Candidate genes associated with the effect of rosiglitazone on glycemic control and cardiovascular system in the treatment of type 2 diabetes mellitus

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Abstract. In the present study, candidate genes affected by rosiglitazone to exert glycemic control in the treatment of type 2 diabetes mellitus (T2DM) and associated with its adverse cardiovascular effects were identified using a bioinformatics analysis. The gene expression profiles of the dataset GSE36875 from the Gene Expression Omnibus database, including heart samples from 5 non-diabetic control mice (NC), 5 untreated diabetic mice (NH) and 5 rosiglitazone-treated diabetic mice (TH), were used to identify differentially expressed genes (DEGs) in the NC vs. NH, NC vs. TH and TH vs. NH groups. Subsequently, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways enriched by the DEGs were determined. Furthermore, genes associated with the action of rosiglitazone were identified using Short Time-series Expression Miner, which were then subjected to enrichment analysis in gene ontology (GO) terms in the category biological process (BP), and networks of the GO terms, KEGG pathways and genes associated with the action of rosiglitazone were constructed. Finally, biological abnormalities associated with these genes were identified using WebGestalt. A set of 791 DEGs in three groups (NC vs. NH, NC vs. TH and NH vs. TH) were identified.

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Subsequently, 72 DEGs [e.g., apolipoprotein (Apo)A1, ApoA5, cytochrome P450 (Cyp)2c37, Cyp2J5, Cyp2b9 and Cyp2b10] were identified as genes associated with the action of rosiglitazone. In addition, a network of 13 GO terms in the category BP, 6 KEGG pathways and 41 genes associated with the action of rosiglitazone was constructed, with major terms/pathways including oxidation/reduction, lipid transport, peroxisome proliferator-activated receptor signaling pathway and metabolism of xenobiotics by Cyp. Finally, 15 biological abnormalities (including abnormal triglyceride levels, abnormal cholesterol homeostasis, abnormal lipid homeostasis) associated with these genes were identified. ApoA1, ApoA5, Cyp2c37, Cyp2J5, Cyp2b9 and Cyp2b10 were differently expressed after rosiglitazone treatment, which may be accountable for affecting cardiovascular outcomes and glycemic control in T2DM. The present results may expand the current understanding of the mechanism of action of rosiglitazone to exert glycemic control in T2DM, as well as its effects on the cardiovascular system.

Introduction

Diabetes is a complex metabolic disorder associated with increased blood glucose levels (1), and which may be categorized into different types, including type 1, type 2 and gestational diabetes (2). Type 2 diabetes mellitus (T2DM) accounts for >90% of cases of diabetes and is caused by insulin resistance (3,4). Rosiglitazone belongs to the class of thiazolidinedione drugs and is widely used for treating patients with T2DM (5). Rosiglitazone enhances insulin sensitivity by activating peroxisome proliferator-activated receptor-γ (PPAR-γ) (6). Mayerson *et al* (7) reported that rosiglitazone enhanced insulin sensitivity in the peripheral adipocytes of patients with T2DM and reduced fatty acids. Various *in vivo* studies have indicated that the mechanism of action of rosiglitazone is closely associated with the lipid concentration and insulin resistance (8-10). However, the detailed mechanism of action of rosiglitazone in patients with T2DM remains elusive.

Furthermore, cardiovascular disease is the major cause of morbidity and mortality for patients with T2DM. However, rosiglitazone significantly increases the risk of cardiovascular disease in patients with T2DM (11), with a 43% increase in myocardial infarction and a 64% increase

in mortalities associated with cardiovascular morbidity. In addition, a meta-analysis by Singh *et al* (12) revealed that rosiglitazone greatly increases the risk of myocardial infarction and heart failure following long-term treatment. However, another study suggested that rosiglitazone did not increase the overall cardiovascular risk compared with that associated with metformin or a sulfonyl urea (13). Recently, the US Food and Drug Administration concluded that rosiglitazone is safe regarding cardiovascular outcomes (https://www.fda.gov/downloads/Drugs/DrugSafety/UCM477575.pdf). Therefore, the mechanisms of the effects of rosiglitazone associated with cardiovascular outcomes in patients with T2DM should be evaluated.

The present bioinformatics study was performed to identify candidate genes associated with the effects of rosiglitazone to exert glycemic control and cardiovascular conditions in T2DM, and to elucidate the underlying mechanisms of its action. The gene expression profiles of the dataset GSE36875 from the National Center for Bioinformatics analysis (NCBI) Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/), including 5 heart samples from untreated diabetic mice (NH), 5 heart samples from rosiglitazone-treated diabetic mice (TH) and 5 hears samples from non-diabetic control mice (NC), was used to identify differentially expressed genes (DEGs) in the NC vs. NH, NC vs. TH and TH vs. NH groups. Subsequently, all DEGs were used to identify the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways enriched by the DEGs using the Database for Annotation, Visualization and Integrated Discovery (DAVID) tool (version 6.8; https://david.ncifcrf.gov). In addition, genes associated with the effects of rosiglitazone were identified using Short Time-series Expression Miner (STEM), a Gene Ontology (GO) function analysis was performed and a network of KEGG pathways, GO terms and genes associated with the effects of rosiglitazone was constructed. Finally, biological abnormalities associated with these target genes were identified using WebGestalt (http://www.webgestalt.org/option.php).

Materials and methods

Microarray data and pre-processing. The gene expression profiles of the dataset GSE36875 were downloaded from the GEO database. The data of the Agilent-014868 whole mouse genome microarray 4x44K G4122F of heart tissues were deposited on the GPL4134 platform by Wilson *et al* (14), with the groups including the NH group, the TH group and the NC group (n=5 per group).

The probes corresponded to gene symbols according to the latest annotations file from the NCBI gene database. If one gene symbol was matched to multiple probe IDs, the mean expression value was calculated as the expression level of this gene. Subsequently, these data were fitted to a log-normal distribution using a log2-transformed function and normalized using the median function of the limma package in R software (version 3.3.2, https://cran.r-project.org/bin/windows/base/) (15,16).

Identification of DEGs. DEGs in the NC vs. NH, NC vs. TH and TH vs. NH groups were identified using the limma package. The thresholds for the DEGs were set as a |log$_2$ FC

Table I. Count of differentially expressed genes between pairs of the different experimental groups.

Comparison	Upregulated	Downregulated	Total
NC vs. NH	125	87	212
NH vs. TH	216	281	497
NC vs. TH	151	84	235

NC, heart samples of non-diabetic control mice; TH, heart samples of rosiglitazone-treated diabetic mice; NH, heart samples of untreated diabetic mice.

(fold change) >0.585 and a false discovery rate (FDR) <0.05. Finally, a heatmap for the DEGs was generated using the pheatmap package in R software with two-way hierarchical clustering according to the Euclidean distance (17).

Pathway analyses of DEGs. KEGG pathway enrichment analysis of DEGs was performed to determine the pathways of DEGs in the NC vs. NH, NC vs. TH and TH vs. NH groups using DAVID 6.8 according to Fisher's exact test. P<0.05 was considered to indicate a statistically significant difference.

Series test of cluster (STC) and network of GO functions and pathways. First, the set of DEGs in these 3 groups (NC vs. NH, NC vs. TH and NH vs. TH) was obtained using a Venn diagram. STEM is a unique method for clustering, comparing and visualizing a series of gene expression data obtained under different experimental conditions (18). STEM (version 1.3.11, http://www.cs.cmu.edu/~jernst/stem) was used for STC with a clustering coefficient of >0.8 to determine which profile was significantly associated with the different types of samples that were treated with (NC and NH) or without rosiglitazone (TH) under the ordering of time-points compared to the other profiles. P<0.05 was considered to indicate a statistically significant difference. Genes in the significant model profiles were drug function-associated genes. GO function and KEGG pathway enrichment analyses of these genes were performed using DAVID version 6.8. Finally, a GO function and pathway network of drug function-associated genes was constructed.

Identification of biological abnormalities linked to rosiglitazone function-associated genes. To further elucidate the role of rosiglitazone function-associated genes in the body, WebGestalt was used to identify biological abnormalities linked to these target genes. The threshold value was set at P<0.05.

Results

DEGs in the three groups. In diabetic mice, a total of 212 DEGs in the heart tissue of the NC vs. NH group were identified, including 87 downregulated and 125 upregulated DEGs. A total of 497 DEGs were identified for the NH vs. TH group, including 281 downregulated and 216 upregulated DEGs. In the NC vs. TH group, there were 235 DEGs, including 84 downregulated and 151 upregulated DEGs (Table I). In addition, the clustering heatmap demonstrated that different
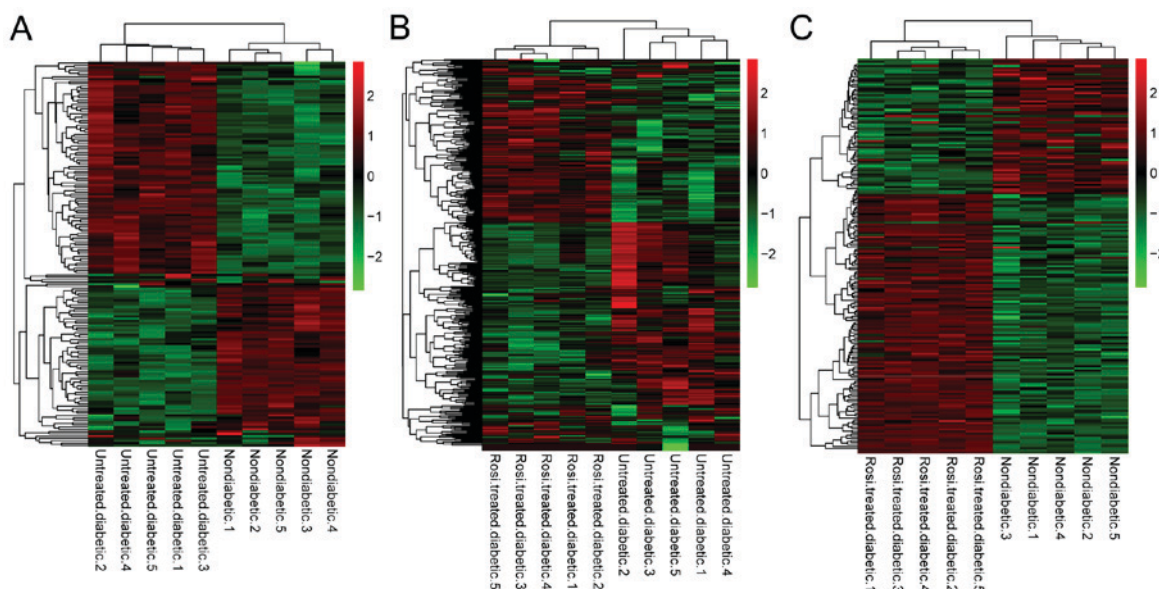
Figure 1. Two-way hierarchical clustering heatmap of DEGs. (A) DEGs in the NC group (n=5) vs. NH group (n=5); (B) DEGs in the NH vs. TH group (n=5); (C) DEGs in the NC vs. TH group. NC, heart samples of non-diabetic control mice; TH, heart samples of rosiglitazone-treated diabetic mice; NH, heart samples of untreated diabetic mice; DEG, differentially expressed gene.
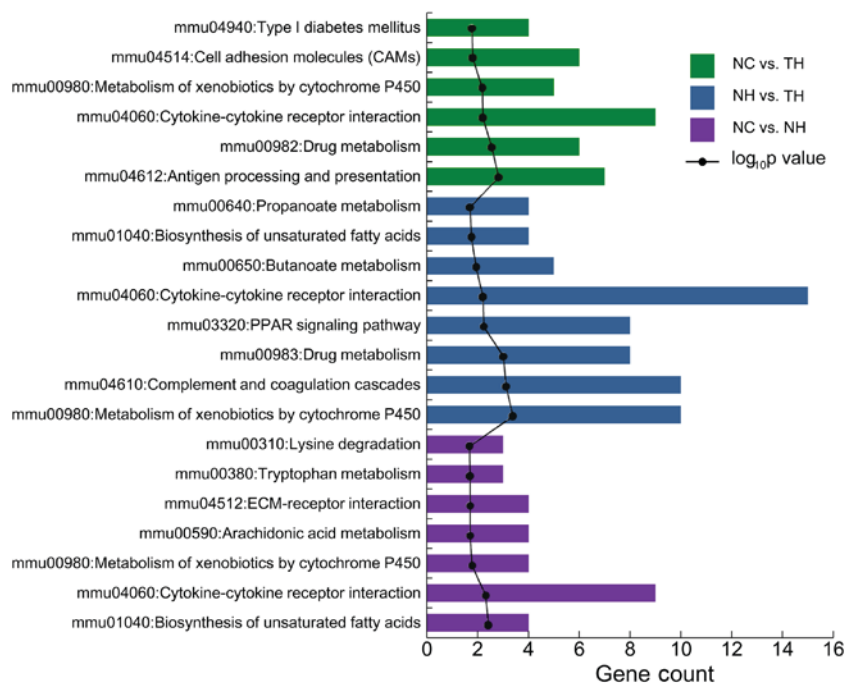

Figure 2. Results of pathway analyses of DEGs in the three groups. Purple indicates the pathways of DEGs in the NC vs. NH group; blue indicates the pathways of DEGs in the NH vs. TH group; green indicates the pathways of DEGs in the NC vs. TH group. ECM, extracellular matrix; PPAR, peroxisome proliferator-activated receptor; NC, heart samples of non-diabetic control mice; TH, heart samples of rosiglitazone-treated diabetic mice; NH, heart samples of untreated diabetic mice; DEG, differentially expressed gene.

types of samples could be separated based on DEG expression values, indicating differences in gene expression characteristic screening was significant (Fig. 1).

Pathways enriched by DEGs of pairs of the three groups. Among the DEGs for the NC vs. NH group 7 enriched pathways were identified, including cytokine-cytokine receptor interaction, biosynthesis of unsaturated fatty acids and metabolism of xenobiotics by cytochrome P450 (Cyp). Furthermore, 8 enriched

pathways were identified to be enriched by the DEGs in the NH vs. TH group, including cytokine-cytokine receptor interaction, metabolism of xenobiotics by Cyps, including Cyp2c37, Cyp3a25 and Cyp3a16, and the peroxisome proliferator-activated receptor (PPAR) signaling pathway, including apolipoprotein (Apo)A1 and ApoA5. A total of 6 pathways were identified to be enriched among the DEGs in the NC vs. TH group, including cytokine-cytokine receptor interaction, antigen processing and presentation, and drug metabolism (Fig. 2).

Construction of network based on GO function and pathways of rosiglitazone function-associated genes. As presented in Fig. 3, there were 791 DEGs in the set of the three groups (NC vs. NH; NC vs. TH and NH vs. TH). These 791 DEGs were clustered into 8 profiles, among which profiles 5 and 6 were significantly associated with the different types of samples that were treated with or without rosiglitazone (P=1x10^{-11} or 4x10^{-3}; Fig. 4A). In profile 5, DEG expression changed from upregulation to downregulation in diabetic mouse heart samples after treatment with rosiglitazone (Fig. 4A). The variation tendency of profile 6 was the same as that of profile 5. Thus, the DEGs in the two profiles were defined as rosiglitazone function-associated genes, including 57 DEGs (e.g., ApoA1, ApoA5, Cyp2c37 and Cyp2J5) in profile 5 and 15 DEGs in profile 6 (e.g., Cyp2b9 and Cyp2b10). In addition, the DEGs in profiles 5 and 6 were used to identify the GO terms in the category biological process (BP) and KEGG pathways. A total of 10 BP terms (including oxidation/reduction, lipid transport and localization, and triglyceride metabolic process) and 5 pathways (retinol metabolism, drug metabolism, linoleic acid metabolism, PPAR signaling pathway and metabolism of xenobiotics by Cyp) were identified in profile 5 (Fig. 4B). In profile 6, 4 GO terms in the category BP (oxidation reduction, proteolysis, cell adhesion and biological adhesion) and 4 pathways (metabolism of xenobiotics by Cyp, retinol metabolism, drug metabolism and arachidonic acid metabolism) were identified (Fig. 4C). The BP term oxidation/reduction, the metabolism of xenobiotics by Cyp, retinol metabolism and drug metabolism pathways were shared between the two profiles. Subsequently, a network of these BP terms, pathways and DEGs was constructed, which had 60 nodes (13 BP terms, 6 pathways, 32 DEGs in profile 5 and 9 DEGs in profile 6) and 130 edges (Fig. 5). Three BP terms in the oxidation/reduction, lipid transport, lipid localization and retinol metabolism pathways were key factors with a high degree of interaction in the network.

Biological abnormalities linked to rosiglitazone function-associated genes. The rosiglitazone function-associated genes in profile 5 were involved in 10 types of biological abnormalities, including abnormal triglyceride levels, abnormal cholesterol homeostasis and abnormal lipid homeostasis (Table II). In addition, DEGs in profile 6 were involved in 5 types of biological abnormalities, including abnormal mineral homeostasis, abnormal mineral level and abnormal pancreas physiology (Table II).

Discussion

In the present study, A total of 791 DEGs in the set of the NC vs. NH, NC vs. TH and TH vs. NH groups were identified. Next, significant profiles associated with the type of samples were identified, of which the DEGs were clustered based on their trends using STEM analysis (profiles 5 and 6; P=1x10^{-11} or 4x10^{-3}, respectively), including 57 DEGs (e.g., ApoA1, ApoA5, Cyp2c37 and Cyp2J5) in profile 5 and 15 DEGs (e.g., Cyp2b9 and Cyp2b10) in profile 6. The expression of these DEGs exhibited the same variation tendencies among the experimental groups. Therefore, these genes were defined
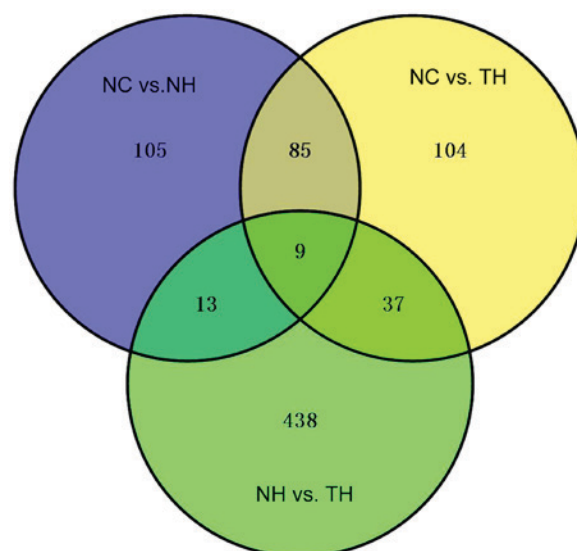

Figure 3. Venn diagram of DEGs in the three groups. A total of 791 DEGs were obtained in set of NC vs. NH, NC vs. TH and TH vs. NH groups. DEG, differentially expressed gene; NC, heart samples of non-diabetic control mice; TH, heart samples of rosiglitazone-treated diabetic mice; NH, heart samples of untreated diabetic mice.

as rosiglitazone function-associated genes. In addition, the genes were enriched in 13 BP terms, including oxidation/reduction and lipid transport, and 6 KEGG pathways, including the PPAR signaling pathway and metabolism of xenobiotics by Cyp. Furthermore, a network of these BP terms, pathways and DEGs (32 DEGs in profile 5 and 9 DEGs in profile 6) was constructed, which had 60 nodes and 130 edges. Finally, the biological abnormalities linked to rosiglitazone function-associated genes were identified, including abnormal triglyceride levels, abnormal cholesterol homeostasis, abnormal lipid homeostasis and abnormal mineral homeostasis.

ApoA1 and ApoA5 are members of the Apo family. ApoA1 is the major protein component in nascent high-density lipoprotein (HDL) formation and lipid trafficking via ATP-binding cassette transporter A1 (ABCA1) in the plasma membrane (19,20). Llaverias *et al* (21) reported that rosiglitazone markedly activated the expression of ABCA1 and scavenger receptor class B type I (SR-BI), and reduced free cholesterol in differentiating monocytes. Similarly, Li *et al* (22) indicated that rosiglitazone increased the expression of ABCA1 in aortic lesions of atherosclerotic rabbits. Furthermore, ApoA1 and its mimetic peptide mediated extracellular cholesterol microdomains deposited depending on macrophage ABCA1 (23). ApoA1 has been demonstrated to promote bidirectional lipid movement via SR-BI (24). Rosiglitazone, as a high-affinity PPARγ agonist, increased high-density lipoprotein cholesterol levels in humanized ApoA1 transgenic mice (24). In addition, ApoA1 inhibited arterial thrombus formation (25) and ApoA5 has a key role in regulating plasma triglyceride levels and is a major risk factor for coronary artery disease (26,27). Similarly, Apoa1 and Apoa5 were involved in lipid transport and lipid localization in the present study. Of note, Apoa1 and Apoa5 were enriched in the PPAR signaling pathway. Apoa5 was also involved in the triglyceride metabolic process. Rosiglitazone regulates
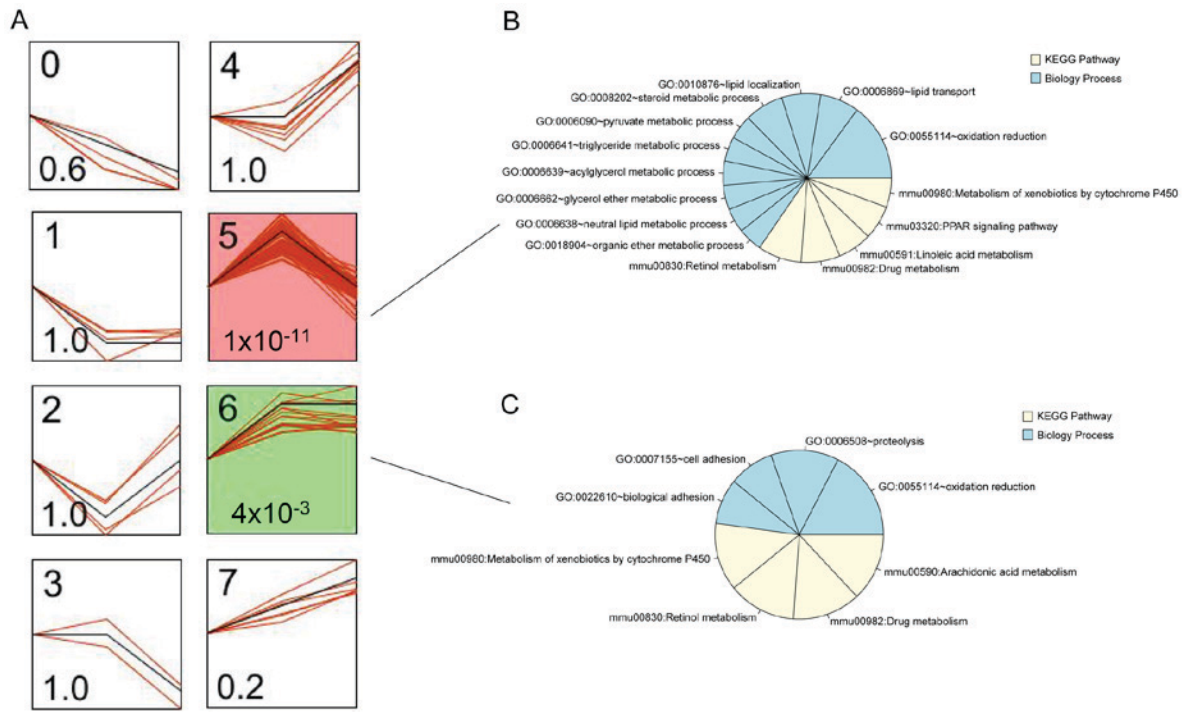
Figure 4. Trend analysis of gene expression profiles. (A) The boxes indicate the model profiles following STEM analysis of the 791 DEGs in the set of NC vs. NH, NC vs. TH and TH vs. NH groups, and the colored profiles have a significant number of genes assigned. The black broken lines in the boxes indicate the trend changes in overall genes in the profile and red lines indicate trend changes of each gene in the profile; the numbers in the lower left corner indicate P-values in the profile compared to other profiles. (B and C) GO functions and KEGG pathways of differentially expressed genes in (B) profile 5 and (C) profile 6 were identified. The yellow segments represent KEGG pathways, while blue segments represent GO terms in the category biological process. GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPAR, peroxisome proliferator-activated receptor.
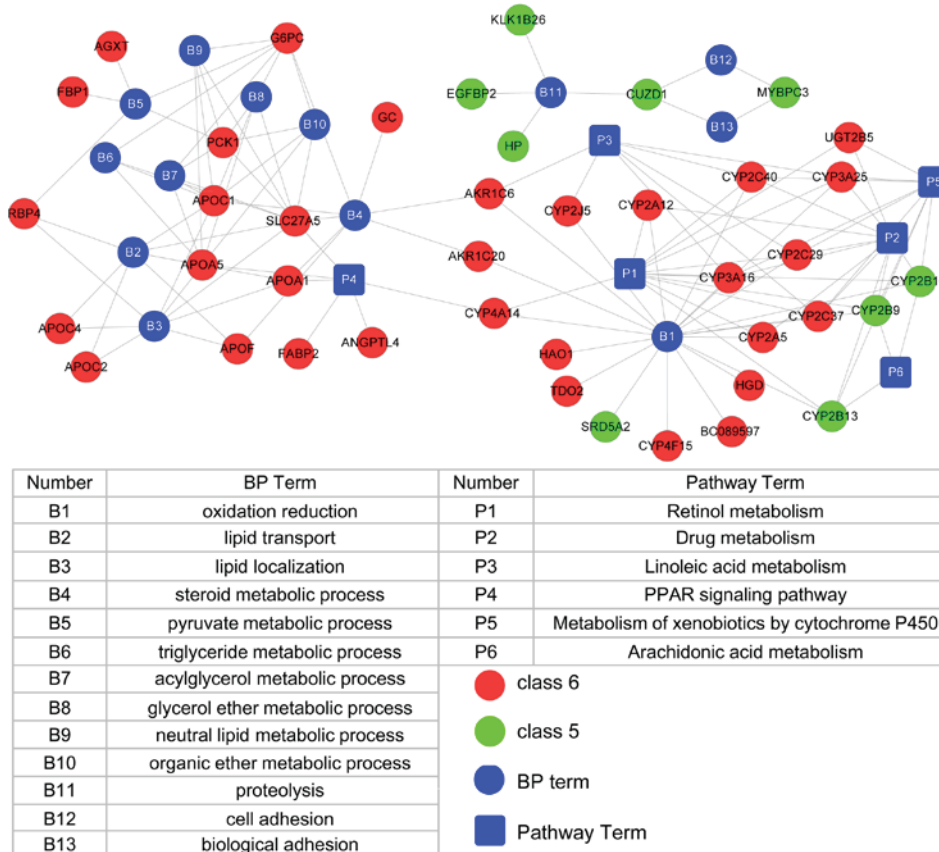
Figure 5. Network based on BP and Kyoto Encyclopedia of Genes and Genomes pathways of rosiglitazone function-associated genes. The red nodes indicate DEGs in profile 6; green nodes indicate DEGs in profile 5; the blue circles indicate DEGs enriched in the gene ontology category BP; blue boxes indicate DEGs involved in pathways. BP, biological process; DEG, differentially expressed gene; PPAR, peroxisome proliferator-activated receptor.

Table II. Biological abnormalities linked with rosiglitazone function-associated genes.

Profile/phenotype	ID	Raw P-value	P-value adjusted using the BH method (37)	Genes
Profile 5				
Abnormal triglyceride level	MP:0000187	1.34×10^{-11}	3.63×10^{-9}	Gcgr, Apoc1, Pck1, Apoa1, Apoa5, Rgn, Fgf21, Bhmt, Angptl4, G6pc, Apof, Slc27a5
Homeostasis/metabolism phenotype	MP:0005376	6.38×10^{-11}	8.64×10^{-9}	Kng1, Pck1, Apoa1, Apoa5, Rgn, Fgf21, Fgg, Bhmt, Pzp, Cyp4a14, Hgd, Mug1, Cyp2j5, Slc27a5, Gcgr, Apoc1, Tdo2, Fabp2, Cyp2a5, Hc, Agxt, Tmprss6, Angptl4, Gc, G6pc, Apof, Rbp4
Abnormal homeostasis	MP:0001764	2.05×10^{-10}	1.30×10^{-8}	Kng1, Pck1, Apoa1, Apoa5, Rgn, Fgf21, Fgg, Bhmt, Pzp, Cyp4a14, Hgd, Mug1, Cyp2j5, Slc27a5, Gcgr, Apoc1, Tdo2, Fabp2, Agxt, Tmprss6, Angptl4, Gc, G6pc, Apof, Rbp4
Abnormal cholesterol homeostasis	MP:0005278	2.40×10^{-10}	1.30×10^{-8}	Gcgr, Apoc1, Apoa1, Fabp2, Apoa5, Rgn, Fgf21, Bhmt, Angptl4, G6pc, Apof, Slc27a5
Abnormal cholesterol level	MP:0003947	1.78×10^{-10}	1.30×10^{-8}	Gcgr, Apoc1, Apoa1, Fabp2, Apoa5, Rgn, Fgf21, Bhmt, Angptl4, G6pc, Apof, Slc27a5
Abnormal circulating cholesterol level	MP:0000180	1.63×10^{-9}	7.36×10^{-8}	Gcgr, Apoc1, Apoa1, Fabp2, Apoa5, Fgf21, Bhmt, Angptl4, G6pc, Apof, Slc27a5
Abnormal circulating triglyceride level	MP:0011969	6.48×10^{-9}	2.23×10^{-7}	Apoc1, Pck1, Apoa1, Apoa5, Fgf21, Angptl4, G6pc, Apof, Slc27a5
Abnormal lipid homeostasis	MP:0002118	6.59×10^{-9}	2.23×10^{-7}	Gcgr, Apoc1, Pck1, Apoa1, Fabp2, Apoa5, Rgn, Fgf21, Bhmt, Cyp4a14, Angptl4, G6pc, Apof, Slc27a5
Abnormal blood homeostasis	MP:0009642	8.46×10^{-9}	2.55×10^{-7}	Kng1, Pck1, Apoa1, Apoa5, Rgn, Fgf21, Fgg, Bhmt, Pzp, Mug1, Cyp2j5, Slc27a5, Gcgr, Tdo2, Apoc1, Fabp2, Tmprss6, Angptl4, G6pc, Apof
Abnormal circulating lipid level	MP:0003949	1.70×10^{-8}	4.61×10^{-7}	Gcgr, Apoc1, Pck1, Apoa1, Fabp2, Apoa5, Fgf21, Bhmt, Angptl4, G6pc, Apof, Slc27a5
Profile 6				
Abnormal ion homeostasis	MP:0001765	0.0076	0.0342	Kcnk1, Hp
Abnormal mineral homeostasis	MP:0005636	0.0063	0.0342	Kcnk1, Hp
Abnormal pancreas physiology	MP:0002693	0.0059	0.0342	Cadps2, Cuzd1
Abnormal mineral level	MP:0000192	0.0056	0.0342	Kcnk1, Hp
Increased sensitivity to induced morbidity/mortality	MP:0009763	0.0134	0.0482	Hp, Cuzd1

the mRNA and protein expression of adipose triglyceride lipase in mature adipocytes *in vitro* and *in vivo* by mediating the activity of PPARγ (28). Furthermore, dyslipidemia is a major risk factor for cardiovascular disease (29). In the present study, the results regarding biological abnormalities linked to rosiglitazone function-associated genes suggested that ApoA1 and ApoA5 were mainly involved in abnormal triglyceride levels, abnormal cholesterol homeostasis and abnormal lipid homeostasis. Therefore, rosiglitazone may improve cardiovascular function by targeting ApoA1 and ApoA5 in the PPAR signaling pathway.

A study by the Nobel laureate Watson (30) revealed that insulin resistance and T2DM may arise through insufficient supply of key reactive oxygen species controlling the blood sugar concentration. In the present study, various Cyp genes, including Cyp2c37, Cyp2J5, Cyp2b9 and Cyp2b10, were identified to be enriched in the BP term oxidation/reduction. Human Cyp enzymes have been previously reported to be involved in the metabolism of rosiglitazone in the treatment of T2DM *in vitro* (31). Similarly, rosiglitazone function-associated genes were enriched in the metabolism of xenobiotics via the Cyp pathway. Cyp2B, Cyp3A and Cyp4A levels in the liver were increased in diabetic rats and mice but reduced to normal levels after treatment with insulin (32). Cyp2c37 is the principal member of the Cyp2c family and is associated with detoxification and drug-metabolizing proteins in T2DM patients treated with a PPAR-α agonist (33). The human ortholog of mouse Cyp2j5 is Cyp2J2 (34), and overexpression of Cyp2J2 attenuates myocardial hypertrophy induced by diabetes (35). The downregulation of Cyp2J2 by rosiglitazone may have counteracted the body's attempt to compensate for cardiovascular effects by upregulating Cyp2J2 in diabetes. Thus, Cyp2j5 may attenuate myocardial hypertrophy and improve cardiovascular function in patients with T2DM. Furthermore, PPAR agonists increase Cyp2b9 and Cyp2b10 mRNA levels in lipid metabolism. Panunti and Fonseca (36) revealed that PPAR agonists possess anti-inflammatory and vascular properties, which may be developed as a method of primary and secondary macrovascular disease prevention in patients by improving various risk factors (including dyslipidemia, hypertension and atherosclerosis) associated with obesity and insulin resistance, and by exerting numerous non-glycemic effects that may improve cardiovascular outcomes. Therefore, Cyp2c37, Cyp2J5, Cyp2b9 and Cyp2b10 are rosiglitazone function-associated genes in T2DM, which may improve cardiovascular function via oxidation/reduction.

Of note, the present study had several limitations. The results of the present bioinformatics analysis should be verified through experiments. For instance, the expression levels of these six genes (ApoA1, ApoA5, Cyp2c37, Cyp2J5, Cyp2b9 and Cyp2b10) should be identified by PCR. In addition, the orthologs of the genes identified in the present study should be verified in human samples. In spite of these limitations, the present results provide a foundation for studying the mechanism of action of rosiglitazone, including its cardiovascular protective effects and blood glucose control in patients with T2DM.

Rosiglitazone may improve cardiovascular function by regulating the PPAR signaling pathway targeting ApoA1 and ApoA5. Furthermore, Cyp2c37, Cyp2J5, Cyp2b9 and Cyp2b10 were identified as rosiglitazone function-associated genes in T2DM via their role in oxidation/reduction. Therefore, ApoA1, ApoA5, Cyp2c37, Cyp2J5, Cyp2b9 and Cyp2b10 are rosiglitazone function-associated genes affecting cardiovascular outcomes and glycemic control in T2DM. Additional studies are required to fully elucidate the mechanisms of action of rosiglitazone on glycemic control and its cardiovascular protective effects in T2DM.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Authors' contributions

XW contributed solely to the present study.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that there are no competing interests.

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