a particular cancer. Chemotherapy greatly promoted tumor progression in colorectal cancer (11,12). These data suggest that the role of LACTB in lung cancer therapy and its underlying mechanism?

Epithelial-mesenchymal transition (EMT) is an important cellular program and is responsible for the aggressive behavior in cancer (15). Activation of the EMT process confers increased metastatic potential and drug resistance to cancer cells. In lung cancer, activation of the EMT signaling pathway greatly promotes tumor progression (16). At the molecular level, LACTB was reported to inhibit EMT and suppress tumor progression in colorectal cancer (17). Based on the information, it is thought that LACTB might regulate progression of lung cancer through EMT signaling.

In the present study, to explore the role of LACTB in lung cancer, the expression of LACTB was overexpressed/knocked down and lung cancer cells were subsequently treated with docetaxel. Then, cell invasive ability, apoptosis and the mechanism of action were determined.

Materials and methods

Bioinformatics analysis. The expression and methylation levels of LACTB in lung cancer were obtained by analyzing data from The Cancer Genome Atlas (TCGA) database (http://ualcan.path.uab.edu/). The association of LACTB expression with the survival of lung cancer patients was obtained from the public database Kaplan-Meier Plotter (http://kmplot.com/analysis/index.php?p=service&cancer=lung).

Cell culture. H1299 (non-small cell lung cancer) and H1975 (lung adenocarcinoma) cell lines were purchased from the Chinese Academy of Sciences (Shanghai, China) and cultured in RPMI-1640 medium (Gibco; Thermo Fisher Scientific, Inc.) containing 10% fetal bovine serum (FBS; Gibco; Thermo Fisher Scientific, Inc.) at 37°C. The culture medium was refreshed every day and the cells were passaged at 1:3 after arriving at 100% confluence.

Reverse-transcription-quantitative polymerase chain reaction (qPCR). Total RNA was extracted from the treated cell lines with RNeasy kit (Beyotime Institute of Biotechnology) according to the manufacturer's instructions. One microgram of total RNA was used as template for the synthesis of the first strand of cDNA with a cDNA synthesize kit (Beyotime Institute of Biotechnology). Then 1 µl of cDNA was used as a template to quantify the expression of target genes with SYBRGreen Mix (Beyotime Institute of Biotechnology). The protocol was as follows: 95°C for 5 min; (95°C for 15 sec; 60°C for 15 sec) for 40 cycles. Then the 2^¬∆∆Cq method was used to analyze the relative expression of target genes (18). GAPDH was used as the internal control. The primers for qPCR are shown in Table I.

Western blot analysis. Total protein was extracted from the treated cell lines with Membrane and Cytosol Protein Extraction Kit (Beyotime Institute of Biotechnology) according to the manufacturer’s instructions. Total protein (10 µg) was separated by SDS-PAGE method and transferred onto PVDF membranes (Beyotime Institute of Biotechnology). Then the PVDF membranes were blocked with 5% non-fat milk (Beyotime Institute of Biotechnology) for 1 h at room temperature followed by incubation with primary antibodies against the target protein at 4°C overnight. After washing with TBST (Beyotime Institute of Biotechnology) for three times, the PVDF membranes were incubated with secondary antibodies for 1 h at room temperature. After washing with TBST for three times, the ECL kit (Beyotime Institute of Biotechnology) was used to detect the protein bands on the PVDF membranes. β-actin was used as the internal control. The primary and secondary antibodies were as below: MMP9 (cat. no. 10375-2-AP; dilution, 1:500), MMP2 (cat. no. 10373-2-AP; dilution, 1:500), N-cadherin (cat. no. 22018-1-AP; dilution, 1:5,000), E-cadherin (cat. no. 20874-1-AP; dilution, 1:5,000), SNAIL (cat. no. 13099-1-AP; dilution: 1:500), LACTB (cat. no. 18195-1-AP; dilution, 1:2,000), Vimentin (cat. no. 10366-1-AP; dilution, 1:5,000), GAPDH (cat. no. 10494-1-AP; dilution, 1:10,000) and Rabbit IgG (cat. no. SA00001-2; dilution, 1:5,000)(all ProteinTech Group, Inc.). Adobe Photoshop CS6 (Adobe Systems, Inc.) was used for quantification of the blots.

Synthesis of shRNA targeting LACTB, construction of the plasmid carrying the LACTB gene and drug administration. shRNA targeting the human LACTB gene (shLACTB) was designed and synthesized, and the negative control was shNC. The target sequences are listed in Table II. Then 40-80 pmol of shLACTB or shNC was used to transfect them into the tumor cells with Lipo2000 agent (Invitrogen; Thermo Fisher Scientific, Inc.) for 6 h. Then fresh medium was added into each well and cultured for another 48 h followed by subsequent experiments.

A lentiviral expression plasmid carrying the coding sequence of the human LACTB gene (pLACTB) was constructed, confirmed by sequencing and the lentivirus-expressing LACTB was prepared by Shanghai GeneChem. Then, 2 µl of the plasmid was added into the cancer cells. After culture for 72 h, subsequent experiments were carried out.

Cells were treated with the designed dosage of docetaxel (10, 50,100 and 200 nmol/l) (QILU Pharmaceutical Co.,Ltd.) in combination with shNC, shLACTB or empty vector pCDH (Ctrl) or pLACTB for 48 h followed by subsequent experiments.

Cell Counting Kit 8 (CCK-8). A total of 3x10^3 cells/well were seeded into 96-well plates and treated as described above. After culture for 72 h, 10% of CCK-8 agent (Yeasen) was added into
The width of the scratch was determined and recorded as $S_{0\ h}$. With PBS (Gibco; Thermo Fisher Scientific, Inc.) two times, the scratch was produced using a 10-µl tip followed by washing culture for 24 h, the confluence of 90% was achieved, and a 4% paraformaldehyde (Beyotime Institute of Biotechnology) at room temperature for 15 min in the dark. The positively marked cells were detected with BD FACSCelesta (BD Biosciences).

**Table I. Primers for quantitative polymerase chain reaction assay.**

| Gene  | Primers (5'-3')                          |
|-------|------------------------------------------|
| LACTB | Forward: GTGGTTGGAGTTTCTGTAGGGAAGAGGCAT |
|       | Reverse: AGTAATCTTGTGACAGAAACCT          |
| GAPDH | Forward: CGTATTGGGGCCTGTTGTCAC           |
|       | Reverse: ATGATGACCCCTTTGGGCTCC           |

$LACTB$, lactamase $\beta$.

**Table II. Target sequence for $LACTB$ gene.**

| Gene   | Targets (5'-3')                        |
|--------|---------------------------------------|
| LACTB  | shRNA-#1: CTTACGTGGGAACTCTCTAT         |
|        | shRNA-#2: CCTAAACCATAGGTGAAAAT         |
|        | shNC: CCTTCGGCTAAAGCATTAGGCAAT         |

$LACTB$, lactamase $\beta$.

Each well and cultured for another 1 h. Then, the absorbance at 450 nm was detected on a microplate reader (Tecan-SPARK).

**Wound-healing assay.** A total of 2x10^5 cells/well were seeded into 24-well plates and treated as described above. After culture for 24 h, the confluence of 90% was achieved, and a scratch was produced using a 10-µl tip followed by washing with PBS (Gibco; Thermo Fisher Scientific, Inc.) two times. The width of the scratch was determined and recorded as $S_{0\ h}$. After culture for another 24 h, the width of each scratch was determined and recorded as $S_{48\ h}$. The relative migration rate was calculated as follows: Migration rate=$(S_{0\ h}-S_{48\ h})/S_{0\ h}$.

**Transwell assay.** The insert chamber with 8-µm pores (Corning, Inc) was pretreated with/without 200 µl of cold Matrigel (BD, Biosciences) at room temperature for 1 h followed by washing with culture medium once. Then a total of 2x10^4 cells/well were added to each room with 300 µl of culture medium containing no serum and the room was inserted into 24-well plates with 300 µl of culture medium containing 10%FBS. After culture for 24 h, cells on the upper surface of the insert room were scraped and cells on lower surface was fixed in 4% paraformaldehyde (Beyotime Institute of Biotechnology) for 10 min at room temperature. After washing with PBS, the insert chamber was stained with 0.5% crystal violet (Beyotime Institute of Biotechnology) for 10 min at room temperature. Then the positive cells were counted under a light microscope (Olympus) at x100 magnification after washing with PBS.

**Flow cytometric analysis.** A total of 2x10^5 cells/well were seeded into 6-well plates and treated as the above. After culture for 48 h, cells were collected and washed with cold PBS once. Then cells were suspended in staining buffer and stained with Annexin V-PE/7-AAD reagent (Beyotime Institute of Biotechnology) at room temperature for 15 min in the dark. The positively marked cells were detected with BD FACSCelesta (BD Biosciences).

**Statistical analysis.** The data in this study were analyzed using SPSS software (SPSS, Inc.; Version 16.0) and was expressed as the mean ± SD. The difference between two groups was analyzed by unpaired Student’s t-test, while one-way ANOVA followed by Tukey’s test was used for more than three groups. $P<0.05$ indicates a significant difference.

**Results**

$LACTB$ is correlated with favorable prognosis in lung cancer. To study the role of the $LACTB$ gene in lung cancer, we extracted information from public databases. Based on the TCGA database, the expression level of $LACTB$ in 515 tissues with lung cancer was significantly downregulated compared to that in the normal tissues (Fig. 1A). The methylation level of $LACTB$ in tumor tissues was significantly higher than in normal control tissues (Fig. 1B). Moreover, survival analysis demonstrated that the survival probability of patients with high $LACTB$ expression was significantly better than that of patients with low $LACTB$ expression (Fig. 1C). These data suggest that $LACTB$ might play an important role in the progression of lung cancer.

$LACTB$ does not affect cell survival in lung cancer. To investigate the role of $LACTB$ in lung cancer, the expression of $LACTB$ was increased or decreased in the H1299 and H1975 cell lines. As shown in Fig. 2A and B, qPCR analysis showed that $LACTB$ was successfully increased in the H1299 and H1975 cells. Additionally, shRNA technology ensured that $LACTB$ was significantly decreased (Fig. 2C and D) in the H1299 and H1975 cells. Then by CCK-8 assay, cell survival was shown to be minimally affected by $LACTB$ (Fig. 2E and F). Therefore, $LACTB$ does not affect cell survival in lung cancer.

$LACTB$ negatively regulates migration and invasion in lung cancer. By wound-healing assay, we found that the cell migration rate was greatly reduced by $LACTB$ overexpression in the H1299 and H1975 cells. As shown in Fig. 3A and B, the relative cell migration rates were 0.31 and 0.12 after $LACTB$ overexpression in H1299 and H1975 cells, respectively, which were significantly lower than those of the control group. However, in H1299 cells with $LACTB$ knockdown, the migration rate was 0.81 while it was 0.44 in the NC group (Fig. 4A and B). The same trend was observed in the H1975 cells. In Figs. 5A and B, and 6A and B, Transwell assays without Matrigel demonstrated that the cell migration was significantly suppressed by $LACTB$ overexpression but promoted by $LACTB$ knockdown. Then, in the Transwell assay with Matrigel, there were fewer cells penetrating through the monolayer membrane in the $LACTB$ overexpression group than in the control group in H1299 cells (18 vs. 99; Fig. 7A.
Figure 1. LACTB is clinically associated with lung cancer. (A) LACTB was found to be significantly decreased in lung cancer tissues compared to that noted in normal tissues based on TCGA database. (B) The methylation level of LACTB in lung cancer tissues was increased significantly compared to normal tissues based on the TCGA database. (C) The survival probability of lung cancer patients with high LACTB expression was much higher than the patients with low LACTB expression. *P<0.05, statistical difference compared to the normal tissues. LACTB, lactamase β; TCGA, The Cancer Genome Atlas.

Figure 2. LACTB negatively regulates the cell survival in lung cancer. (A) LACTB was found to be overexpressed in H1299 cells by transfection with a plasmid carrying LACTB. In the control group (Ctrl), empty vector pCDH was transfected into cells. (B) LACTB was overexpressed in H1975 cells by transfection with a plasmid carrying LACTB. (C) LACTB was knocked down in H1299 cells by shRNA targeting LACTB. (D) LACTB was knocked down in H1975 cells by shRNA targeting LACTB. (E) Overexpression of LACTB inhibited cell survival in H1299 and H1975 cells. (F) Knockdown of LACTB promoted cell survival in H1299 and H1975 cells. *P<0.05, statistical difference compared with the Ctrl or shNC group. LACTB, lactamase β.
Figure 3. Overexpression of LACTB suppresses lung cancer cell migration in a wound-healing assay. (A) Cell migration behavior was determined by a wound-healing assay in H1299 and H1975 cells. (B) The statistical analysis of data in (A). *P<0.05, statistical difference compared with the Ctrl group. LACTB, lactamase β.

Figure 4. Knockdown of LACTB promotes lung cancer cell migration in a wound-healing assay. (A) Cell migration behavior was determined by a wound-healing assay in H1299 and H1975 cells. (B) The statistical analysis of data in (A). *P<0.05, statistical difference compared to the shNC group. LACTB, lactamase β.
However, in contrast, LACTB knockdown significantly increased the cell number (Fig. 8A and B). Therefore, LACTB negatively regulates cell migration and invasion abilities in lung cancer cells.

**LACTB increases the inhibitory effect of docetaxel on cell proliferation.** The combination of drugs in cancer is often surprising. Here, we found that LACTB overexpression significantly inhibited the cell proliferation in H1299 and H1975 cells treated with docetaxel, which indicates that LACTB has additive effects with docetaxel (Fig. 9A and B). In contrast, knockdown of LACTB greatly reduced the inhibitory ability of docetaxel on lung cancer cells (Fig. 9C and D). These data suggest that LACTB might be applied to increase the efficacy of docetaxel in lung cancer therapy.

**LACTB induces apoptosis of lung cancer cells induced by docetaxel.** Docetaxel induces cell apoptosis in cancer. As shown in Fig. 10A and B, the cell apoptotic rate was 48.96% in the H1975 cells treated with the combination of LACTB and docetaxel while the rate was 33% in the Ctrl/docetaxel group, and the difference was significant. However, LACTB knockdown reduced the apoptotic rate of docetaxel in the H1975 cells (Fig. 11A and B). The apoptotic rate in the shNC/docetaxel group was 53.86% while it was 26.84% in the shLACTB/docetaxel group. In conclusion, LACTB plays an additive role with docetaxel in the apoptosis of lung cancer cells.

**LACTB regulates the expression of members of the EMT signaling pathway.** By western blot analysis, we detected obvious changes in typical molecules in the EMT process. As
shown in Fig. 12A and B, the expression levels of Snail, matrix metalloproteinase (MMP2), MMP9, N-cadherin and vimentin were significantly downregulated while E-cadherin was significantly increased after LACTB overexpression in H1975 cells. Conversely, knockdown of LACTB reduced E-cadherin levels while increasing the levels of Snail, MMP2, MMP9, N-cadherin and vimentin (Fig. 12A and C). This indicates that LACTB negatively regulates the EMT process in lung cancer.

Discussion

Thousands of humans succumb to lung cancer each year, and overall survival is a major challenge in the clinic (1,2). This is due to the lack of knowledge concerning lung cancer including how and when lung cancer begins or progresses.

Based on TCGA database (19), lactamase β (LACTB) was shown to be downregulated in lung cancer while the methylation level of LACTB was enhanced. Methylation is an important mechanism regulating the switch-on/off of target genes (20). Reduced expression of LACTB in lung cancer tissues might be due to increased methylation levels of LACTB. In colorectal cancer, LACTB was also found to be silenced by elevated methylation of the promoter domain, which promoted metastasis and advanced clinical stages (10). In the Kaplan-Meier Plotter database, high LACTB expression was associated with better survival of lung cancer patients. This is consistent with a study in hepatocellular cancer that found that low LACTB expression was associated with poor prognosis (21). These data suggest that LACTB might also be a suppressor in lung cancer.
cancer and a potential risk factor when evaluating the prognosis of lung cancer patients. In the present study, overexpression of LACTB was found to suppressed cell proliferation, migration and invasion in lung cancer cells. However, knockdown of LACTB reversed the inhibitory effect in lung cancer. Generally, expansion of tumors and
Figure 11. Knockdown of LACTB reduces the cell apoptotic rate by docetaxel in H1975 cells. (A) Cell apoptosis rate in H1975 cells was detected by FACS analysis. (B) The statistical analysis of data in (A). *P<0.05, statistical difference compared to the shNC group. LACTB, lactamase β.

Figure 12. LACTB regulates the EMT signaling pathway. (A) Overexpression of LACTB promoted E-cadherin expression and reduced the level of Snail, N-cadherin, vimentin, MMP2 and MMP9 in H1975 cells. By contrast, knockdown of LACTB increased the level of Snail, N-cadherin, vimentin, MMP2 and MMP9 while reducing E-cadherin in H1975 cells. (B) Gray value analysis of the protein bands (on the left) shown in in A. (C) Gray value analysis of the protein bands (on the right) in (A). *P<0.05, statistical difference compared to the Ctrl or shNC group. LACTB, lactamase β; EMT, epithelial-mesenchymal transition; MMP, matrix metalloproteinase.
distant metastasis are two typical events observed in cancer patients (22). This study confirmed the suppressor role of LACTB in lung cancer.

Docetaxel is a specific inhibitor of the M-phase of the cell cycle and has been successfully applied in the clinic to treat patients with breast cancer or non-small cell lung cancer. Docetaxel was demonstrated to increase the ratio of Bax to Bcl-2 followed by the apoptosis response when combined with Stattic in prostate cancer (23). In another study, docetaxel enhanced lysosomal function followed by activated autophagy (24). In the present study, docetaxel induced apoptosis in lung cancer and this effect was reinforced by LACTB overexpression. This suggests that synergistic or additive effects between docetaxel and LACTB exist. LACTB might increase the efficacy of docetaxel or may allow a decrease in the dosage of docetaxel, which would relieve the adverse effects of docetaxel. Thus, combination therapy could achieve much better outcomes and fewer adverse effects. A potential combination therapy could be the combination of immunotherapy with radiation therapy or targeted therapy (25,26). Therefore, LACTB has the clinical potential to increase the efficacy of docetaxel.

EMT is critical in cancer transformation and confers aggressive ability to cancer cells (27). In lung cancer, activation of EMT was reported to cause a series of events favorable for cancer progression. For example, the efficacy of EGFR-targeted therapy in lung cancer was greatly reduced through the EMT mechanism (28). T-cell infiltration in lung cancer was negatively regulated by EMT (29). In the present study, LACTB exhibited potent inhibition of cell migration and invasion in lung cancer. At the molecular level, LACTB was shown to regulate the expression levels of E-cadherin, N-cadherin, vimentin and Snail. E-cadherin is a typical marker of epithelial cells while N-cadherin and vimentin are typical markers of mesenchymal cells (30). Snail was reported to bind to the E-box element in the promoter of the E-cadherin gene and suppress the transcription of E-cadherin (31). Therefore, LACTB suppressed EMT in lung cancer. The inhibitory role of LACTB on cell migration or invasion might be partially due to the deficiency of EMT in lung cancer. EMT was also shown to cause drug resistance to docetaxel in lung cancer therapy (32). In this study, LACTB suppressed the EMT process and induced cell apoptosis in lung cancer. Therefore, it is possible that LACTB may suppress EMT by inhibiting Snail and increase the sensitivity of lung cancer cells to docetaxel. The above data suggest that LACTB is a good candidate for lung cancer therapy. However, further experiments are necessary before the clinical application of LACTB is realized.

In conclusion, LACTB showed a clinical correlation with the suppressed progression in lung cancer by negatively regulating cell migration, invasion and EMT while increasing apoptosis. LACTB exerts additive effects with docetaxel in the treatment of lung cancer cells. This study suggests that LACTB is a new suppressor for lung cancer.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HL and YW designed the study and reviewed the manuscript. YX acquired the majority of the data and drafted the manuscript. HS, MW and PH analyzed the data and revised the manuscript. MX and SH confirmed the authenticity of all raw data, interpreted the data, provided literature support and revised the manuscript. All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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