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REVIEW ARTICLE

Developing Diagnostic and Therapeutic Target for T2DMthrough Bioinformatics Approaches.

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Abstract

Among the most hazardous conditions affecting human health is diabetes mellitus (DM). Type 2 diabetes (T2DM) is the most prevalent type and represents about 90% of all diabetic cases globally and this form is characterized by hyperglycemia,which results from insulin resistance or inadequate insulin production.The severity of this metabolic disorder is attributed to its microvascular and macrovascular complications. In this study,in silico analysis was used to define the most putative pathways implicated in the occurrence and progression of T2DM by using bioinformatics tools as GEO2R to identify differential expression of genes (DEGs), Shiny Go 0.8 web program to identify gene-ontology (GO) terms and Kyoto- Encyclopedia of genes and genomes (KEGG) pathways, STRING database to determine protein-protein interaction, and Cytoscape software to visualize this interaction and to identify hub genes. The results showed that hub genes that regulate the pathogenesis of T2DM are Signal-transducer-and activator of transcription three (Stat3), discs large homolog 4(Dlg4), carnitine palmitoyltransferase 1 (Cpt1a), aldehyde dehydrogenase- 1- family member A1 (Aldh1a1), galectin 3 (Lgals3), integrin subunit alpha D (Itgad), epoxide hydrolase 2 (Ephx2), colony stimulating factor 1 receptor (Csf1r), transferrin receptor (Tfrc),UDP glucuronosyltransferase 2 family, and polypeptide B1 (Ugt2b1). Additionally, the most implicated pathway is the peroxisome proliferator-activated receptors (PPAR) signaling pathway.Finally, we can modulate T2DM progression by targeting STAT3 pathway and PPAR signaling pathway.

Key words: T2DM, Rats, STAT3, PPAR signaling pathway, bioinformatics.

Introduction

A worldwide epidemic, diabetes mellitus (DM)affects about one in ten people between the ages of 20 and 79, and it is one of the main causes of premature death. It is predicted that by 2045, its prevalence and incidence will have increased to 784 million worldwide[1].The hallmarks ofType 2 diabetes (T2DM) include inadequate insulin production and insulin resistance [2].

Individualshave T2DM experiencing a range of clinical symptoms and disease progressions,which result in a delay in diagnosis, numerouspathophysiological abnormalities and variable susceptibilities to sever complications.Among themmicrovascular and macrovascular complications, the first one includes retinopathy, neuropathy and nephropathy

and the latest includedisorders in the heart, brain, and peripheral arteries[3].A complicated multifactorial condition, obesity is associated with an increased risk of cardiometabolic disorders, T2DM, and most recently COVID-19[4].

Glucotoxicity and lipotoxicity are important aspects in the pathogenesis of T2DM because they produce numerous reactive oxygen species (ROS) and oxidative strains. Because mitochondria are essential for regulating fatty tissue formation, triglyceride synthesis, ester bond formation, and breakdown of fat in adipocytes, lipotoxicity results in mitochondrial dysfunction, which is characterized by an excess of ROS and a decrease in mitochondrial capacity and the creation of ATP. This reduces the sensitivity to insulin [5].

The liver, a vital metabolic organ, is essential for preserving glucose homeostasis.Glycolysis, gluconeogenesis, glycogenolysis, and glycogen synthesis are some of the mechanisms that contribute to hepatic glucose production (HGP) [6].About half of human Hepatic glucose production (HGP) during overnight fasting is attributed to gluconeogenesis, which comprises the three essential enzymes:1-phosphoenolpyruvate-carboxykinase(PCK), 2-fructose one and six-bisphosphatase (FBPase), 3-glucose six phosphatase (G6PC) [6].A previous research has indicated that diabetic mice and rats exhibit elevated hepatic phosphoenolpyruvate- carboxykinase (PCK), fructose one and six-bisphosphatase (FBPase), glucose six phosphatase (G6PC) expression levels [7].

The liver's constitutive STAT3 activation suppresses the level of G6PC, PCK1, and FBPase[8].By increasing the level of pyruvate-kinase (PKM) and hexokinase two (HK2), STAT3 can stimulate glycolysis [9].PCK is the enzyme that controls the rate of gluconeogenesis and catalyzes the alteration of oxaloacetate into phosphoenolpyruvate [10].

The catalytic result of PCK is phosphoenolpyruvate, which transformed into fructose one and six biphosphate (1,6 F-bP) after undergoing a number of metabolic processes. FBPase triggers the conversion of 1,6 F-bP to fructose six phosphate (F6P). After that, F6P is changed to glucose 6 phosphate (G6P), and G6PC catalyzes the dephosphorylation of G6P to produce glucose. The research revealed that FBPase suppression enhances the impaired glucose tolerance in T2DM rats and mice and decreases the excessive endogenous glucose production [11,12].

The current study aimed to analyze the microarray Gene Expression Omnibus **(**GEO) dataset of type 2 diabetic rats to exploit a valid diagnostic and therapeutic target for obesity inducing insulin resistance (T2DM).

Materials and methods

Microarray data

Gene Expression Omnibus **(**GEO) provided the GSE13270, which is constructed using the Rat230-2 Affymetrix Rat Genome 230 2.0 Array (GLP1355 platform).10 Goto-Kakizaki rats were kept in an isolated chamber with rigorous environmental controls, including rigorous adherence to 12 hours:12-hour cycles of light and dark. Fivespecimens from rats fed a normal diet and five specimensfrom Goto-Kakizakirats fed on a high-fat diet (HFD)containing 45% energy from fatfor 16 weeks were examined.This database

was explored using the following terms: insulin resistance, high-fat diet (HFD), or type-2 diabetes- mellitus -T2DM.

Identification of the differentially expressed genes (DEGs)

The DEGs between HFD and normal liverspecimens were investigated using GEO2R. The conventional criteria for identifying genes that are differentially expressed (DEGs) include fold change [($\log_2$ FC)greater than 1.5] and a *P*-value below 0.05[13].

Functional and pathway enrichment analysis of DEGs

A well-known*in silico* tool called GO provides comprehensive information on the gene function of specific genomic products according to predetermined criteria[14]. The investigation comprises three sections: molecular functions (MF), cellular components (CC), and biological processes (BP).. Additionally, KEGG database facilitates a higher degree of understanding of biological pathways and processes. Researchers can use a variety of functional annotation methods offered by the ShinyGo 0.8 web program (http://bioinformatics.sdstate.edu/go80/) to assess and comprehend the biological significance of certain gene lists. We justify KEGG and GO analyses of DEGs with afalse discovery rate (FDR)below 0.05.

Protein-protein interaction (PPI) network

The PPI network of DEGs was created by STRING (https://string-db.org/), an online tool for studying how genes and proteins interact.With the species specified as Rattus norvegicus and with medium confidence score of 0.400 and 0.700.Next, the PPI networks were analyzed using Cytoscape software (3.9.1) (http://www.cytoscape.org/).

Hub genes identification

CytoHubba, a cytoscapeplugin tool that offers an intuitive interface for examining significant nodes in biological networks, along with the maximal clique centrality (MCC) technique was used to explore the PPI network for hub genes.

Different diseases associated with hub genes

We usedShinyGO to retrieve and identifythe most important diseases associated with the dysregulated genes.

Result

Differentially expressed genes (DEGs)Identification

From the top 250 differentially expressed genes identified by GEO2R analysis, 118 showed downregulation and 132 showed upregulation (Figure 1A–C).

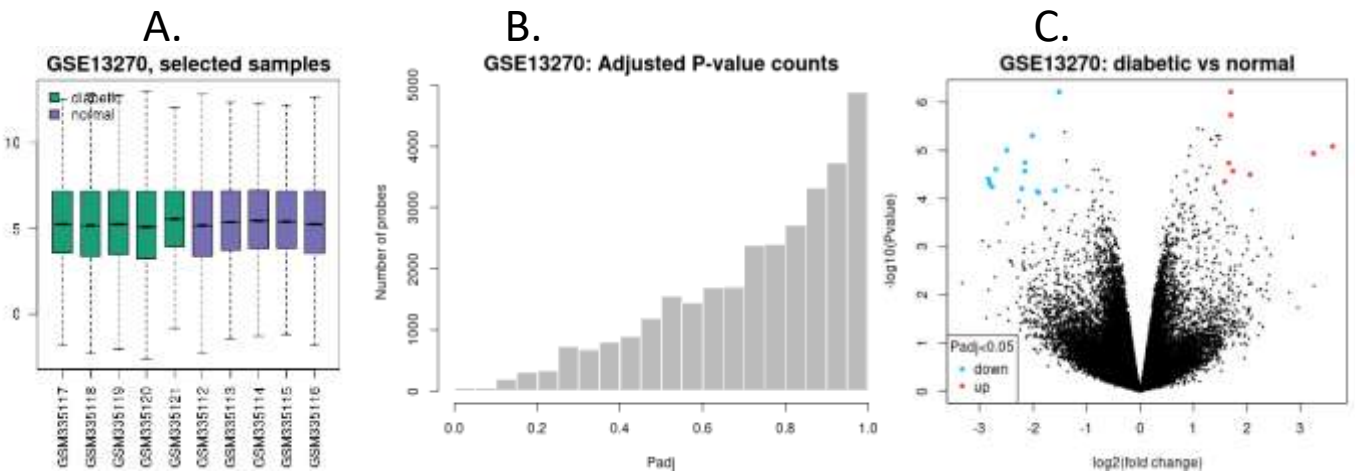

Figure 1. GEO2R revealeddifferentially expressed genes with adjusted *P*-value below 0.05 and a fold change Figure 1: Sample distribution and differentially expressed genes identification: A. samples (control, diabetic); B. Adjusted p-value for the obtained genes; and C. volcano plot of the differentially expressed genes.(log2 FC > 1.5).

Functional enrichment analysis of DEGs

The gene ontology (GO) results for cellular components (CC) include glycerol-3-phosphate dehydrogenase complex, perinuclear endoplasmic reticulum,endoplasmic reticulum membrane, endoplasmic reticulum subcompartment, nuclear outer membrane-endoplasmic reticulum membrane network,cytosol, and others.Additionally, the GO results for biological process (BP) are the fatty acid metabolic process, the lipid metabolic process, cellular lipid metabolic process, small molecule metabolic process, and others.

Furthermore, the molecular function (MF) contained protein homodimerization activity, oxidoreductase activity, phosphatase binding, protein phosphatase binding, oxidoreductase activity acting on paired donors with incorporation or reduction of molecule 2, steroid dehydrogenase activity acting on the CH-OH group of donors NA, oxidoreductase activity acting on the CH-OH group of donors NAD or NA, oxidoreductase activity acting on NAD(P)H, oxidoreductase activity acting on paired donors with incorporation or reduction of molecule 2, and others. Finally, The KEGG pathways analysis exhibited PPAR signaling pathway and metabolic pathways (Figure 2A–D).

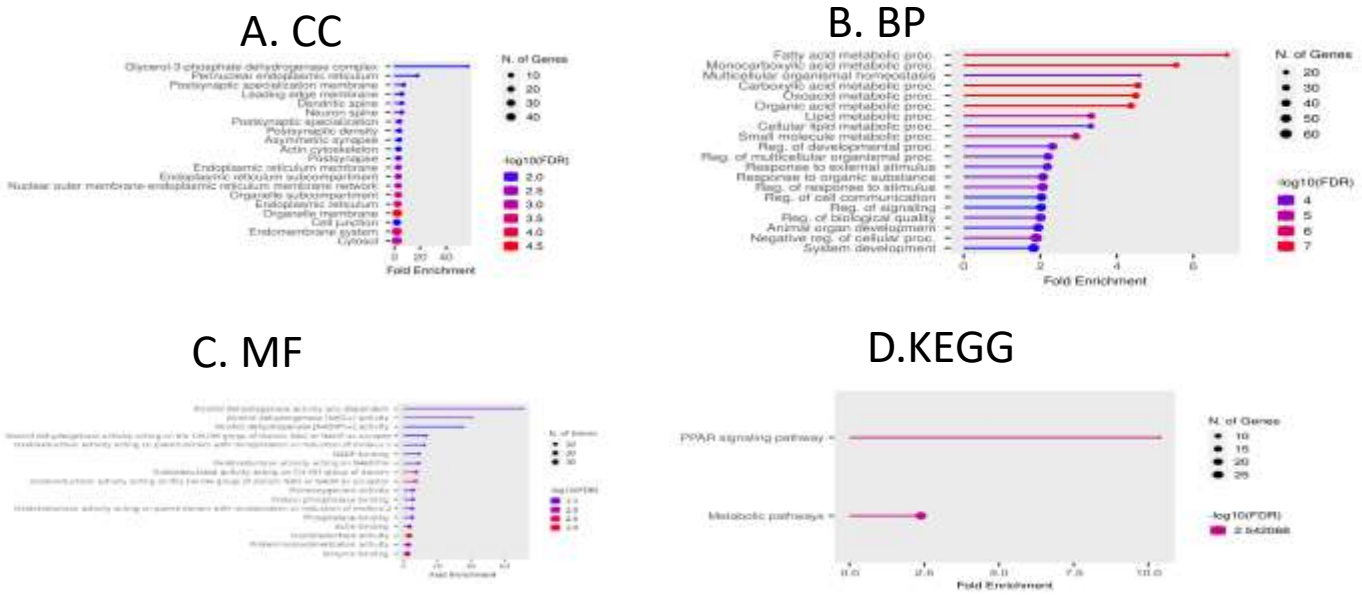

Figure 2. Gene ontology and kyoto encyclopedia of genes and genomes pathways of the differentially expressed genes (A - C). A. Cellular- components [CC].B. Biological -process [BP]. C. Molecular -functions [MF]. D. The KEGG pathways analysis.

Protein-protein interaction

Herein,PPI showed 10 clusters mentioned as cluster one include acyl-CoA-thioesterasetwo **(**Acot2), acyl-CoA-synthetase-family-member-two (Acsf2), actinin alpha 1 (Actn1), ADAM-metallopeptidase-with-thrombospondin-type one-motif 1 **(**Adamts1), alcohol dehydrogenase 4 (Adh4), Adh6a, Aldo-keto- reductase-family-one- member-C1(Akr1c1), 5'-aminolevulinate synthase 1 **(**Alas1), Aldh1a1, Rho guanine nucleotide exchange factor 1 (Arhgef1), activating transcription factor 4 (Atf4), ATPase plasma membrane Ca2+ transporting 1 **(**Atp2b1), D-beta-hydroxybutyrate dehydrogenase (Bdh1), Bcl-2-modifying factor (Bmf), complement C1q C chain (C1qc), carbonic anhydrase 8 (Ca8), capping actin Protein, gelsolin like (Capg), coiled-coil domain containing 58 (Ccdc58), C-C Motif chemokine ligand 21 (Ccl21), cluster of differentiation 38 (Cd38), clusterin **(**Clu), coronin, actin binding protein, 1A (Coro1a), coactosin-like-f-actin-binding-protein one (Cotl1), Cpt1a, Csf1r, cytochrome B-245 beta chain (Cybb), cytochrome-P450;family3; subfamily a; polypeptide-eighteen (Cyp3a18), Cyp4a8, Cyp7a1, DEAD-(Asp.Glu.Ala.Asp) box-polypeptide eighteen (Ddx18), 2,4-dienoyl-CoA reductase 1 (Decr1), Dlg4, ELAV like RNA binding protein 1 (Elavl1), ELOVL-fatty-acid-elongase-two (Elovl2), Ephx2, fatty-acid-binding protein two (Fabp2), Fabp7, fatty acid desaturase 2 (Fads2), flavin containing dimethylaniline monoxygenase 1 (Fmo1), Fmo5, guanine deaminase (Gda), G-patch domain-

containing protein 4 (Gpatch4), glycerol-3-phosphate dehydrogenase 1 like (Gpd1l), Gpd2, Hydroxyacyl-CoA-Dehydrogenase- Trifunctional-Multienzyme-Complex subunit alpha (Hadh), 17β-Hydroxysteroid dehydrogenase 2 (Hsd17b2), IlvBacetolactate synthase like (Ilvbl), Itgad, Potassium-voltage-gated-channel-subfamilyD-member three (Kcnd3), krüppel-like factor 2 (Klf2), Lgals3, myelin basic protein (Mbp), moesin (Msn), myosin heavy chain 1 gene (Myh1), myosin IC (Myo1c), NADPH Oxidase 4 (Nox4), nuclear-receptor-subfamily one-Group D- Member-one (Nr1d1), Nr1d2, osteomodulin (Omd), pantothenate kinase 2 (Pank2), pdzandlimdomainprotein 1 (Pdlim1), peroxisomal biogenesis factor 11 alpha (Pex11a), cytochrome p450 oxidoreductase (Por), proteasome (prosome, macropain) 26S subunit, non-ATPase, 14 (Psmd14), protein tyrosine phosphatase receptor type S (Ptprs), ring-box 1 (Rbx1), ribosomal protein L7 (Rpl7), ribonuclease P/MRP Subunit P21 (Rpp21), ribosomal protein S27 Like (Rps27l), short chain-dehydrogenase/reductase-family 42E, member one (Sdr42e1), shisa-Family-member seven (Shisa7), ST3-beta-galactoside-Alpha-2,3-sialyltransferase one (St3gal1), St6gal1, Stat3, transgelintwo (Tagln2), transferrin receptor (Tfrc), TIAM rac1 associated GEF 1 (Tiam1), TIMP metallopeptidase inhibitor 2 (Timp2), transmembrane protein 135 (Tmem135), trio rho guanine nucleotide exchange factor (Trio), uncoupling protein 2 (Ucp2), Ugt2b1, VANGL planar cell polarity protein 2 (Vangl2), Vanin 1 (Vnn1), WD repeat domain 43 (Wdr43), and WT1 associated protein (Wtap), cluster two consist fromccdc141, oxysterol-binding protein Like three (Osbpl3), and protein phosphatase- 1-regulatory Subunit 3B (Ppp1r3b), cluster three include regulator of G protein signalling domain, cluster four include msl Complex Subunit 3B (Msl3l2) and putative homeodomain transcription Factor 2 (Phtf2), cluster five include leucine-rich- alpha-2-glycoprotein one (Lrg1)and leucine rich repeat containing 8 VRAC Subunit C (Lrrc8c), cluster six include lgalsl and tsukushi, small leucine rich proteoglycan (Tsku),cluster seven include dab Adaptor Protein 1 (Dab1)and forkhead box P2 (Foxp2), cluster eight include adipoR/haemolysin-III-related, cluster nine consist fromset Domain containing 5 (Setd5) and spt5 Homolog, dsifelongation factor subunit (Supt5h), and cluster ten include cyclin G2 (Ccng2) and heat shock protein family B (small) member eleven (Hspb11) (Figure 3).

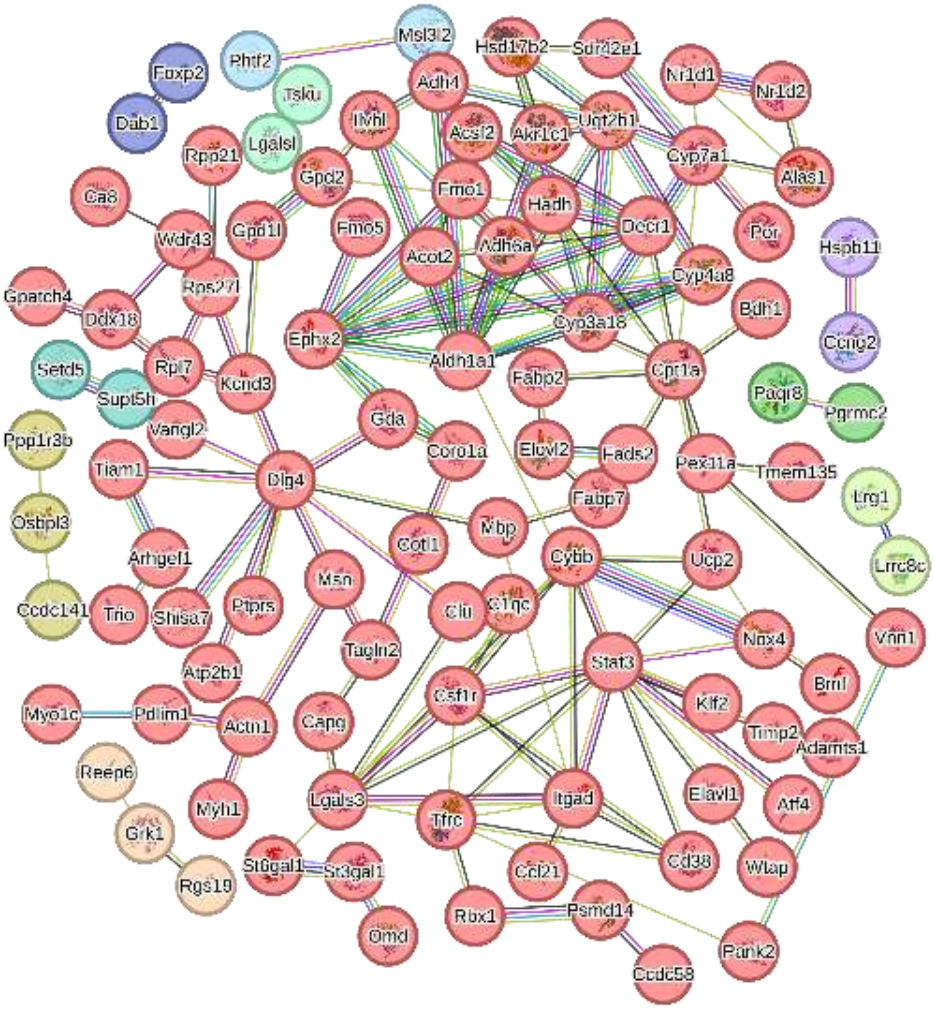

Figure 3. Protein-protein interactions with 174 nodes and 145 edges and ten cluster(According to order, the colors of the clusters are red, olive, misty rose, sky blue, light green, aquamarine, slate blue, forest green, pale turquoise, and light purple.).This PPI reveled from STRING database (https://string-db.org/).

Top Ten Hub Genes

The study revealed that the top ten hub genes dysregulated in HFD inducing T2DM are Stat3, Dlg4, Cpt1a, Aldh1a1, Lgals3, Itgad, Ephx2, Csf1r, Tfrc, and Ugt2b1 (Figure 4).

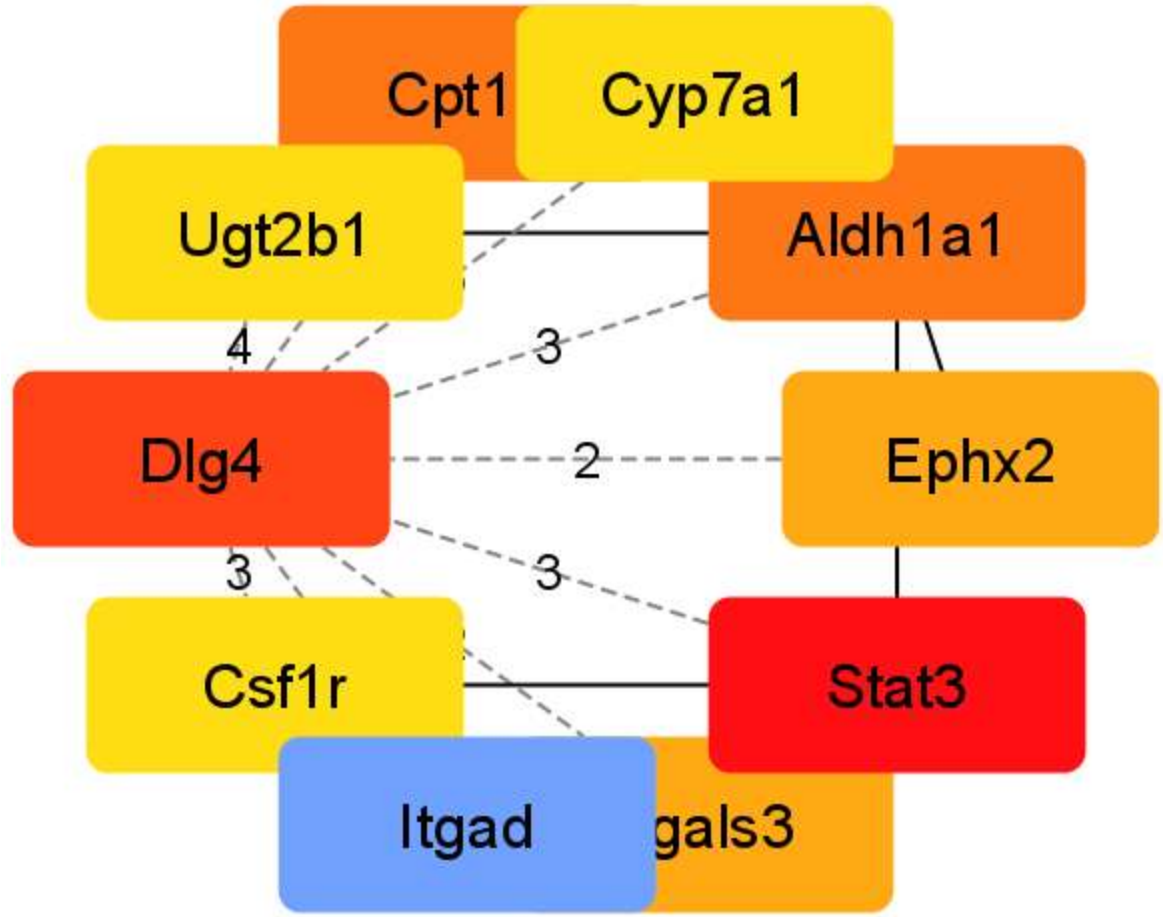

Figure 4. Top ten hub genes involved in the type 2 diabetes (T2DM) progressionfrom protein-protein interaction (PPI) network

Different diseases associated with DEGs

Shiny GO analysis showed that the most important diseases associated with DEGs are experimental liver cirrhosis, diabetic nephropathies, experimental diabetes mellitus, andetc.(Figure5).

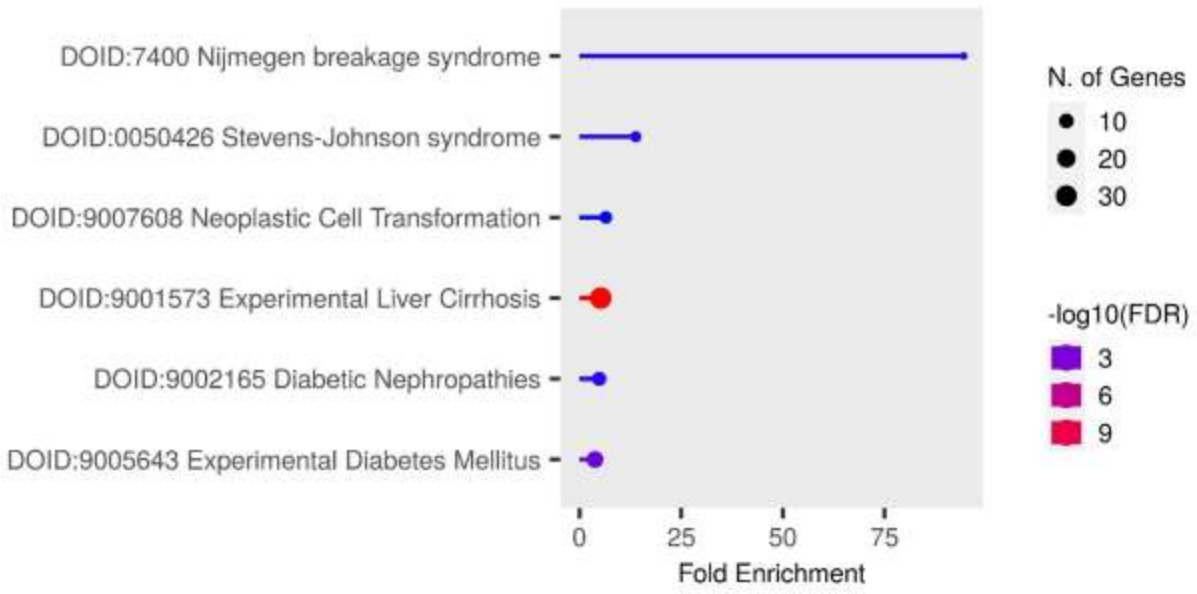

Figure5. Diseases that associated with the differentially expressed genes (DEGs).

Discussion

The metabolic disorder known as Type 2 Diabetes Mellitus (T2DM) is typified by elevated blood glucose levels brought on by peripheral tissue resistance to insulin action and/or inadequate insulin production. Diabetes Mellitus causes insufficient glycemic control, which leads to higher medical costs and early mortality [15].Therefore, there is a need for new therapeutic methods. Numerous studies have employed high-throughput omics data to investigate disease the causes and toidentifypotential therapies.

According to the current study, we found that the top genes associated with T2DM are *Stat3, Dlg4, Cpt1a, Aldh1a1, Lgals3, Itgad, Ephx2, Csf1r, Tfrc,* and *Ugt2b1*which is in agreement with [16–25].Through the higher level of PKM2 expression and the enhancement of RAC-alpha serine/threonine-protein kinase (AKT) phosphorylation and mitogen-activated protein kinase 3/1 (ERK1/2) stimulation, STAT3 accelerated glucose consumption[26].The enhanced synthesis of HIF-1α by STAT3 transcriptionally activated GLUT1 and glycolysis-related enzymes ENO-1, PFKL, and PKM2[26].STAT3 activation decreased PCK1 and G6PC expressions while boosting GLUT2, GCK, PFKL, and PKM expressions, as reported in the latest research[27].

The results of the currentstudyrevealed that STAT3 is downregulated in the liver samples from Goto-Kakizakerats fed a high-fat diet for 16 weeks and is one of the most hub genes, which is in agreement with a previous research[28]. This downregulation of STAT3 in liver tissues was attributed to the decrease in hepatic STAT3 phosphorylation in T2DM[27].peroxisome proliferator–activated receptors (PPARs),a crucial part of controlling the synthesis of genes linked to fibrogenesis, inflammatory processes, and the metabolism of lipids and carbohydrates[29].Triglyceride levels

are lowered when PPARα is activated, but insulin sensitivity and improved glucose metabolism result from PPARγ activation [30,31].

Our results exposed that the most important KEGG pathway regulating T2DM is the PPAR signaling pathway. This result was in agreement with previous reports[32,33].PPARγ is associated with T2DM risk due to its regulation of lipid metabolism, inflammation, and insulin resistance [34,35].The most significant GO finding for BP was found in this present research is listed asfatty acid metabolic process, lipid metabolic process, cellular lipid metabolic process, and small molecule metabolic processwhich is consistent withthat reported previously [36,37]. Besides, CC comprises the glycerol-3-phosphate dehydrogenase complex, perinuclear endoplasmic reticulum, endoplasmic reticulum membrane, endoplasmic reticulum subcompartment, nuclear outer membrane-endoplasmic reticulum membrane network, cytosol that in conformity with that documented elsewhere [38–40].Lastly, MF comprehend protein homodimerization activity, oxidoreductase activity, phosphatase binding, protein phosphatase binding, oxidoreductase activity acting on paired donors with incorporation or reduction of molecule 2, steroid dehydrogenase activity acting on the CH-OH group of donors NA, oxidoreductase activity acting on the CH-OH group of donors NAD or NA, oxidoreductase activity acting on NAD(P)H, oxidoreductase activity acting on paired donors with incorporation or reduction of molecule 2 that are referenced in previous reports[41–45].

Conclusion

In summary, according to the present *in silico* study we found that the top ten hub genesthat are essential to the emergence of T2DM and its problems are Stat3, Dlg4, Cpt1a, Aldh1a1, Lgals3, Itgad, Ephx2, Csf1r, Tfrc, and Ugt2b1. These genes could be utilized as possible biomarkers to generate innovative treatment tactics and approaches.Additionally, the PPAR signaling pathway was the most significant KEGG pathway contributing to T2DM and its problems; by focusing on this pathway, we can slow the disorder's progression and improve its therapy. However, there are certain drawbacks in this study. Therefore, to validate these findings, clinical investigations are required.

Conflicts of Interest:

No conflicts of interest for publication of this paper

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الملخص العربي

تطوير الهدف التشخيصي والعلاجي لداء السكري من النوع الثاني من خلال مناهج المعلوماتية الحيوية

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يعد مرض السكري من أكثر الأمراض المدمرة التي تؤثر على صحة الإنسان، ويعتبر داء السكري من النوع الثاني هو النوع الأكثر انتشارًا ويمثل حوالي 90% من جميع حالات مرض السكري على مستوى العالم ويتميز هذا الشكل بارتفاع السكر في الدم الناتج عن مقاومة الأنسولين , أو عدم كفاية إنتاج الأنسولين. تعزى شدة هذا الاضطراب الأيضي إلى مضاعفات الأوعية الدموية الدقيقة والأوعية الدموية الكبيرة. في هذه الدراسة، تم استخدام تحليل in silico لتحديد معظم المسارات المفترضة المسببه لحدوث وتطور السكري من النوع الثاني باستخدام أداة المعلوماتية الحيوية مثل GEO2R لتحديد جينات التعبير التفاضلي (DEG)، وبرنامج الويب Shiny Go 0.8 لتحديد مصطلحات (GO). وموسوعة كيوتو لمسارات الجينات والجينوم (KEGG)، وقاعدة بيانات STRING لتحديد تفاعل بروتين البروتين، وبرنامج Cytoscape لتصور هذا التفاعل وتحديد الجينات المحورية. أظهرت النتائج أن الجينات المحورية المسببة لمرض T2DM هي محول الإشارة ومنشط النسخ 3 (Stat3)، والأقراص المتجانسة الكبيرة 4 (Dlg4)، كارنيتين بالميتويل ترانسفيراز 1 (Cpt1a)، ألدهيد ديهيدروجينيز 1 فرد من العائلة)1Aldh1a1 (A، Lgals3 (galectin 3 بالإضافة إلى ذلك، فإن المسار الأكثر مشاركة هو مسار إشارات مستقبلات البيروكسيسوم المنشط (PPAR). أخيرًا، يمكننا تعديل تقدم داء السكري من خلال استهداف مسار STAT3 ومسار إشارات PPAR.