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ORIGINAL ARTICLE

Association of the key genes in the pathophysiology between the Type 2 diabetes and Lung cancer

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Abstract

BACKGROUND: Although several studies have demonstrated that preexisting diabetes mellitus (DM) may increase the risk of lung cancer (LC), rare research of the certain pathophysiology was reported up to now.
METHODS: Aiming to identify the differentially expressed genes (DEGs) between type 2 diabetes mellitus (T2DM) and LC, gene expression profiles GSE55650 and GSE136043 were downloaded in the Gene Expression Omnibus (GEO) database. We carried out biological function analysis to seek significantly enriched pathways and functions for DEGs. A protein-protein interaction (PPI) network was performed to explore hub genes for diabetes and LC during Metformin's treatment.
RESULTS: Finally, the study found that there were 756 genes overlapped between T2DM and LC samples. It contained 133 common genes up-regulated both in T2DM and LC (DEGs1), 275 independent genes down-regulated in LC (DEGs2), 246 common genes down-regulated in both (DEGs3), and 102 independent genes down-regulated in diabetes (DEGs4). Glycine, serine and threonine metabolism, arginine and proline metabolism, TGF-beta signaling pathway, and pathways in cancer were significantly enriched in DEGs2 and DEGs4. Four hub genes (C3, THBS1, CXCL1, and TTN) were identified after treatment of Metformin (p<0.05, T-test).
CONCLUSION: Our findings demonstrated that the above-mentioned hub genes might play functional roles in the treatment of metformin for patients with diabetes and LC.

INTRODUCTION

Lung cancer (LC) has become the number one cancer killer all over the world (Torre, *et al.* 2015). Despite huge efforts to develop screening and treatment modalities, the prognosis of LC patients is still unsatisfactory (Dillman and McClure, 2014). Recent studies have shown an elevated prevalence of lung cancer among diabetic patients (Lee, *et al.* 2013; Yu, *et al.* 2018). Moreover, diabetes is associated with a poor prognosis for lung cancer (Luo, *et al.* 2012, 2016; Zhu, *et al.* 2016). Unfortunately, the specific mechanism behind how and why diabetes influences lung cancer development and mortality is still unclear.

Meanwhile, metformin, a first-line oral medication for the management of type 2 diabetes (T2D), has been proved to improve the prognosis

in diabetic patients with lung cancer (Mazzone, *et al.* 2012; Xu, *et al.* 2018). Previous studies have confirmed that the use of metformin is associated with a lower likelihood of developing LC in diabetic patients (Lai, *et al.* 2012; Mazzone, *et al.* 2012; Ruiter, *et al.* 2012). Although data from the vivo trial of lung cancer has demonstrated that metformin therapy might ameliorate the status of hyperinsulinemia, hyperglycemia, and chronic inflammation (Memmott RM, *et al.* 2010), the molecular mechanism remains to be explained.

As we know, no research has grasped the mystery of the process that diabetes triggered LC. Our study collected the gene expression datasets of T2DM, LC and Metformin treated cell lines. After comparing differences in gene expression between tumor samples and healthy controls, biological function analysis was performed to find out the key genes or pathways in the developing process of LC with T2DM. Then PPI network was built to mine Metformin's potential mechanism for the treatment of T2DM and LC. Those hub genes appear to be strongly associated in the treatment of metformin for diabetes and LC. The present study first identified the rough relationship between DM and LC at the molecular level, which might provide reference to explain the underlying pathophysiology association between T2DM and lung cancer.

MATERIAL AND METHODS

Microarray data screening

Three gene expression data series – GSE55650 (Brown, *et al.* 2015), GSE136043(Jiang, *et al.* 2020), and GSE146982 (Xie, *et al.* 2020), -were collected from Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/). For GSE55650, 12 diabetics and 11 controls of Human skeletal muscle were included. GSE136043 data set was a collection of 5 lung tumor tissues and 5 non-tumor tissues. In addition, three LC cell lines with the management of Metformin (12.5 mM) for 48h and paired three LC cell line controls (GSE146982) were recognized with the platform of GPL24676 [Illumina NovaSeq 6000] (Homo sapiens). The detailed information of these datasets was shown in Table 1.

Identification of differentially expressed genes (DEGs)

The microarray data of the GSE55650 and GSE136043 were first analyzed using R 4.0.2 statistical software (https://www.r-project.org), then the identified dysregulated genes were further analyzed to find the overlapped genes of the 2 data series. Fold change (FC) was set as the threshold for the mean value of gene expression in the experimental groups and in the respective controls, as previously described; DEGs were respectively recognized as upregulated or downregulated, and identified as fold change (FC ≥2 or FC≤0.5).

Biological function analysis of the DEGs

The functional and pathway enrichment analysis was performed in the use of Database for Annotation, Visualization, and Integrated Discovery (DAVID, http://david.ncifcr.gov) (Dennis Jr, *et al.* 2003). The analysis contained two parts- gene ontology (GO) (Kuznetsova, *et al.* 2019) and Kyoto Encyclopedia of Genes and Genomes (KEEG) (Ogata, *et al.* 1999). The GO enrichment includes biological process (BP), cellular component (CC), and molecular function (MF). The adjusted p value < 0.05 and DEGs counts ≥ 2 were the cut-off criteria for the identification of significantly enriched pathways and functions.

Protein–protein (PPI) network analysis and hub gene identification

The Search Tool for Retrieval of Interacting Genes (STRING) online tool (https://string-db.org) was used for a PPI network analysis. Two target genes of the Metformin were selected from the Drug Repurposing Hub(Corsello, *et al.* 2017). The PPI network tends to explore Metformin's essential genes in the treatment of LC with diabetes. The target hub genes were detected by the criteria of the top 10 genes according to 5 Cytohubba ranking method using Cytoscape software (https://cytoscape.org/) (Doncheva, *et al.* 2019).

RESULTS

Identification of the DEGs

For GSE55650, we identified 475 up-regulated and 1285 down-regulated DEGs between 12 T2DM samples and 11 controls. For GSE136043, there were 4598 up-regulated and 3917 down-regulated DEGs between LC and their normal control. As illustrated in Figure 1, there were 756 overlapped differentially expressed genes among the 1760 T2D DEGs and 8515 LC DEGs. 133 up-regulated genes (DEGs1) and 246 down-regulated genes (DEGs3) in both diabetes and LC were identified. 275 genes (DEGs2) were included for further analysis,

Tab. 1. Description of data used in this study

Accession	Platform	Normal/Control	Cancer/Treat	Type
GSE136043	GPL13497	5normal	5cancer (homogenized)	LC tissues
GSE55650	GPL570	11control	12diabetes	skeletal muscle
GSE146982	GPL24676	3control	3treated#	LC cells

#Human derived A549 cells were treated with Metformin (12.5 mM) for 48h

Tab. 2. The results of functional enrichment analysis for the DEGs2 and DEGs4

DEGs	Pathway names	*p*-value
DEGs2	Glycine, serine and threonine metabolism	0.00025
	Arginine and proline metabolism	0.00622
	Glutathione metabolism	0.00667
	ECM-receptor interaction	0.00919
	Protein digestion and absorption	0.00963
	Focal adhesion	0.01114
	p53 signaling pathway	0.01711
	Biosynthesis of amino acids	0.02172
DEGs4	Pathways in cancer	0.00113
	TGF-beta signaling pathway	0.01089
	Signaling pathways regulating pluripotency of stem cells	0.04145
	Jak-STAT signaling pathway	0.04524

P-value < 0.05

of which were upregulated in T2D and downregulated in LC. Besides, there were 102 genes (DEGs4) upregulated in LC and downregulated in T2D.

GO and KEGG analysis for the DEGs2 and DEGs4

To explore the function of the DEGs2 and DEGs4, GO and KEGG analyses were carried out in the use of DAVID. The DEGs2 had gene ontology enrichment in terms of BP, CC, and MF. In BP, there are three most significantly enriched processes: cell division, mitotic nuclear division, and cell proliferation (Figure 2A). For the CC, the DEGs2 were enriched in the cytoplasm, nucleus, and cytosol (Figure 2A). In the aspect of MF, the top three functions were 'protein binding', 'ATP binding', and 'identical protein binding' (Figure 2A). KEGG pathway analysis suggested that the 275 dysregulated genes were enriched in 'glycine, serine and threonine metabolism', 'arginine and proline metabolism', and 'glutathione metabolism' (Table 2).

Meanwhile, functional enrichment analyses of DEGs4 were performed in the same way. The enriched BP was mainly associated to 'signal transduction', 'multicellular organism development', and 'positive regulation of cell proliferation' (Figure 2B). In the aspect of CC, the top three significantly enriched cellular components were 'extracellular space', 'extracellular region', and 'perinuclear region of cytoplasm' (Figure 2B). In MF, DEGs4 were significantly enriched in the functions of 'signal transducer activity', 'hormone activity', and 'heparin binding' (Figure 2B). KEGG pathway analysis demonstrated that DEGs4 were significantly enriched in 'pathways in cancer', 'TGF-beta

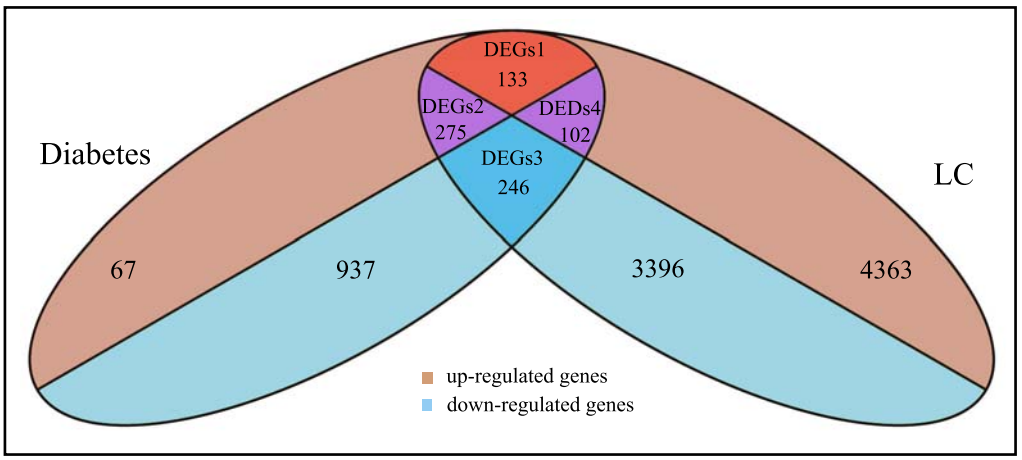

Fig. 1. Differentially expressed transcripts among diabetes DEGs and LC DEGs. DEGs1 represents up–regulated genes in the expressed transcripts of diabetes and LC. DEGs2 represents up–regulated genes in the expressed transcripts of diabetes, but down–regulated genes in the expressed transcripts of LC. DEGs3 represents down–regulated genes in the expressed transcripts of diabetes and LC. DEGs4 represents down–regulated genes in the expressed transcripts of diabetes, but up –related genes in the expressed transcripts of LC.

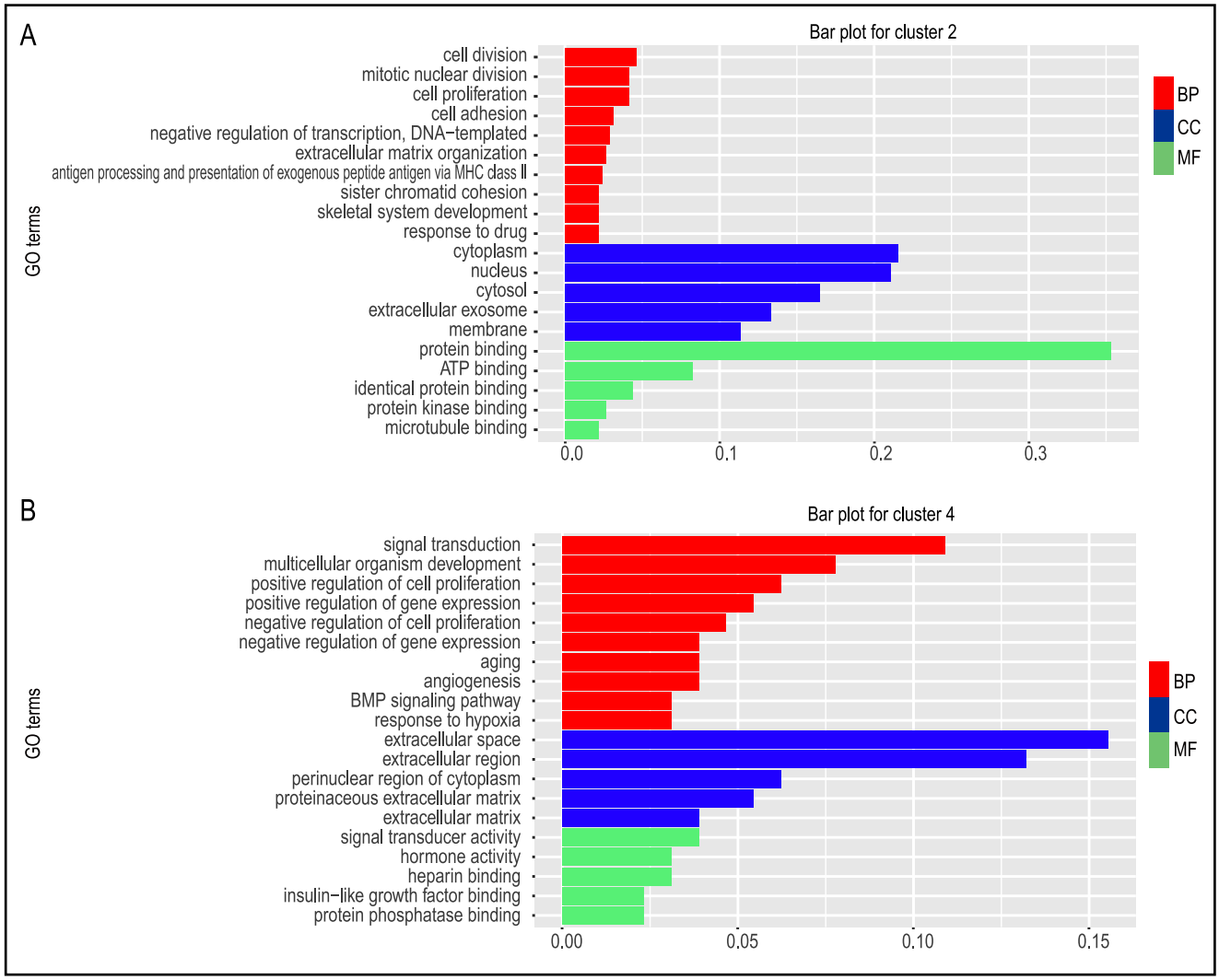

Fig. 2. Gene ontology enrichment analysis for the DEGs2 and DEGs4.
The abscissa number represents the ratio of genes that are differentially expressed in the BP, CC and MF.

signaling pathway', and 'Signaling pathways regulating pluripotency of stem cells' (Table 2).

PPI network analysis of the DEGs1 and DEGs 3

The DEGs1 and DEGs3, as well as the target genes of Metformin, were used for PPI network analysis, exploring the potential role of Metformin in the treatment of both diabetes and LC. In Figure 3, the target genes of Metformin were PRKAB1 and ACACB (blue rhombus). We also use Cytohubba to select the hub genes, showing that HGF, VCAM1, C3, THBS1, CXCL1, TTN, CXCL12, AGT, and ITGB2 (Figure 3). It is indicated that these nine hub genes may play a key role in T2DM and LC development when be treated with metformin.

Changes of mRNA expression values of the nine hub genes in LC cell lines via therapy with metformin

Our study revealed the expression values of these hub genes in a group of A549 cells (the Human derived LC cell line) with the management of Metformin (12.5 mM) for 48h. C3, THBS1, CXCL1, and TTN changed their expression values remarkably via the treatment of Metformin ($p<0.05$, T-test). There were no significant differences in mRNA expression values in the rest hub genes after the management of Metformin. It further confirmed that these four genes might play essential biological roles in the treatment of metformin for T2DM and LC.

DISCUSSION

Diabetes mellitus and lung cancer are both huge threat to human health around the world. Several researchers have demonstrated that T2DM was an independent risk factor for lung cancer and may serve as a poor prognostic factor (Luo, *et al.* 2012; Lee, *et al.* 2013; Bergamino, *et al.* 2019). Metformin, a commonly used drug for the treatment of diabetes, has recently been reported to be used to treat LC patients (Xin, *et al.* 2018; Xu, *et al.* 2018). Previous researches failed to determine the key biomarkers of T2DM and LC as well as their

biofunctions and interactions. The present study firstly explored the potential pathophysiology association between T2D and LC at the genomic level.

Our study found 756 overlapped genes between T2D and LC samples. These genes were divided into four groups: a) 133 common up-regulated genes (DEGs1), b) 275 independent up-regulated genes (DEGs2) in T2D, c) 246 common down-regulated genes (DEGs3) and d) 102 independent up-regulated genes (DEGs4) in LC. DEGs2 are significantly enriched in the biological function of cell division, cytoplasm, and protein binding. Meanwhile, DEGs4 are remarkably enriched in the biological function of signal transduction, extracellular space, and signal transducer activity. The KEGG pathway analysis showed that glycine, serine and threonine metabolism, arginine and proline metabolism, TGF-beta signaling pathway, and pathways in cancer were mainly enriched in the DEGs2 and DEGs4, which are associated with metabolism and genetic information processing. Results of the PPI network analysis showed that HGF, VCAM1, C3, THBS1, CXCL1, TTN, CXCL12, AGT, and ITGB2 were hub genes. Further analysis showed 4 genes (C3, THBS1, CXCL1, and TTN) with significant changes in expression values (P<0.05, T-test), which may be potential pathogeneses in Metformin's treatment of diabetes and LC.

The third complement component (C3) is the central component of the complement system and plays a vital role in the immune system (Janssen, *et al.* 2006). Previous studies have revealed that C3 is related to insulin resistance (Bratti, *et al.* 2017), obesity (Al Haj Ahmad and Al-Domi,2017), and coronary heart disease (Jiang, *et al.* 2014). To the best of our knowledge, no study has found the differential expression of gene C3 in Metformin-treated T2D and LC samples before. Gene thrombospondin 1 (THBS1) encodes a 450 kDa glycoprotein that interacts with various ligands and conducts various physiological and pathological processes (Hynes, 2009). Mounting research suggests that THBS1 also serves as an endogenous tumor suppressor. The decline in expression of the THBS1 protein indicated a bad prognosis in LC (Yamaguchi, *et al.* 2002). Meanwhile, increased THBS1 mRNA levels were associated with diabetes and obesity (Varma, *et al.* 2008; Kong, *et al.* 2014). Based on the current evidence, the present study further proves the correlation between dysregulation of MYC and the process of diabetes and LC at a molecular level. C-X-C motif ligand 1 (CXCL1) is a neutrophil attractant chemokine that is associated with processes as diverse as angiogenesis, wound healing, and tumorigenesis. It was reported that CXCL1 was significantly upregulated in lung cancer-bearing mice (Yuan, *et al.* 2016). Increased serum levels of CXCL1 have also been reported in patients with type 2 diabetes(Sajadi, *et al.* 2013). Combining with these previous studies, our results further confirmed that CXCL1 might play a significant biological role in Metformin's therapy for DM and LC. Up to now, titin (TTN) is the largest protein in cardiac and skeletal muscles that plays pivotal structural,

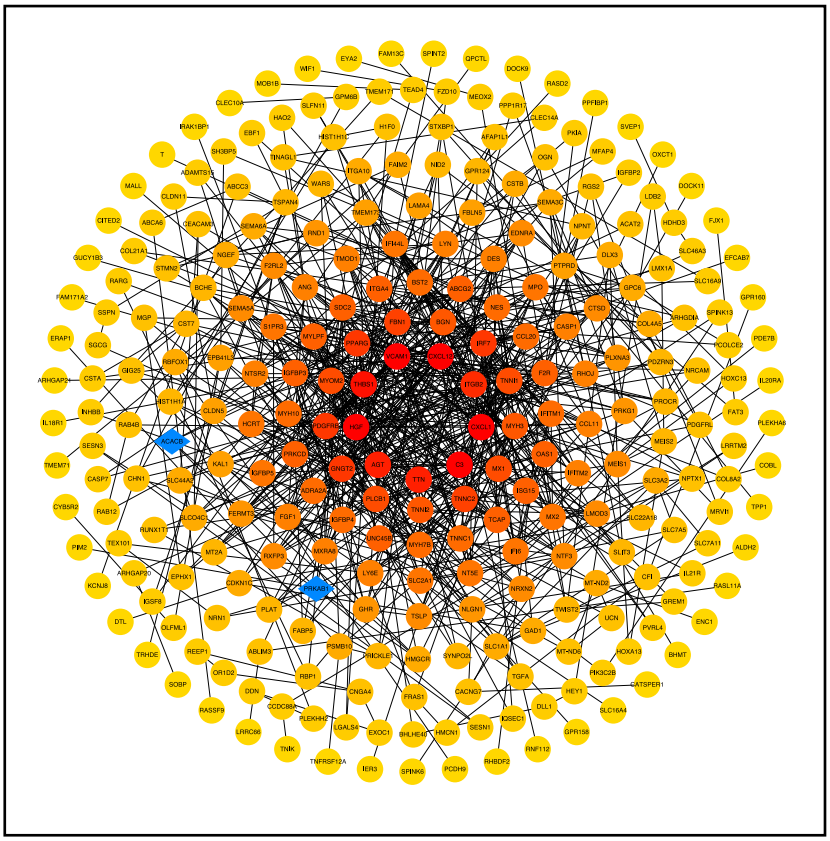

Fig. 3. PPI network analysis on the DEGs1, DEGs3 and the target genes of Metformin. The blue rhombic point represents the Metformin drug target gene. The red dot represents the hub gene in the PPI network.

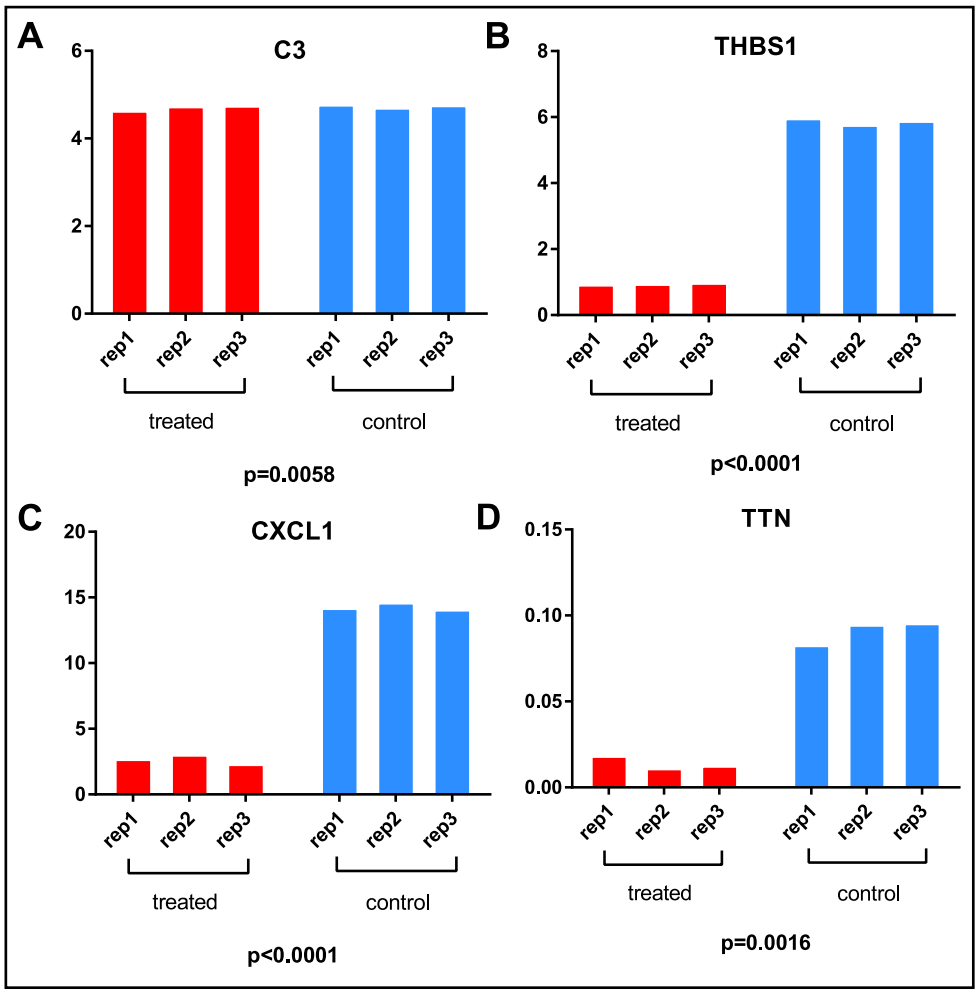

Fig. 4. Changes of gene expression values of C3, THBS1, CXCL1 and TTN after treatment of LC cell lines with Metformin.
A-D represents the expression of C3, THBS1, CXCL1 and TTN genes in Metformin-treated LC cell lines (red) and three control LC cell lines (blue).

developmental, mechanical, and regulatory roles. For patients with LC, TTN and the tumor suppressor p53 (TP53) are the two most frequently mutant genes and also correlates with a favorable prognosis in LC (Cheng, *et al.* 2019). However, no relevant study of TTN mutation in diabetes is reported so far. Our study may discover a new path towards the correlation between T2D and LC. Above all, the present research may shed light on the role of gene C3, THBS1, CXCL1, and TTN in Metformin's treatment for diabetes and LC. Gene C3, THBS1, CXCL1, and TTN might interact together to regulate the function of complement, glycoprotein, and chemokine and then result in oncogenes mutation and or mechanical changes. These above-mentioned genes provide novel perspectives for the extensive comprehension of T2DM and LC. These genes are relevant to diverse aspects of T2D, including disease onset, development, complications, and treatments. Moreover, the enriched pathways (glycine, serine, and threonine metabolism, arginine and proline metabolism, TGF-beta signaling pathway, and pathways in cancer) of the independent DEGs indicated that metformin may play predominant roles in the regulation of metabolism and genetic information processing in T2DM and LC development. Further exploration of these genes and pathways might help to figure out the underlying mechanisms of metformin in lung cancer among diabetic patients.

Our study had limitations. Firstly, the number of samples in our study is limited. Secondly, our results were not validated through animal or clinical experiments. Thirdly, experimental research was in need to verify the specific functions of every gene. Therefore, further vivo and clinical studies are urgent to confirm the results.

CONCLUSION

In conclusion, genes C3, THBS1, CXCL1, and TTN were identified in the present study, and the gene products are highly involved in Metformin's treatment of diabetes and LC. Glycine, serine and threonine metabolism, arginine and proline metabolism, TGF-beta signaling pathway, and pathways in cancer were significantly enriched in the independent DEGs. The results of our study may shed light on the development of diabetes towards LC roughly and promote the further exploration of treatment for LC. However, this conclusion needs further confirmation by laboratory experiments.

CONTRIBUTIONS

(I) Conception and design: TT Tao, J Li; (II) Administrative support: P Duan; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: TT Tao, TT Hang; (V) Data analysis and interpretation: TT Tao, J Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors

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FOOTNOTE

Conflict of interest: The authors have no conflicts of interest to declare.
Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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