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The Therapeutic Potential of Metformin for Metabolic Associated Fatty Liver Disease: Bioinformatics Analysis

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Abstract

Metabolic associated fatty liver disease (MAFLD) is associated with obesity and metabolic dysfunctions, but its molecular mechanisms remain elusive and effective treatments are lacking. Metformin is a potential therapeutic agent for MAFLD due to its effects on insulin resistance and fat metabolism dysregulation. This study used bioinformatics analysis to identify differentially expressed genes (DEGs) in MAFLD and explore the potential targets of metformin treatment. We selected a MAFLD dataset from the Gene Expression Omnibus (GEO) database and screened 425 DEGs, including 278 up-regulated and 147 down-regulated genes. We also identified 183 genes related to metformin treatment using the Genclip3 database and found 13 common genes with the DEGs. The Genome Ontology (GO) enrichment analysis of these genes revealed biological processes such as suppression of inflammation and promotion of glycolipid metabolism, while the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways involved diabetic complications and inflammatory signaling. The protein-protein interaction (PPI) analysis identified IL1B, IL6, IL10 and CCL2 as the core proteins. Based on the PPI network, we selected the top 9 genes as hub genes, including IL6, IL1B, IL10, CCL2, FOXO1, PIGS2, IGFBP1, GCK, and MYC. The study suggests that metformin may target multiple pathways for the treatment of MAFLD, mainly involving anti-inflammation, regulation of glycolipid metabolism, and anti-hepatic fibrosis.

Keywords: Bioinformatic Analysis; Metformin; Metabolic Associated Fatty Liver Disease; Mechanism

Introduction

Metabolic associated fatty liver disease (MAFLD), formally known as non-alcoholic fatty liver disease (NAFLD), is associated with obesity and metabolic dysfunction [1]. MAFLD is strongly associated with the high prevalence of type 2 diabetes. Currently, there are limited therapeutic agents due to the uncertain pathogenesis of MAFLD. Insulin resistance is considered to play a dominant role in the pathogenesis of MAFLD. Metformin has been demonstrated to have significant effects in the treatment of MAFLD but its mechanism needs further exploration [2]. Bioinformatics analysis can provide insight into the molecular mechanisms of metabolic diseases, which is a powerful research method to predict molecular mechanisms and relations among different genes. In this study, the core genes had been screened and the mechanism of metformin treatment for MAFLD has been further explored by bioinformatic analysis.

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Materials and Methods

Data acquisition of gene expression profiles

Three datasets (GSE89632, GSE11518, and GSE66676) were downloaded from the GEO database (http://www.ncbi.nlm.nih.gov/geo/) to obtain gene expression datasets of MAFLD in this study. The GSE11518 and GSE66676 datasets were removed because of insufficient variability between sample groups. The GSE89632 dataset was screened and included 39 NAFLD liver tissues and 24 normal liver tissues. The detailed information is shown in Table 1.

Screening of DEGs

DEGs were identified and selected by GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r/) analysis from the GEO database. Genes with P value <0.05 and | logFC | > 1 were considered as DEGs in this dataset. The heatmap and volcano plot were generated using R programming language based on differential gene analysis.

Table 1: Detailed data of GSE89632.

Sequence number of chip	GSE89632
Platform	GPL14951
Disease	NAFLD
Chip Provider	University Health Network
Address	585 University Ave, 9-NU-973, Toronto, Ontario, Canada
Research object	Human
Sample type	Liver
Number of Chip Samples（used/total）	63/72
Time of uploading chip	Public on Nov 08, 2016

Identification of metformin treatment-related genes by text-mining

We used GenCLiP3 (http://ci.smu.edu.cn/genclip3/), a text-mining tool, to identify the reported genes related to metformin treatment from the literature.

Identification of the common genes between MAFLD and metformin treatment

We used the Draw Venn Diagram online tool (http://bioinformatics.psb.ugent.be/webtools/Venn/) to identify the common genes between MAFLD and metformin treatment-related genes.

The analyses of the biological functions and pathways of the common genes

We used the Database for Annotation, Visualization, and Integration Discovery (DAVID) website (https://david.ncifcrf.gov/) to analyze the biological functions and pathways of differentially expressed genes (DEGs) in the common genes between MAFLD DEGs and metformin-treat related genes. First, we performed gene ontology (GO) enrichment analysis to identify the biological processes, cellular components, and molecular functions associated with these genes. Next, we performed KEGG pathway enrichment analysis to investigate the potential signaling pathways involved in these genes.

The core proteins identification in the protein interaction network

We used the Interaction Gene Search tool (STRING) (http://string.embl.de/) to investigate the interactions among the proteins related to the common genes. First, we integrated and visualized the protein interaction network by Cytoscape software. Next, we applied the molecular complex detection (MCODE) plug-in to screen the modules of the network and to select the core proteins.

Finding the common genes with the highest centrality in the protein interaction network

We used the cytoHubba plug-in of Cytoscape software to find the common genes with the highest centrality in the protein interaction network. First, we calculated the maximum group centrality of each gene in the network by the maximal clique centrality (MCC) score. Next, we identified the top nine genes as the common genes with the highest MCC score.

Results

Identification of DEGs

A total of 425 DEGs were obtained via the analysis of the GSE89632 dataset by the NCBI GEO2R online tool, including 278 up-regulated genes and 147 down-regulated genes. The DEG expression volcano map and heat map were shown in Fig. 1 and Fig. 2.

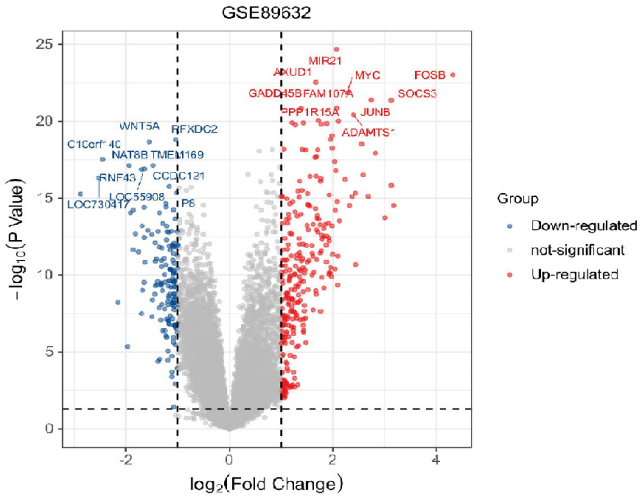

Figure 1: Volcano map of DEGs between NAFLD and normal group. Red dots indicated up-regulated genes, whereas blue dots denoted down-regulated genes. Gray dots represented no significant difference genes.

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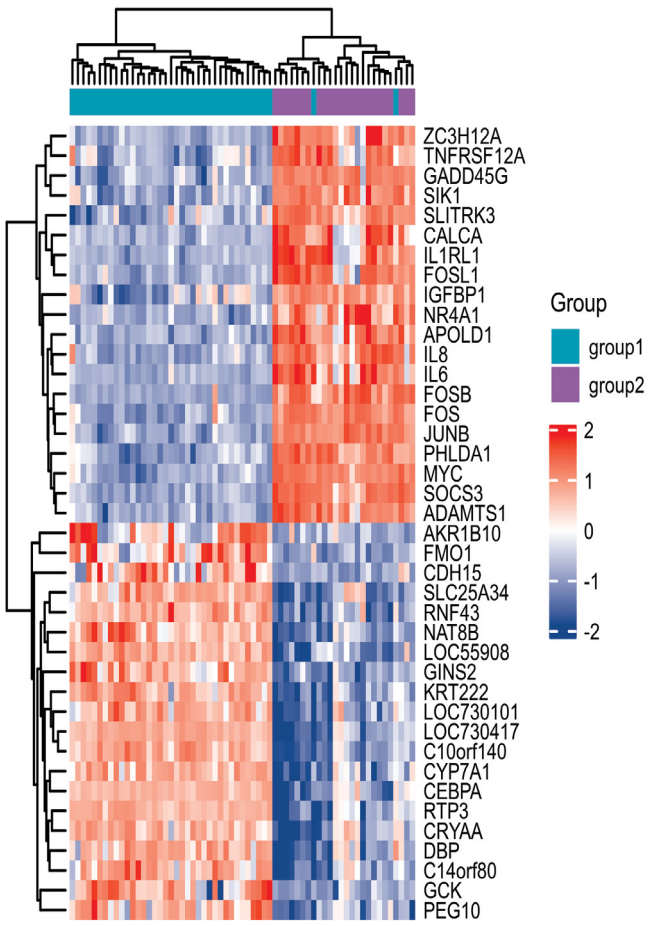

Figure 2: Heat map of all DEGs between NAFLD and normal group. Each column represented a tissue sample, and each row represented a DEG. The gradual color change from blue to red indicated the changing process from down-regulation to up-regulation.

Text mining for metformin treatment-related genes

Identification of the common genes between MAFLD DEGs and metformin-treatment related genes

To identify the common genes between MAFLD DEGs and metformin-treatment related genes, we used the Draw Venn Diagram online tool. A total of 13 common genes were identified, which were IL6, IGFBP1, MYC, GCK, MIR21, PTGS2, CCL2, IL1B, EGR3, SERPINE1, CD274, IL10, and FOXO1. The Venn diagram showing the overlap of the two gene sets is presented in Fig. 3.

GO and KEGG pathway enrichment analyses of the common genes

We performed GO and KEGG pathway enrichment analyses using the DAVID website to explore the biological functions of the common genes. The results showed that the common genes were mainly involved in cellular response to lipopolysaccharide, negative regulation of apoptotic process,

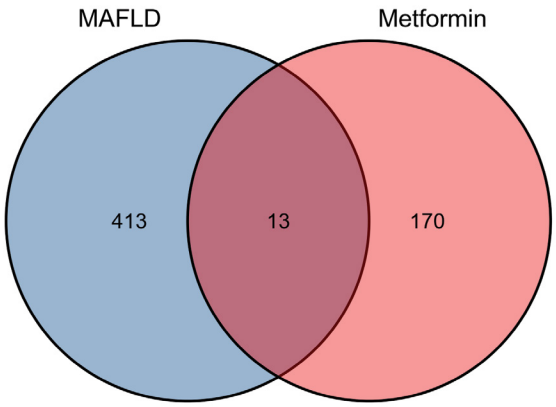

Figure 3: A Venn diagram of MAFLD DEGs and metformin treatment-related genes. A comparison between 425 MAFLD DEGs and 183 metformin treatment-related genes revealed 13 common genes.

Table 2: lists the genes associated with metformin treatment.

Metformin-treatment related genes
DPP4,PRKAA1,MTOR,GLP1R,GCG,SLC5A2,AKT1,LPA,PRKAB1,ADIPOQ,MAPK1,LEP,SLC22A1,CRP,SLC22A2,ATIC,SLC47A1,TP53,CASP3,SIRT1,STK11,EGFR,STAT3,IGF1,VEGFA,BCL2,IL6,ERBB2,SHBG,INSR,BAX,ALB,MAPK3,NFE2L2,TNF,PRKAA2,CCND1,PRL,CDKN1A,MYC,SLC47A2,CCL2,CAT,PIK3CA,MAPK8,SOD1,NLRP3,REN,MMP9,PPARG,ATM,IRS1,INS,CYP19A1,NOS3,SERPINE1,GDF15,GPT,SLC2A4,PTEN,IL10,EGR3,ACACA,TLR4,PTGS2,SQSTM1,SLC22A3,RUNX2,IAPP,RELA,SMAD3,PARP1,SREBF1,FGF21,FOXO3,PPARA,CD274,CDH1,BECN1,MAPK14,HIF1A,ABCB1,FASN,AGT,PPP1R1A,NAMPT,RPS6KB1,RETN,SIRT3,APRT,MAPT,GHRL,SLC2A1,IGF1R,G6PC,HSPA5,PPARGC1A,FOXO1,BDNF,MMP2,VIM,HMOX1,MAP1LC3A,ICAM1,AR,PTPA,SLC29A4,MCL1,MGAM,NOS2,GIP,CDK4,SOD2,TGFB1,HMGCR,IGFBP1,TNFSF11,DUOXA1,HMGB1,PKM,BIRC5,VCAM1,HK1,CDH2,IL17A,TNFRSF11B,RBP4,PDCD1,ABCG2,DDIT3,BGLAP,PROM1,POMC,YAP1,CREB1,APOE,PGR,BCL2L1,CASP1,MAP2K7,CXCL8,AGER,SLC2A2,IL1B,HSD11B1,EIF4EBP1,SMAD2,CD44,PCK2,KRAS,FOXP3,HBA1,ALPP,AMH,CASP9,MPO,GCK,FNDC5,HK2,SST,TNFSF10,ACE2,SLCO1B1,PCNA,NPY,SLC22A8,SPP1,ATG5,MIR34A,SERPINA12,TIMP1,SLC5A1,MAP1LC3B,GLI2,CD4,PRKN,CD36,SULT2A1,NR0B2,MIR21,APOA1,TXNIP,EDN1

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positive regulation of glial cell proliferation, negative regulation of cell proliferation and positive regulation of vascular endothelial growth factor production in biological process. In cellular component, the common genes were enriched for endoplasmic reticulum lumen, extracellular space and extracellular region. In molecular function, the common genes had significant roles in cytokine activity, receptor binding, transcriptional activator activity, RNA polymerase II transcription regulatory region sequence-specific binding and transcription factor activity, sequence-specific DNA binding. In KEGG pathways, the common genes were associated with AGE-RAGE signaling pathway in diabetic complications, IL-17 signaling pathway and TNF signaling pathway.

Construction of PPI network and identification of hub genes

We constructed a PPI network from the STRING database to predict the potential interactions of the common genes at the protein level. We imported the PPI network from the STRING database into Cytoscape software and obtained a co-expression network consisting of 13 nodes and 12 edges (Fig. 4). We applied MCODE to screen modules of the PPI network and selected the most pivotal module including IL1B, IL6, IL10 and CCL2. We also identified hub genes in the network using the cytoHubba application in Cytoscape software and selected the top 9 genes as hub genes: IL6, IL1B, IL10, CCL2, FOXO1, PTGS2, IGFBP1, GCK, and MYC.

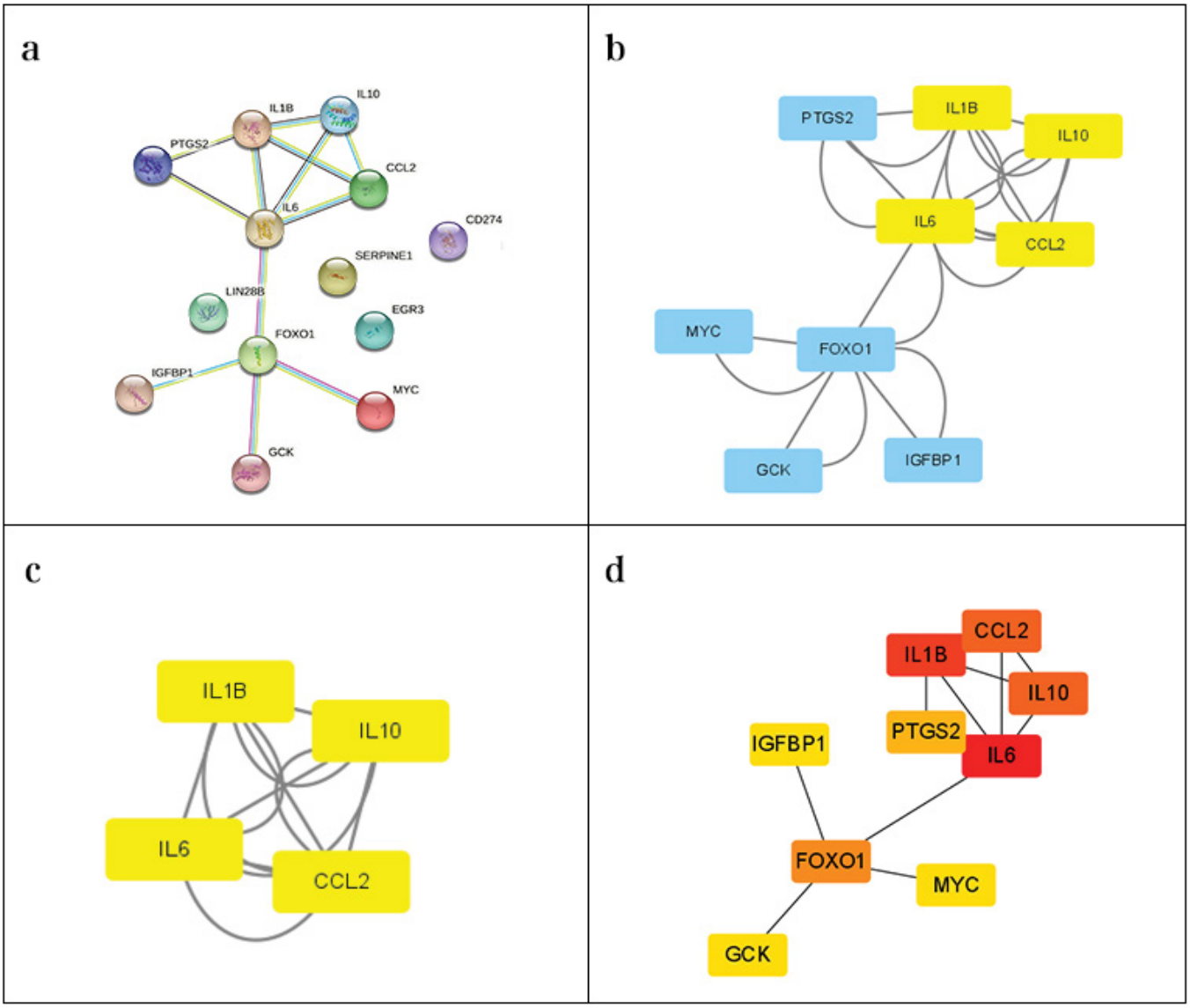

Figure 4: (a): PPI network by STRING analysis; (b): PPI network produced by Cytoscape Software; (c): Core modules designed by MCODE; (d): Top 9 genes network.

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Discussion

MAFLD is a new term that replaces NAFLD to reflect the association between this disease and metabolic disorders. Insulin resistance is an important factor in the pathogenesis of MAFLD. By bioinformatics analysis, we selected the top 9 genes as hub genes of metformin treatment for MAFLD, including IL6, IL1B, IL10, CCL2, FOXO1, PIGS2, IGFBP1, GCK, and MYC. The 8 common genes（IL6, IL1B, IL10, CCL2, FOXO1, PIGS2, IGFBP1 and MYC）were expressed up-regulated; while the expression of GCK was down-regulated in the liver tissues of the MAFLD group. IL6 and IL1B were identified as the most significantly upregulated genes in MAFLD, which encoded cytokines associated with inflammation. It was found that IL-6 expressions increased in the livers of NASH patients compared to patients with simple steatosis or normal controls. A positive correlation was observed between hepatocyte IL-6 expression and the degree of inflammation and the stage of fibrosis [3]. The liver IL-6 expression also positively correlated with systemic insulin resistance. Another study suggested that the hepatic expression of IL1B increased in early-stage NASH patients [4]. The IL-10 gene was the top 3 upregulation DEGs in MAFLD, which also has anti-inflammatory effects. Cintra et al. [5] observed that IL-10 gene expression increased in the liver tissues of the fatty liver mice. While the endogenous IL-10 was inhibited, it induced the production of inflammatory factors, worsened the insulin signaling, activated the hepatic gluconeogenesis, and promoted fat accumulation. In contrast, the exogenous IL-10 treatment improved the insulin sensitivity in the liver of NAFLD mice. Another study also found that metformin diminished the hepatic mRNA levels of IL6 and IL1B in the high-fat diet fed mice [6]. Furthermore, Nna et al. [7] reported that metformin treatment decreased the immunoexpression of IL-1B, increased the immunoexpression of IL-10 and attenuated inflammation in the liver of diabetic mice. These evidences suggest that metformin attenuates inflammation of MAFLD by modulating the genes of IL6, IL1B and IL10, which are involved in the inflammatory response and may contribute to the pathogenesis of MAFLD.

The CCL2 gene was the top 4 upregulation DEGs in MAFLD. CCL2 is a chemokine that regulates macrophage recruitment and is a therapeutic target for inflammatory diseases [8]. The CCL2 gene was also founded to be related with hepatic injury and liver fibrosis which was involved in the progression from simple steatosis to NASH [9]. Some studies found that genetic depletion or pharmacological inhibition of CCL2 in mice ameliorated steatosis progression, alleviated the hepatic inflammatory response and liver injury [10, 11]. Ye et al. [12] observed that metformin suppressed the protein and mRNA expression of CCL2 and prevented the stimulating effect of lipopolysaccharide on the chemokine in the mice macrophage cells. These evidences suggested that metformin ameliorated steatosis progression, alleviated the hepatic inflammatory response and reduced liver injury of MAFLD by inhibiting the expression of CCL2 gene. The FOXO1 gene was the top 5 upregulation DEGs in MAFLD，which encoded the FOXO1 transcription factor to regulate glucose and lipid homeostasis [13]. FOXO1 may be a promising target for alleviating insulin resistance in MAFLD. In clinical settings, both the gene expression and protein activity of FOXO1 are elevated in NASH patients compared to steatosis alone and normal liver subjects [14]. Another study reported that the constitutive expression of the hepatic FOXO1 gene under insulin resistance conditions leads to hyperglycemia and hyperlipidemia [15]. Qian LL et al. revealed that the up-regulation of FOXO1 gene expression induces hepatocyte necroptosis in NAFLD mice. Increased FOXO1 gene expression in hepatocytes is associated with the histopathological progression of NAFLD [16]. Ramadan NM et al. [17] found that metformin reduced the hepatic gene expression of FOXO1 in the hepatocyte of the NAFLD mice; metformin also significantly decreased the NAFLD score. Guo X et al. [18] found metformin exerted therapeutic effect on MAFLD by reducing hepatocyte necroptosis and HGP associated with FOXO1 gene. The PTGS2 gene, also known as cyclooxygenase-2 (COX-2) gene, was the top 6 upregulation DEGs in MAFLD. It encodes the COX-2 enzyme which is considered to initiate inflammation and promote the synthesis of prostaglandin [19]. The COX-2 enzyme may play an important role in the progression of hepatic fibrosis and be associated with liver inflammation, autophagy, and cell senescence [20]. Both the mRNA and protein expressions of hepatic COX-2 increased significantly in NASH mice, and increased COX-2 expression paralleled the histological development of steatohepatitis. Metformin was found to reduce inflammation by decreasing the activity of COX-2 [21]. A study showed that metformin reduced hepatic protein expression of COX-2 and significantly attenuated liver fibrosis in mice with biliary cirrhosis [22]. The IGFBP1 gene was the top 7 upregulation DEGs in MAFLD which encodes a binding protein that has a high affinity to insulin-like growth factors (IGFs) [23]. The IGFBP1 protein is negatively regulated by insulin levels through transcriptional regulation of hepatic IGFBP1. A pilot study found that NAFLD patients with advanced fibrosis had higher levels of serum IGFBP1 [24]. Another study showed that the IGFBP1 gene expression was significantly up-regulated in human hepatocellular carcinoma (HCC) tissues and over-expressed in mouse with NASH-related HCC [25]. Both mRNA and protein expression of IGFBP1 were found increased in liver tissues of NAFLD patients and mice [26]. Salatino, A. et al. observed that metformin reduced the protein expression of IGFBP1 in human extragonadal SEM-1 cells compared with controls [27]. There was currently lack of evidence that metformin affected hepatic IGFBP1 gene expression directly. The relationship between metformin and hepatic IGFBP1 expression needs to be explored.

The cellular myelocytomatosis oncogene (c-MYC) (referred to here as MYC) was the top 7 upregulation DEGs in MAFLD which encoded a transcription factor involved in cell proliferation, metabolism, angiogenesis, apoptosis, adhesion and differentiation [28]. Some studies indicated that overexpression of the MYC gene prompted hepatocellular proliferation and tumorigenesis [29]. A study indicated that transcriptional repression of the MYC gene alleviated hepatic steatosis in diet-induced obese mice [30]. In another study, metformin reduced hepatic expression of c-MYC gene in an HCC mouse model featuring severe steatosis [31]. There have been several publications that reported MYC inhibition by metformin [32, 33]. Taken together, these studies demonstrated that metformin might be effective for attenuating hepatocellular steatosis and tumorigenesis of MAFLD through reducing expression of MYC gene. The glucokinase (GCK) gene was the downregulated DGE in MAFLD. It encodes glucokinase that is the rate-limiting enzyme in glycolysis. GCK gene expression in the liver was associated with hepatic glucose metabolism [34]. A study found that hepatic gene expression of GCK decreased in patients with severe steatosis [35]. Another study showed that metformin increased mRNA expression of GCK in the liver of NAFLD mice [36]. In another study, metformin attenuated triglyceride levels in the liver of corticosterone treated rats and increased expression of GCK gene in the muscle of corticosterone treated rats [37].

Conclusion

In conclusion, we identified 9 hub genes including IL6, IL1B, IL10, CCL2, FOXO1, PTGS2, IGFBP1, MYC and GCK genes by bioinformatics analysis for metformin treatment of MAFLD. These hub genes may play essential roles in metformin treatment of MAFLD through anti-inflammation, regulating glycolipid metabolism, anti-hepatic fibrosis and attenuating hepatocellular tumorigenesis.

Conflicts of interest

There are no conflicts of interest.

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