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Bioinformatics analysis to reveal the key genes related to obstructive sleep apnea

Xiandong Gu[1] · Wei Yang[1] · Xuming Luo[1] · Xiongbiao Wang[1] · Jihong Tang[1] · Zhuying Cai[1]

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Abstract

Purpose Obstructive sleep apnea (OSA) is induced by obstruction of the upper airway, which can raise multiple health risks. This study is designed to reveal the key genes involved in OSA.

Methods GSE38792 was extracted from Gene Expression Omnibus database, including ten visceral adipose tissues from OSA patients and eight visceral adipose tissues from normal controls. Differential expression analysis was conducted using limma package, and then the functions of the differentially expressed genes (DEGs) were analyzed using DAVID database, followed by protein-protein interaction (PPI) network, and integrated regulatory network analysis was performed using Cytoscape software.

Results A total of 368 DEGs (176 upregulated and 192 downregulated) were identified in OSA samples. Epstein-Barr virus infection (involving *IL10RB*, *MAPK9*, and *MAPK10*) and olfactory transduction were the main pathways separately enriched for the upregulated genes and the downregulated genes. After the PPI network was built, the top ten network nodes (such as TXN) were selected according to node degrees. Two significant PPI network modules were identified. Moreover, the integrated regulatory network was constructed.

Conclusion *IL10RB*, *MAPK9*, *MAPK10*, and *TXN* might function in the pathogenesis of OSA.

Keywords Obstructive sleep apnea · Differentially expressed genes · Enrichment analysis · Protein-protein interaction network · Integrated regulatory network

Introduction

As the most common form of sleep apnea, obstructive sleep apnea (OSA) is induced by obstruction of the upper airway [1]. OSA is characterized by loud snoring, restless sleep, and daytime sleepiness, which is diagnosed based on medical history and polysomnography tests [2]. The improvement measures for OSA patients include avoiding drugs relaxing the central nervous system, mandibular advancement devices, quitting alcohol and tobacco, weight loss, physical training, and continuous positive airway pressure (CPAP) [3–5]. OSA can raise multiple health risks such as aortic and cardiovascular diseases [6], stroke [7], high blood pressure [8, 9], clinical depression [10], diabetes [11], weight gain, and obesity [12]. The daytime sleepiness induced by OSA influences 2–5% of women and 3–7% of men, and OSA is more common in middle-aged males [13]. Therefore, investigating the mechanisms of OSA is important for improving the patients' life quality.

Intermittent hypoxia induces the overexpression of 5-lipoxygenase-activating protein (*FLAP*) in polymorphonuclear cells, indicating that *FLAP* may promote early vascular remodeling and serve as a promising therapeutic target for cardiovascular disease in OSA patients [14]. Nuclear factor κB (*NF-κB*) activation has a positive correlation with apnea severity, which may link OSA with cardiovascular disease and systemic inflammation [15, 16]. Serum vascular endothelial growth factor (VEGF) is increased in OSA patients with severe hypoxia and correlated with nocturnal oxygen desaturation, which may contribute to counterbalancing the occurrence of cardiovascular disease in OSA patients [17]. NADPH oxidase functions in maintaining hypersomnolence and oxidative and proinflammatory responses in OSA, suggesting that inhibiting NADPH oxidase may be an approach for restraining oxidation-mediated morbidities in patients with

Xiandong Gu and Wei Yang are co-first authors.

✉ Zhuying Cai
czy224cai@yeah.net

[1] Department of Respiratory Medicine, Putuo Hospital, Shanghai University of Traditional Chinese Medicine, No.164, LanXi Road, Shanghai 200063, China

the disease [18]. Although these studies have reported the genes related to OSA, the pathogenesis of the disease have not been thoroughly revealed.

In 2013, Gharib et al. evaluated the influences of OSA on the transcription activities of adipocytes through pathway-focused analyses, finding that OSA is related to the gene expression changes in visceral fat and several key pathways may promote the metabolic dysregulation [19]. Nevertheless, Gharib et al. [19] have not further explored the key genes implicated in OSA. Using the data deposited by Gharib et al. [19], comprehensive bioinformatics analyses were conducted to fully reveal the mechanisms of OSA.

Materials and methods

Microarray data

The expression profile of GSE38792 was extracted from Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) database. GSE38792, which was based on the platform of GPL6244 [HuGene-1_0-st] Affymetrix Human Gene 1.0 ST Array [transcript (gene) version], included ten visceral adipose tissues from OSA patients and eight visceral adipose tissues from normal controls. The patients were from University Hospitals Case Medical Center in Cleveland, Ohio. Visceral adipose tissues were isolated from the omentum during ventral hernia repair surgery. The samples were washed with PBS, minced, frozen in liquid nitrogen, and finally kept at − 80 °C. Gharib et al. [19] uploaded GSE38792, whose study were approved by their institutional review board. All subjects signed informed consent.

Data preprocessing and identification of differentially expressed genes

Using the R package Oligo [20] (version 1.34.0, http://bioconductor.org/help/search/index.html?q=oligo/), background correction of expression values and data normalization were conducted for the raw data. Subsequently,

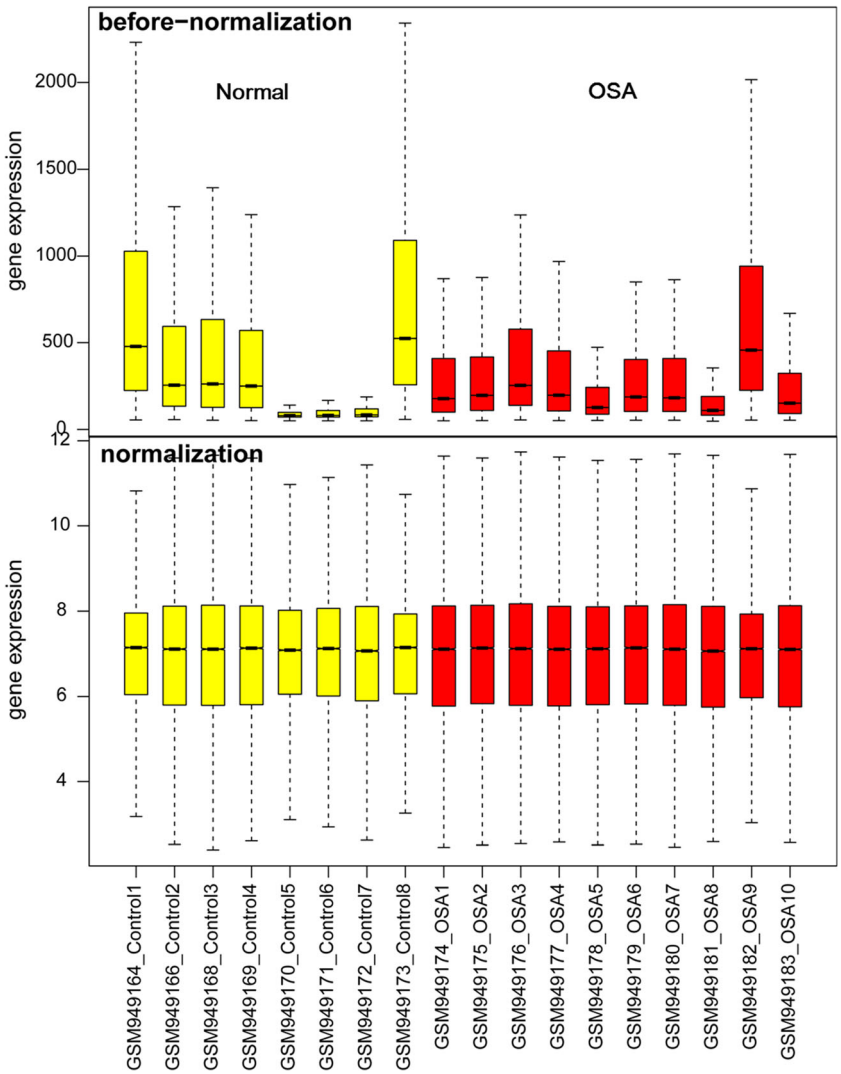

Fig. 1 The distribution diagrams of gene expression values before and after normalization. Red and yellow represent obstructive sleep apnea (OSA) samples and normal samples, respectively

probes were annotated based on the platform annotation files. The probes without matching gene symbols were removed. For different probe mapping to the same gene, the mean value of the probes was taken as the final expression value of the gene. Then, the Linear Models for Microarray Analysis (limma; version 3.10.3; http://www.bioconductor.org/packages/release/bioc/html/limma.html) package [21] in R was applied for differentially expression analysis. The genes with p value < 0.01 were deemed to be differentially expressed genes (DEGs).

Functional and pathway enrichment analysis

The Database for Annotation, Visualization, and Integrated Discovery (DAVID; version 6.8; https://david-d.ncifcrf.gov/) is a web-accessible database that can be utilized for the functional annotation of genes or proteins [22]. Based on DAVID database, Gene Ontology (GO) functional [23] and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway [24] enrichment analyses were carried out for the DEGs. The p value < 0.05 and the count of involved genes ≥ 2 were significant thresholds.

Protein-protein interaction network and module analyses

The Search Tool for the Retrieval of Interacting Genes (STRING; version 10.0; http://string-db.org/) database includes protein-protein interactions (PPIs) related to more than 1100 organisms [25]. Combined with STRING database (combined score > 0.4) [25], PPIs among the DEGs were analyzed. Then, a PPI network was built using Cytoscape software (version 3.2.0, http://www.cytoscape.org) [26]. To screen the key nodes, topology analysis was conducted for network nodes using the CytoNCA plug-in [27] (version 2.1.6, http://apps.cytoscape.org/apps/cytonca) in Cytoscape software. Furthermore, the MCODE plug-in [28] (version1.4.2, http://apps.cytoscape.org/apps/MCODE) in Cytoscape software was utilized for identifying the significant network modules. The score ≥ 4 was set as the threshold.

Integrated regulatory network analysis

Using the iRegulon plug-in [29] (version 1.3, http://apps.cytoscape.org/apps/iRegulon) in Cytoscape software, TF-target pairs among the PPI network were predicted. The TF-target pairs with normalized enrichment score (NES) > 4 were selected. Using the overrepresentation enrichment analysis (ORA) method in WebGestalt GAST tool [8] (http://www.webgestalt.org/option.php), miRNA-target pairs were predicted for the PPI network nodes. The number of enriched genes ≥ 2 and p value < 0.05 were defined as thresholds. Finally, the TF-target and miRNA-target pairs were integrated into a regulatory network using Cytoscape software [26].

Results

Identification of DEGs

The median values after data preprocessing were at the same level, indicating a good effect (Fig. 1). There were 368 DEGs

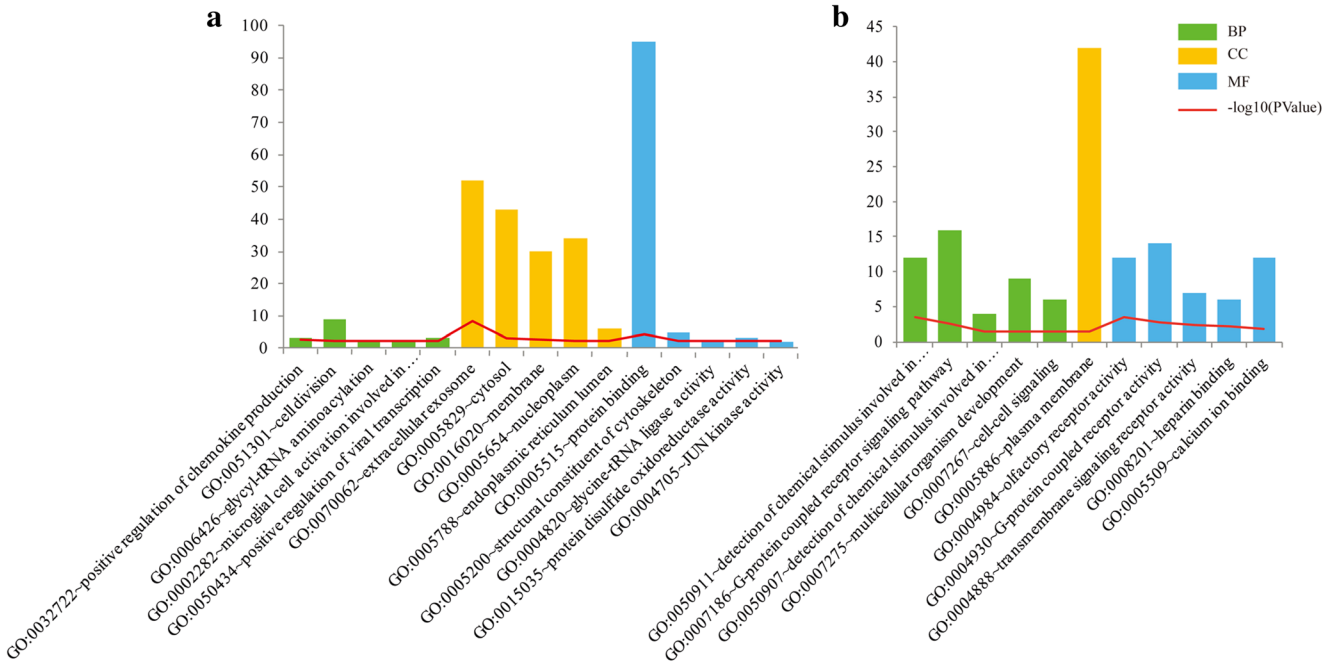

Fig. 2 The top 5 GO (gene ontology)_biological process (BP), GO_cellular component (CC), and GO_molecule function (MF) terms separately enriched for the upregulated genes (**a**) and the downregulated genes (**b**)

Table 1 The pathways enriched for the upregulated genes and the downregulated genes

Category	Pathway ID	Pathway name	Count	*p* value	Genes
Up	hsa05169	Epstein-Barr virus infection	10	8.01E-05	*POLR2K*, *IL10RB*, *RAN*, *SHFM1*, *MAPK9*, *RB1*, *MAPK10*, *EIF2AK2*, *YWHAE*, *GTF2B*
	hsa04141	Protein processing in endoplasmic reticulum	7	5.70E-03	*UBE2G1*, *DNAJC10*, *PDIA6*, *MAPK9*, *MAPK10*, *EIF2AK2*, *LMAN1*
	hsa05164	Influenza A	7	6.55E-03	*IRAK4*, *HLA-DRB5*, *TLR3*, *MAPK9*, *IL33*, *MAPK10*, *EIF2AK2*
	hsa05145	Toxoplasmosis	5	2.72E-02	*IRAK4*, *IL10RB*, *HLA-DRB5*, *MAPK9*, *MAPK10*
	hsa05152	Tuberculosis	6	2.80E-02	*IRAK4*, *IL10RB*, *HLA-DRB5*, *MAPK9*, *NFYB*, *MAPK10*
	hsa05160	Hepatitis C	5	3.96E-02	*TLR3*, *MAPK9*, *MAPK10*, *EIF2AK2*, *PPP2R2A*
Down	hsa04740	Olfactory transduction	11	1.55E-04	*OR13C3*, *OR4C15*, *OR52I2*, *OR10X1*, *OR1L6*, *OR4C11*, *OR11A1*, *OR9A2*, *OR1L1*, *OR2M3*, *OR2M5*

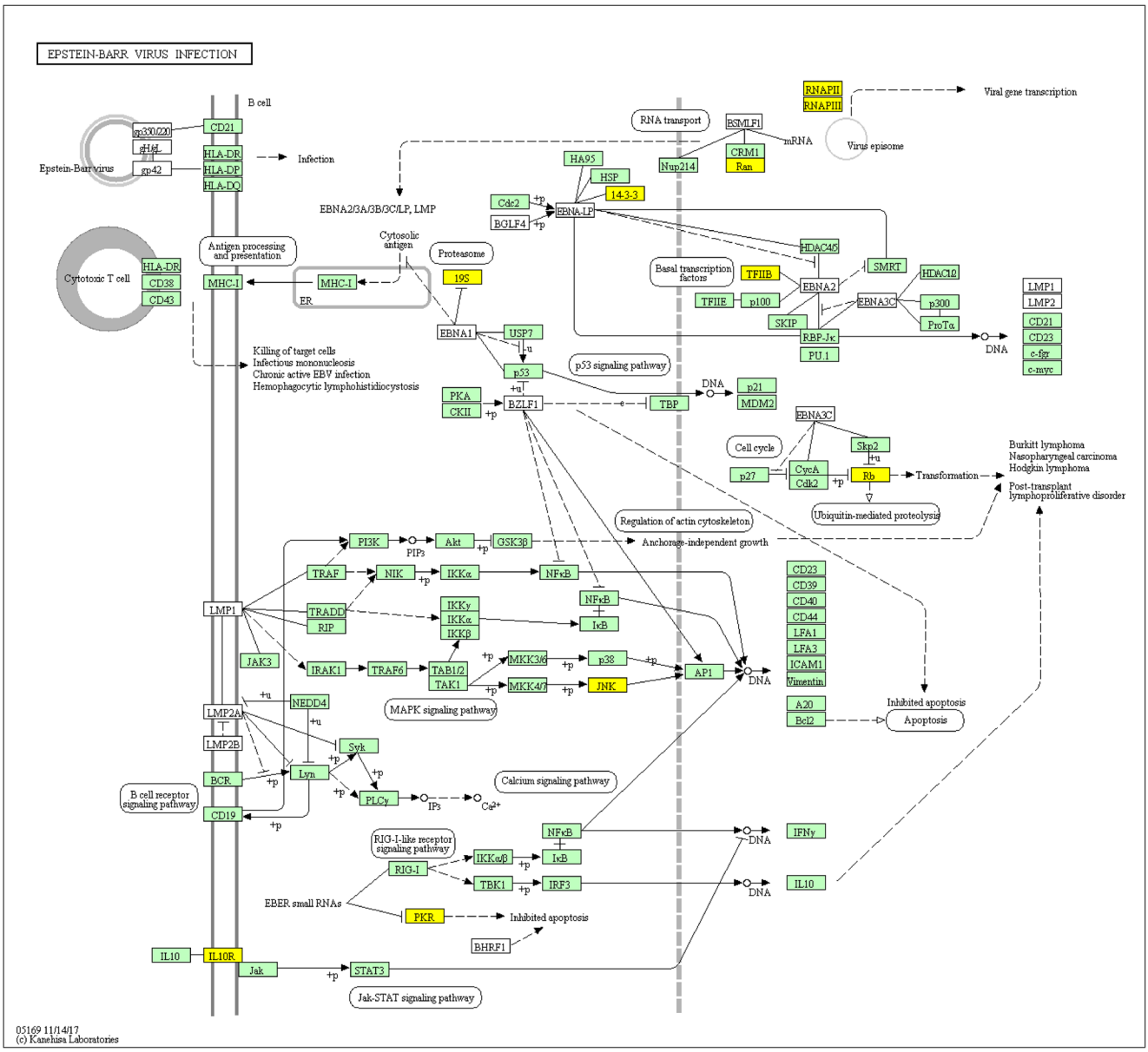

Fig. 3 The most significant pathway enriched for the upregulated genes. The highlights were enriched genes

(176 upregulated and 192 downregulated) in OSA samples in relative to normal samples.

Functional and pathway enrichment analysis

As multiple GO terms in biological process (BP), cellular component (CC), and molecule function (MF) categories were enriched for the DEGs, only the top five terms (according to *p* values) were presented (Fig. 2). The upregulated genes were mainly implicated in positive regulation of chemokine production (GO_BP, *p* value = 9.25E−03), extracellular exosome (GO_CC, *p* value = 2.09E−08), and protein binding (GO_MF, *p* value = 1.97E−04). Besides, the downregulated genes were mainly enriched in detection of chemical stimulus involved in sensory perception of smell (GO_BP, *p* value = 2.91E−04), plasma membrane (GO_CC, *p* value = 3.53E−02), and olfactory receptor activity (GO_MF, *p* value = 3.37E−04).

The upregulated genes were enriched in six pathways (Table 1), and the top 1 pathway was Epstein-Barr virus infection (*p* value = 8.01E−05; involving interleukin 10 receptor, beta (*IL10RB*), mitogen-activated protein kinase 9 (*MAPK9*), and mitogen-activated protein kinase 10 (*MAPK10*)) (Fig. 3). Meanwhile, only one pathway (olfactory transduction, *p* value = 1.55E−04) was enriched for the downregulated genes (Table 1, Fig. 4).

Network analysis

The PPI network for the DEGs were built, which had 160 nodes and 258 edges (Fig. 5). Subsequently, 2 significant

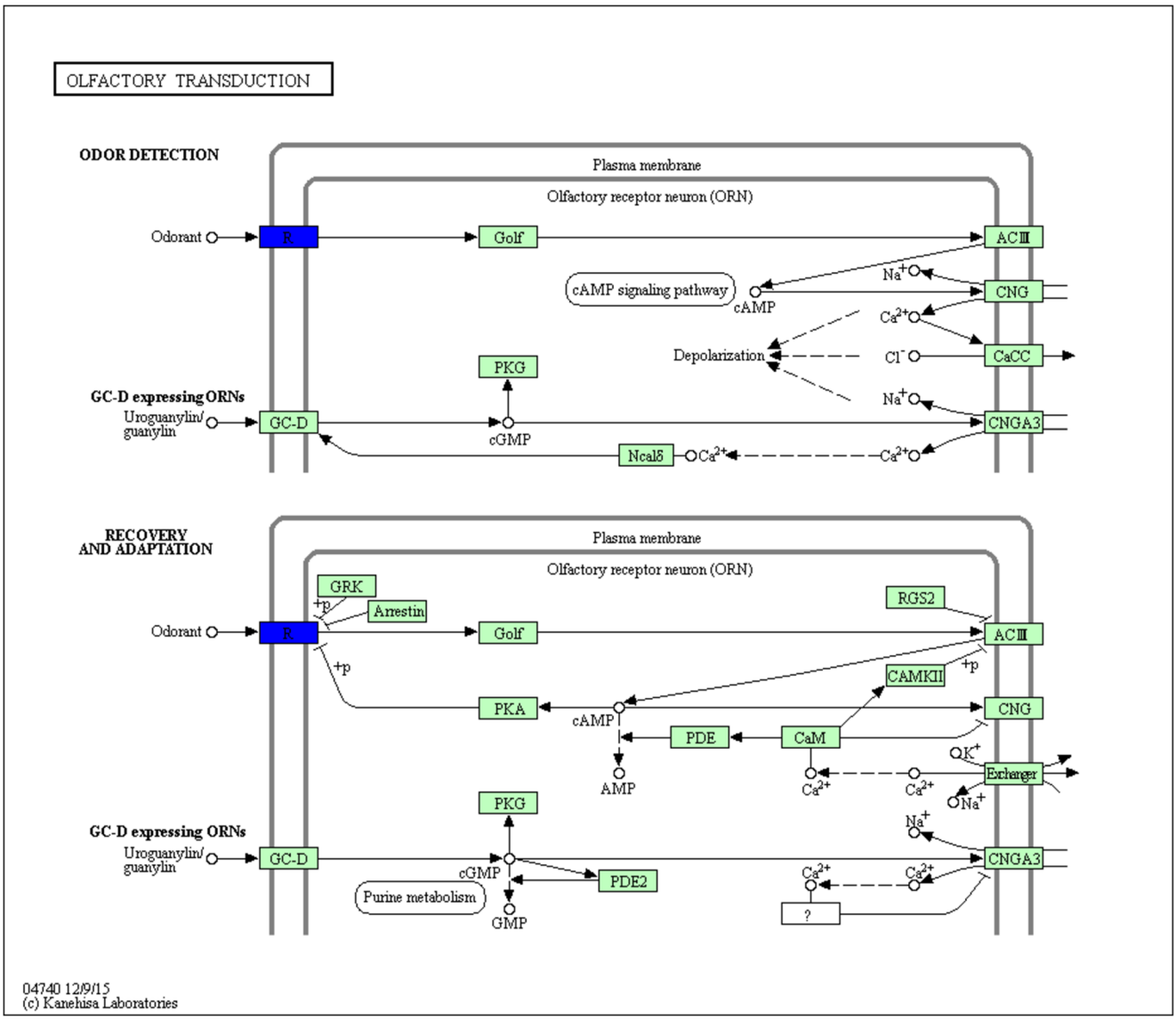

Fig. 4 The pathway enriched for the downregulated genes. The highlights were enriched genes in the pathways

network modules (module a: score = 4.6, 11 nodes and 23 edges; module b: score = 4, 10 nodes and 18 edges) were identified (Fig. 5). The top 10 network nodes (according to degrees; such as thioredoxin (TXN)) and the module nodes were listed in Table 2. A total of three TFs and eight miRNAs were predicted, involving 156 relation pairs. Afterwards, the integrated regulatory network was built and presented in Fig. 6.

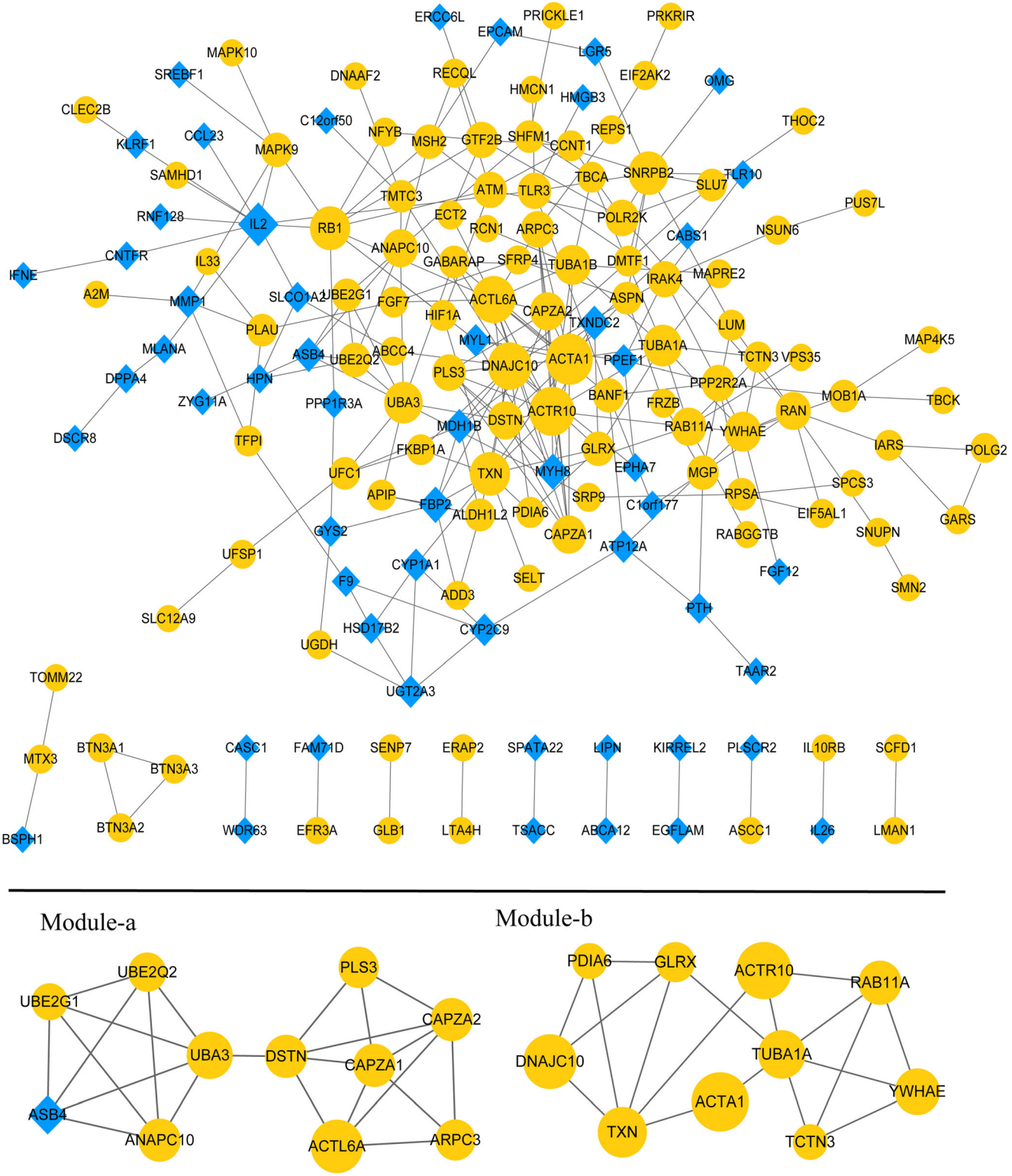

Fig. 5 The protein-protein interaction network (PPI) for the differentially expressed genes, as well as the modules a and b identified from the PPI network. Yellow circles and blue diamonds represent upregulated genes and downregulated genes, respectively

Table 2 The top 10 network nodes and the module nodes

Interaction network			Module a			Module b		
Nodes	Description	Degree	Nodes	Description	Degree	Nodes	Description	Degree
ACTA1	Up	14	ACTL6A	Up	12	ACTA1	Up	14
ACTR10	Up	13	UBA3	Up	9	ACTR10	Up	13
ACTL6A	Up	12	ANAPC10	Up	7	DNAJC10	Up	12
DNAJC10	Up	12	CAPZA1	Up	7	TXN	Up	10
IL2	Down	10	CAPZA2	Up	7	TUBA1A	Up	9
TXN	Up	10	DSTN	Up	7	YWHAE	Up	8
SNRPB2	Up	10	ARPC3	Up	6	RAB11A	Up	7
RB1	Up	10	PLS3	Up	6	GLRX	Up	5
TUBA1A	Up	9	ASB4	Down	5	TCTN3	Up	3
UBA3	Up	9	UBE2Q2	Up	5	PDIA6	Up	3
			UBE2G1	Up	4			

Discussion

In this study, 368 DEGs (176 upregulated and 192 downregulated) in OSA samples were identified. There were multiple GO terms enriched for the DEGs. Pathway enrichment showed that the upregulated genes and the downregulated genes separately were mainly enriched in Epstein-Barr virus infection (involving *IL10RB*, *MAPK9*, and *MAPK10*) and

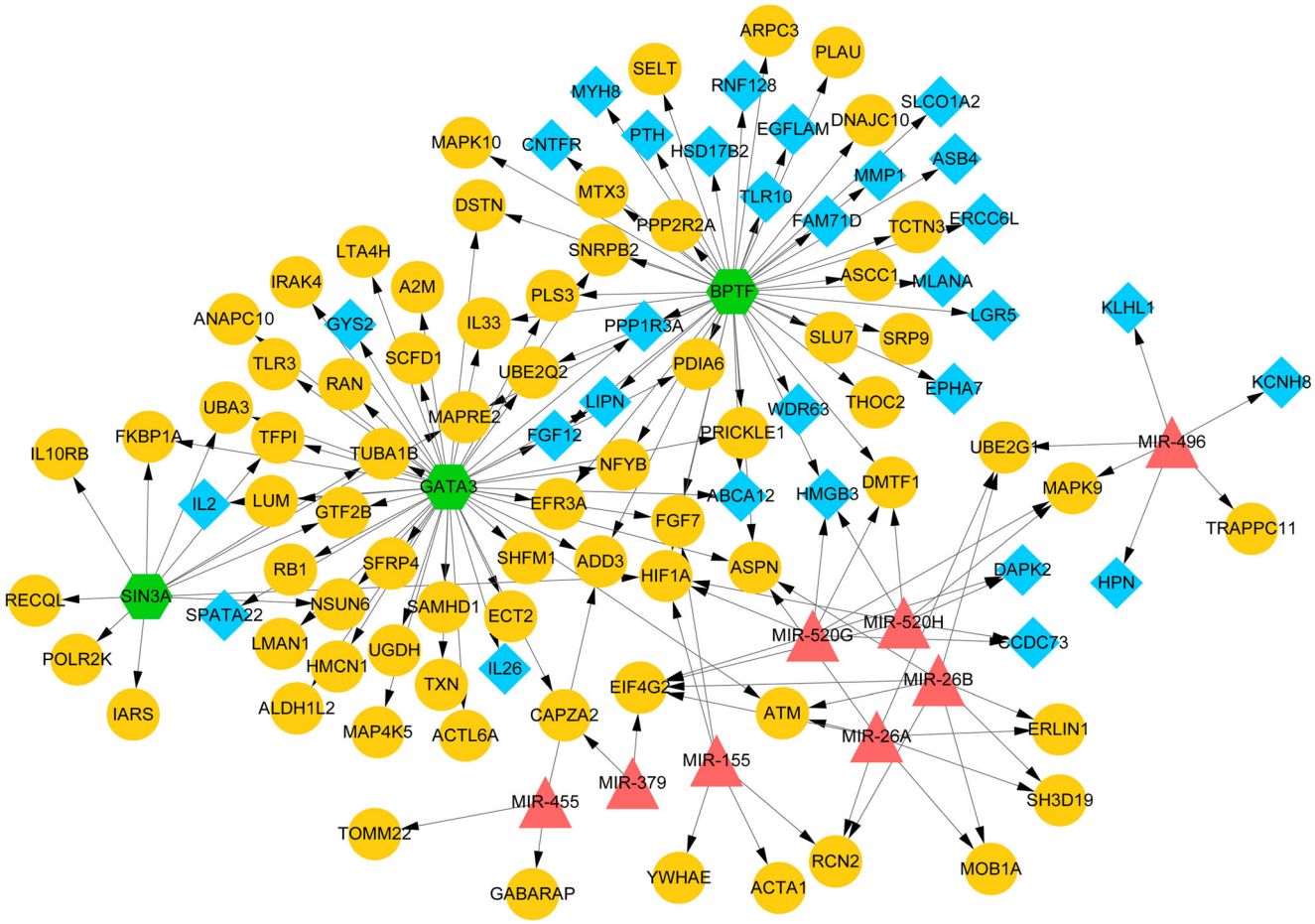

Fig. 6 The integrated regulatory network. Yellow circles, blue diamonds, green hexagons, and red triangles represent upregulated genes, downregulated genes, transcription factors, and microRNAs, respectively

olfactory transduction. After the PPI network was built, 2 significant network modules were identified. In addition, the integrated regulatory network was constructed.

The promoter polymorphisms in *IL-10* may result in the changes of inflammatory cascade and thus promote obstructive sleep apnea syndrome (OSAS) [30, 31]. Serum levels of IL-10 were significantly reduced in obstructive sleep apnea hypopnea syndrome (OSAHS) patients compared with normal controls, indicating that *IL-10* may be correlated with intermittent hypoxia during sleep [32]. Tumor necrosis factor-2 (TNF-2)/IL-10 ratio is significantly higher in OSAHS patients and increases correlate with the severity of the disease, suggesting that TNF-2/IL-10 ratio may be of great usefulness for the management and severity monitoring of OSAHS patients [33]. OSA is correlated with the occurrence of insulin resistance in subjects with morbidly obese (MO), and IL-10 serum level is significantly decreased in MO individuals with severe OSA [34]. Therefore, *IL10RB* might function in OSA through participating in Epstein-Barr virus infection.

Grape seed proanthocyanidin enhances learning and memory function following OSA hypoxia via suppressing phosphorylated *p38MAPk* and *IL-1Beta* in a rat OSA model [35]. Chronic intermittent hypoxia (CIH) interferes with insulin secretion and induces inflammation in pancreatic tissue through the MAPK signaling pathway, which may be important for type 2 diabetes mellitus (T2DM) and OSA therapy [36, 37]. OSA is related to nonalcoholic fatty liver disease and leads to CIH during night, and CIH can result in liver fibrosis through toll-like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MyD88)/MAPK/NF-κB signaling pathways [38]. This suggests that *MAPK9* and *MAPK10* involved in Epstein-Barr virus infection might also play a role in the development of OSA.

The plasma level of TXN is upregulated in OSA patients, which may be a promising oxidative stress marker used for monitoring the therapeutic effect of nasal CPAP for the disease [39]. The protein disulphide reductase *TXN* plays a role in antioxidant defense, and its plasma level indicates the severity of OSA [40]. Oxidative stress is a typical trait of OSAHS, and TXN levels in untreated OSAHS patients is lower than that in treated OSAHS patients [41]. *TXN*, superoxide dismutase, malondialdehyde, and reduced iron are the most common oxidative stress markers, which may contribute to evaluating and monitoring the patients with OSAS [42]. TXN was among the top 10 PPI network nodes, indicating that *TXN* might be involved in the pathogenesis of OSA.

In conclusion, 368 DEGs in OSA samples were identified via bioinformatics analysis. *IL10RB*, *MAPK9*, *MAPK10*, and *TXN* might be key genes acting in OSA. However, more experimental studies should be carried out to confirm the roles of these genes in OSA.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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