Construction of a Prognostic Signature of Autophagy-Related IncRNAs in Non-Small Cell Lung Cancer

Xinyang Zhang
Medical College of Nantong University

Yu Cao
Third People's Hospital of Nantong

Li Chen (ntchenli1@163.com)
Nantong University

Research Article

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Abstract

**Background:** Autophagy inhibits tumorigenesis by limiting inflammation, LncRNA regulates gene expression levels in the form of RNA at various levels, so both of them are closely related to the occurrence and development of tumors.

**Methods:** 232 autophagy-related genes were used to construct a co-expression network to extract autophagy-related lncRNAs. A prognostic signature was constructed by multivariate regression analysis. Kyoto Encyclopedia of Genes and Genomes (KEGG) was applied to analyze pathway enrichment in cancer pathways. Immunoinfiltration analysis was used to analyze the relationship between the prognostic model and the tumor.

**Results:** Nine autophagy-related lncRNAs were used to construct a prognostic model for non-small cell lung cancer. The median value of the value at risk was used to distinguish between the high and low risk groups, and the low-risk group had better survival. Because the KEGG pathway analysis showed that the prognostic model was enriched in some immune pathways, further exploration of immune infiltration was conducted and it was found that the prognostic model did play a unique role in the immune microenvironment. And the prognostic model was associated with clinical factors.

**Conclusion:** The prognostic model of autophagy-related lncRNAs constructed by us can predict the prognosis of non-small cell lung cancer.

1. Introduction

Lung cancer is one of the most malignant tumors that threaten the health, and its incidence has increased mainly owing to the rise in smokers, a known risk factor [1]. Autophagy is a process that swallows cytoplasmic proteins or organelles and coats them into vesicles, and fuses with lysosomes to form autophagosomes, which degrades the contents they encapsulate, to achieve the metabolic needs of the cell itself and the renewal of certain organelles [2–4]. The relationship between autophagy and tumorigenesis needs to be confirmed by our further study. As autophagic drugs have been reported to induce lung cancer cells death, we investigated the potential prognostic role of autophagy-associated long non-coding RNA in lung cancer patients, lncRNA plays a part in many life activities such as dose compensation effect, cell cycle regulation and cell differentiation [5–7]. Although the molecular events in the progression of lung cancer have been well studied, the complicated interaction between mRNA and lncRNA that exerts crucial influence on the progression and prognosis of lung cancer is yet unclear. In this study, 9 autophagy-related lncRNAs with prognostic value (AC020765.2, AC254562.3, AL031666.1, LINC01426, MMP2-AS1, AC102953.2, AP000695.2, LINC00941 and NKILA) were identified in patients using multivariate Cox regression analysis, then a prognostic signature was established based on these prognostic lncRNAs, which may serve as an independent prognostic factor in lung cancer. We divided patients into low-risk and high-risk groups based on risk score and constructed co-expression network. Gene set enrichment revealed that the gene sets were significantly enriched in cancer-related pathways,
including small cell lung cancer, pathways in cancer, thyroid cancer, P53 signaling pathway, WNT signaling pathway and PAR signaling pathway. Moreover, other enriched pathways were closely related to metabolism, such as Butanoate metabolism, Fatty acid metabolism, α-linolenic acid metabolism and arachidonic acid metabolism. We also examined the relationship between the risk grouping and tumor-infiltrating immune cells (TIICs) using TIMER and CIBERSORT. In summary, our signature of 9 autophagy-related IncRNAs has prognostic potential for lung cancer.

2. Materials And Methods

2.1 Isolation and sorting of IncRNAs and mRNAs

Data including transcriptome profiling and clinical information for all lung adenocarcinomas and squamous cell carcinomas were downloaded from The Cancer Genome Atlas (TCGA, http://cancergenome.nih.gov/). Sorted by perl script (https://www.perl.org), a total of 108 normal samples and 1037 tumor samples were obtained, at the same time, we deleted missing information. Through human transfer gene format, we performed ID conversion and distinction of IncRNAs and mRNAs

2.2 Autophagy gene and IncRNA screening

The autophagy gene list was gained from the Human Autophagy Database (HADb, http://autophagy.lu/clustering/index/.html). When extracting autophagy genes, we performed an average operation on the same gene that appeared multiple times, normal samples and low-expressing genes (expression of autophagy-related mRNA or IncRNA <0.5) were deleted. Pearson correlation was applied to calculate the correlation between the IncRNAs and autophagy-related genes. A IncRNA with a correlation coefficient $|R^2| >0.3$ and $P <0.001$ was considered to be an autophagy-related IncRNAs.

2.3 Signature development

Univariate and multivariate Cox regression analysis were performed to evaluated the prognostic value of autophagy-related IncRNAs. To establish the risk score, the IncRNAs with a P-value <0.01 by univariate analysis were included in the multivariate stepwise regression Cox analysis. The following formula was used to determine the risk score for each patient: $\beta_{gene1} \times expr_{gene1} + \beta_{gene2} \times expr_{gene2} + \ldots + \beta_{gene n} \times expr_{gene n}$. Cox analysis was performed to establish a signature for predicting survival. Specifically, we assigned risk scores by a linear combination of the expression levels of IncRNAs weighted by regression coefficients (β). The β value was calculated by log transformation of the hazard ratio (HR) from the multivariate Cox regression analysis. High risk and low risk groups was established based on the median risk score. The lnRNAs expression is defined as expr gene n [8].

2.4 Construction of Cox network

It was vital to match the autophagy-related IncRNAs and mRNAs according to the hypothesis of Cox, thus, the network which visualized by CYTOSCAPE (version 3.7.1) could highlight the connection and
mechanism involved in the development of lung cancer. Furthermore, as the number of lncRNAs was high, it was valuable to create a signature comprising a limited number of variables and the best Akaike information criterion (AIC).

2.5 Gene set enrichment analysis

Gene set enrichment analysis (GSEA) is an analysis method for whole genome expression profile chip data, comparing genes with predefined gene sets [9]. This method derives its function by analyzing gene sets, so it can be used to determine whether the gene set shows a statistically significant difference between the two biological states. In this study, we verified whether genes that are differentially expressed between two groups are enriched during autophagy.

2.6 Immune infiltrates analyses

TIMER is a comprehensive resource for systematic analysis of immune infiltrates across diverse cancer types (https://cistrome.shinyapps.io/timer/), which was used to evaluate potential relationships between risk grouping and tumor-infiltrating immune cells. TIMER employs a recently published statistical method known as deconvolution to deduce the prevalence of TIIGs from gene expression profiles. In order to approximate the abundance of TIIGs, the TIMER database used TCGA data on 10897 samples across 32 types of cancer. To assess the relative variations of gene expression amongst sets in the samples [10, 11], we used a deconvolution algorithm based on gene expression called CIBERSORT (http://cibersort.stanford.edu/). With CIBERSORT, we measured the immune response of 22 TIICs to evaluate their association with risk grouping in lung cancer and to uncover correlation between TIICs. We used standard annotation files to establish gene expression datasets and used the defaults signature matrix at 1000 permutations. Through Monte Carlo Sampling, approximately a P-value for deconvolution to determine the levels of confidence in outcomes. In order to analyze the influence of high and low risk grouping on the microenvironment of the immune system, we utilized 999 tumor samples that we classified into two groups. To determine the types of lymphocytes affected by grouping, we set up the P-value <0.05 [12, 13].

2.7 Statistical analysis

Survival status was the basis for univariate cox regression analysis, and R software (version 3.6.2) was used to generate Kaplan-Meier curves. GSEA (http://www.broadinstitute.org/gsea/index.jsp) was used to distinguish between two sets of functional annotations. Statistical significance was set at a threshold of a two-tailed P <0.05.

3. Results

3.1 Collation of transcriptome data

We identified 14142 lncRNAs which were extracted from TCGA datasets, a total of 210 autophagy-related genes were downloaded from the Human Autophagy Database (HADb, http://
We conducted co-expression analysis of autophagy genes and IncRNAs to obtain autophagy-related IncRNAs (|R2| > 0.3 and P < 0.001). According to the properties of genes, we separated 1496 IncRNAs which were determined for further screening prognostic genes. We combined the two data of futime and fustate which were from clinical data (downloaded from TCGA) into the expression matrix of IncRNAs. Patients with incomplete clinical information (futime, fustate, age, gender, grade, state and TNM) were excluded from the following procedure.

3.2 Construction of Cox model

Through univariate Cox regression analysis, 18 IncRNAs had prognostic value for lung cancer (P ≤ 0.01) and these IncRNAs were subjected to multivariate Cox regression analysis. A risk score formula based on AC020765.2, AC254562.3, AL031666.1, LINC01426, MMP2-AS1, AC102953.2, AP000695.2, LINC00941 and NKILA had the lowest AIC (Akaike information criterion), of which, five IncRNAs were favorable factors (AC020765.2, AC254562.3, AL031666.1, LINC01426, MMP2-AS1) and four IncRNAs were considered as unfavorable prognostic factors (AC102953.2, AP000695.2, LINC00941 and NKILA). The risk assessment score for the prediction of overall survival was calculated as follows: \[ \text{exp(AC020765.2) \times 0.176009} + \text{exp(AC254562.3) \times 0.138779} + \text{exp(LINC01426) \times 0.103983} + \text{exp(MMP2-AS1) \times 0.145198} + \text{exp(NKILA) \times 0.048298} + \text{exp(AP000695.2) \times 0.187273} + \text{exp(LINC00941) \times 0.086274} + \text{exp(LINC01426) \times 0.150477} + \text{exp(LINC00941) \times 0.054391} \]

3.3 Visualization of co-expression network

To better present the connection and mechanism between prognosis-related autophagy IncRNAs and mRNAs, in the first place, we visualized co-expression results with cytoscope and constructed heat maps for IncRNAs and mRNAs in the co-expression network to show the difference in expression data, respectively (Fig. 2A-C). The distribution of the different patients which were separated into two groups by median value of risk scores was significantly different with the Cox of autophagy-related genes, while it was not significantly separated between the two groups in the whole expression genes (Fig. 3A-B). Risk survival curve indicated that the five-year survival rates for low risk (CI: 0.446-0.579) and high risk (CI: 0.32-0.443) groups were more than 0.5 and 0.38, respectively (P< 0.0001) (Fig. 3C). In the next place, we constructed Sankey diagram for further distinguishing IncRNAs into protective IncRNAs (the higher the expression of IncRNAs, the lower the risk) and risky IncRNAs and more comprehensive display of their connection (Fig. 3D).

3.4 Validation of Cox model

Three parts constituted the risk curve and patients' risk from left to right increased sequentially. The first part implied that we divided these patients into high-risk and low-risk groups on the basis of the median value of the risk score. The result of the survival state graph was that as the risk value increased, the patients' survival time decreased. The expression heat map indicated that risk increased with increased expression of some IncRNAs (LINC00941, AP000695.2, NKILA and AC102953.2), while risk increased with decreased expression of other IncRNAs (AC020765.2, AC254562.3, AL031666.1, LINC01426 and MMP2-
AS1) (Fig. 4A). In order to evaluate whether the constructed model was independent of other clinical traits as an independent predictive factor, we constructed an independent prognostic analysis. It was found that stage (P< 0.001), T (P< 0.001), M (P= 0.007), N (P< 0.001) and risk score (P< 0.001) were directly related to prognosis of patients (Fig. 4B), while multivariate Cox regression analysis showed that only T (P= 0.023), N (P= 0.029) and risk score (P<0.001) were statistically independent predictive factors (Fig. 4C) [17]. The prediction efficiency of the model is evaluated by ROC curve, and it can be seen that the area under the curve is 0.685 for one year, 0.648 for two years, and 0.638 for three years. This indicates that the prediction efficiency of our model is good (Fig. 4D). The area under the red curve in multiple indicators ROC curve was 0.673, suggesting that our model had a promising power in predicting the clinical outcome of patients. Furthermore, compared with other clinical traits, the area of risk value was the largest, so our model to predict the survival of patients was also superior to other clinical traits (Fig. 5A) [18].

3.5 Gene set enrichment analysis

Further functional annotation was conducted through GSEA, the results revealed that the differentially expressed genes between two groups were enriched in the metabolism-related and tumor-related pathways. As result, a total of 45 genes sets were significantly enriched at a nominal P value < 0.05. Among them, several pathways were well established in cancers, including small cell lung cancer, pathways in cancer, thyroid cancer, P53 signaling pathway, WNT signaling pathway, which were promoting the development of tumors, indicating that these pathways were active in high risk patients, while other pathways were silent in high risk patients. PAR signaling pathway participated in lipid metabolism and induced anti-cancer effect in human tumors. Butanoate metabolism, which significantly increased the metabolic pressure of tumor cells’ mitochondria, promoted specific apoptosis of lung cancer cells, and inhibited tumor growth. Fatty acid metabolism, α-linolenic acid metabolism and arachidonic acid metabolism inhibited the occurrence and metastasis of cancer (Fig 5B) [19, 20].

3.6 Differences in immune cells in high and low risk models

Independent tumor-infiltrating lymphocytes contribute to the prediction of the overall survival and the status of sentinel lymph node. Hence, TIMER was applied to analyze the possible relationship between the risk grouping of lung cancer and immune infiltration. As shown in Fig.5C, a negative correlation exists between risk classification and the levels of B cells (P-value= 7.192 × 10-6), Macrophages(P-value=0.022) and CD4 T cells(P-value=0.027) [21,22]. To estimate whether there exists a difference between the tumor immune micro-environment of the two groups of patients, 999 tumor patients were divided into low-risk and high-risk groups, which contain 500 and 499 patients, respectively. A comprehensive algorithm, CIBERSORT was employed to ascertain the different levels of 21 immune cells in gene expression profile which was separated into two groups based on median value of risk. Memory activated CD4 cells and M0 Macrophages show a low expression in low-risk groups, while resting mast cells show a high expression in low-risk groups (Fig.5D). The correlation heat map obtained with the 22 types of immune cells revealed that CD8 T cells correlated positively with activated memory CD4 T cells, while showed negative
relationship with resting memory CD4 T cells (Fig. 6A). The immune score and matrix score of the patients can contribute to establishing the degree of immune cell infiltration in the tumor microenvironment and tumor purity. The matrix microenvironment showed that there was no significant difference among the patients who were divided into two groups based on the median value of matrix score, while for those divided into two groups based on the median value of immune score, significant differences were revealed by the immune micro-environment. (Fig. 6B-C) [23-26].

3.7 Clinical correlation analysis

We conducted clinical correlation analysis to assess whether the risk score and the IncRNAs in the cox model were related to clinical traits. We conducted a clinical correlation analysis to evaluate whether the risk score and IncRNA in the Cox model are related to clinical characteristics, and found that the risk model is significantly related to stage and T staging. At the same time, AP00695.2 in the model is significantly related to age, gender and T staging, while AC020765.2 is related to gender, AC254562.3 is related to stage staging, AC102953.2 is significantly different between ages, and LINC00941 is in T staging. The difference is significant, AL031666.1 has significant difference in age and stage staging, LINC01426 has significant difference in gender, and MMP2-AS1 has obvious difference in stage and T (Fig. 7).

4 Discussion

Lung cancer, which is one of the most fatal malignant tumors, is contemporarily jeopardizing the well-being of all nations. It is of great urgency to find a way of predicting the overall survival rate of lung cancer. Epigenetic of genes, especially IncRNAs have shown close links to lung cancer [26–28]. LncRNAs as supplemental genes/ miRNAs are promising the prediction of the risk of recurrence of lung cancer. Due to the limitation of technology, there still exist problems when involved in the functional research field of IncRNAs in comparison with those of coding RNAs. Therefore, it is vital to establish a risk model to better predict the prognostic of lung cancer.

In this research, we identified 9 prognosis-related autophagy IncRNAs and divided patients into high-risk and low-risk groups based on the median risk score. Through univariate and multivariate Cox regression analysis, we could conclude that the risk model is an independent prognostic factor.

The origin of autophagy occurs in the formation of membranous structures called phagocytic cells or membranes. After phagocytic cell formation begins, the double membrane grows to surround the cell contents during a process called the autophagic extension phase. Autophagy can promote the survival of tumor cells, but can also lead to cell death. It can be up-regulated or inhibited by cancer treatment agents. Up-regulation of autophagy during cancer treatment can promote the survival or death of tumor cells. Although little is known about the role of autophagy in cancer therapy to date, recent studies suggest that autophagy therapy will become a new approach to lung cancer treatment [29–31]. For one thing, autophagy as a tumor suppressor. Autophagy is a valuable mechanism used by cells to maintain cell maintain cell integrity and genome stability. The absence of autophagy genes will naturally interfere with
this homeostasis, so it may initiate cell tumor development. Further, a variety of autophagy mechanisms contribute to tumor suppression. Under stress, autophagy is activated to remove damaged proteins and organelles, including mitochondria. Inhibition or lack of autophagy will lead to an increase in reactive oxygen levels, which will cause the accumulation of DNA damage, which is manifested by gene amplification, increased double-strand breaks and polyploid nuclei. This increased DNA damage may lead to a subsequent higher susceptibility to the onset and development of cancer.

For another, autophagy as a carcinogenic process, both mechanical tissue and genetic research support the hypothesis that autophagy is a carcinogenic process. When the intracellular and extracellular environments are poor and the cells are under metabolic stress, autophagy is activated as an adaptation mechanism. In the early stages of tumor formation, cancer cells often experience hypoxia and an environment in which nutrients are limited due to tumor growth due to a lack of an effective blood supply. These conditions cause metabolic stress and lead to reduced mitochondrial oxidative phosphorylation. Subsequently, cancer cell proliferation is restricted and the cells can enter a dormant state. During dormancy, tumor cells rely on autophagy as a survival strategy, thereby, removing nutrients to promote cell survival. When the stress environment improves, cancer cells can resume proliferation. Recent studies have shown that LINC01426 was available to act as a predicting gene of SQCLC and GC, as well as LINC00941 was defined as optimal diagnostic IncRNA biomarker for HNSCC, GC and LUAD.

Equally important, our study used the TIMER database to uncover connections between risk model and immune infiltration levels in lung cancer. We found that the associations of risk model with B cells, CD4 T cells and macrophages are the strongest. Moreover, our CIBERSORT analysis revealed that activated mast cells, M0 macrophages and CD4 memory activated T cells were found at increased levels in the high-risk group, whereas levels of naive B cells, follicular helper T cells, resting dendritic cells and resting mast cells were decreased. Our results could indicate a possible mechanism where risk model regulates the functions of mast cells in cells. Mast cells are a kind of multifunctional cells, and related studies have confirmed that they are related to the pathological process of neoplastic diseases. For example, mast cells can promote tumor angiogenesis by releasing heparin, or dissolve surrounding connective tissue by releasing proteolytic enzymes, which is beneficial to tumor growth and metastasis. While other studies have shown that the mast cells surrounding the tumor have the role of fighting the tumor and protecting the host. Combined with our research, we can propose corresponding explanations that activated mast cells promote tumor growth, and resting mast cells inhibits tumor cells.

In conclusion, the IncRNAs investigated using this model demonstrate that they can serve as therapeutic targets for lung cancer’s precise treatment. Practical research will be conducted to further verify the biological function and explore inner molecular mechanism.

Declarations

Author Contributions
Xinyang Zhang participated in the design of the article’s ideas and the implementation of the specific steps, while Yu Cao provided assistance in the compilation of the data for this study, and Li Chen participated in the revision and approval of the article.

Consent to Publish

Not applicable

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Ethical approval and consent to participate

Not applicable.

Conflict of Interest

The authors have no conflicts of interest to declare.

Data Availability Statement

All data were from TCGA databases, which are publicly available (https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga).

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