论著·基础研究

糖尿病相关 hsa-miR-223-3p 靶基因预测及生物信息学分析

余梦娜[1]，杨　标[2]，仰礼真[1]
1. 上海交通大学医学院附属第九人民医院内分泌科，上海 200011；2. 上海交通大学医学院附属第九人民医院神经外科，上海 200011

[摘要] **目的**·分析人类 miR-223-3p（hsa-miR-223-3p）的靶基因及其参与的生物学过程，并寻找与糖尿病相关的生物标志物。**方法**·利用 starBase 数据库筛选 hsa-miR-223-3p 靶基因，并对其行基因本体数据库（Gene Ontology，GO）富集分析、京都基因与基因组百科全书（Kyoto Encyclopedia of Genes and Genome，KEGG）和 Reactome 通路分析。通过构建蛋白 - 蛋白相互作用（protein-protein interaction，PPI）网络获得中枢基因，筛选最有意义的模块，并利用 Venn 图对糖尿病相关的中枢基因进行分析。**结果**·共筛选出 870 个 hsa-miR-223-3p 靶基因。GO、KEGG 和 Reactome 富集分析显示，靶基因主要与 RNA 聚合酶Ⅱ启动子的调节、细胞对胰岛素刺激的反应、RNA 结合等相关，且主要富集于胰岛素分泌、泛素介导的蛋白水解、雌激素依赖型基因表达等通路。PPI 网络共得 31 个中枢基因，且中枢基因 *PRKACB* 参与胰岛素分泌通路；共筛选出 3 个最有意义的基因模块，其中模块 1 参与泛素介导的蛋白水解作用，模块 2 参与 RNA 转运和细胞周期，模块 3 参与内吞作用。**结论**·Hsa-miR-223-3p 可能通过靶基因参与多种生物学过程，中枢基因 *PRKACB* 或可为糖尿病发生机制的探索提供帮助。

[关键词] 糖尿病；hsa-miR-223-3p；生物信息学；模块化；基因
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Prediction and bioinformatics analysis of hsa-miR-223-3p target genes related to diabetes mellitus

YU Meng-na[1], YANG Biao[2], YANG Li-zhen[1]
1. Department of Endocrinology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China; 2. Department of Neurosurgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China

[Abstract] Objective·To analyze target genes of human miR-223-3p (hsa-miR-223-3p) and their biological processes, and explore biomarkers related to diabetes mellitus (DM). **Methods**·starBase database was used to screen hsa-miR-223-3p target genes, and Gene Ontology (GO) enrichment analysis, Kyoto Encyclopedia of Genes and Genome (KEGG) and Reactome pathway analysis were performed. Hub genes were obtained by constructing protein-protein interaction (PPI) network, and the most significant modules were screened out. The hub genes related to DM were analyzed by Venn diagram. **Results**·A total of 870 hsa-miR-223-3p target genes were screened out. The GO enrichment analysis, KEGG and Reactome pathway analysis showed that the target genes were mainly related to the regulation of RNA polymerase Ⅱ promoter, cell response to insulin stimulation, RNA binding, etc, and were mainly enriched in insulin secretion, ubiquitin-mediated proteolysis and estrogen-dependent gene expression. There were 31 hub genes in PPI network, and hub gene *PRKACB* participated in insulin secretion pathway. Top 3 modules were identified as follows: module 1 was involved in ubiquitin-mediated proteolysis, module 2 was involved in RNA transport and cell cycle, and module 3 was involved in endocytosis. **Conclusion**·Hsa-miR-223-3p may participate in a variety of biological processes through target genes, and the hub gene *PRKACB* may provide assistance for exploring the pathogenesis of DM.

[Key words] diabetes mellitus (DM); hsa-miR-223-3p; bioinformatics; module; gene

糖尿病（diabetes mellitus，DM）是一种以高血糖为特征的常见代谢性疾病。据统计 2015 年全球 DM 患者已超过 4.15 亿，预计 2030 年将达 5.52 亿[1]。DM 的发生过程受多种因素的影响，包括 DM 病程、肥胖、遗传等。若未能得到及时控制，患者将出现糖尿病性视网膜病变、肾病、心血管系统疾病等并发症[2-3]。因此，探究 DM 的发生机制、优化其治疗策略对控制 DM 病情进展十分必要。

微小 RNA（microRNA，miRNA）是一种高度保守的非编码小 RNA，其可通过识别、特异性结合信使 RNA（messenger RNA，mRNA）的 3′非翻译区（3′-untranslated region，3′-UTR），调控 mRNA 翻译。研究[4]显示，miRNA 参与了多种生物学过程的调控，包括细胞分化、增殖、凋亡，血管生成以及细胞周期等。有研究[5-6]发现 hsa-miR-223 在 DM 患者中的表达水平显著低于健康人群，尤其是外周单个核细胞中，继而推测 hsa-miR-223 可能是 DM 发生与发展过程中的潜在生物学靶标。本文拟通过生

[作者简介] 余梦娜（1992—），女，硕士生；电子信箱：853093124@qq.com。
[通信作者] 仰礼真，电子信箱：dryanginsh@yahoo.com。
[Corresponding Author] YANG Li-zhen, E-mail: dryanginsh@yahoo.com.

物信息学的方法预测 DM 相关 hsa-miR-223-3p 的靶基因，并寻找与 DM 有关的生物标志物，以期为临床诊疗中分子生物学靶点的选择提供可靠的理论依据。

1 材料和方法

1.1 靶基因集获取

以“(miR-223-3p) AND human disease”为检索词，使用 PubMed（http://www.ncbi.nlm.nih.gov/pubmed/）数据库对已发表的 hsa-miR-223-3p 相关文献进行检索，并发现该 miRNA 在多种疾病中发挥作用，故将其作为研究对象。本研究将 hsa-miR-223-3p 提交至 starBase（version 2.0；http://starbase.sysu. edu.cn/）靶基因预测数据库的 miRNA-mRNA 这一导航栏中进行预测，筛选条件为：Program ⩾ 2、CLIP-Data ⩾ 0、low stringency。去除重复 mRNA 之后，得到 hsa-miR-223-3p 的靶基因集。

1.2 功能富集分析和信号通路分析

为研究 hsa-miR-223-3p 及其靶基因潜在的生物功能及信号通路，将已获得的靶基因上传至 DAVID（database for annotation，visualization and integrated discovery）（https://david.ncifcrf.gov/）数据库行基因本体数据库（Gene Ontology，GO）功能分析和京都基因与基因组百科全书（Kyoto Encyclopedia of Genes and Genome，KEGG）通路分析。同时，使用 Reactome（https://www.reactome.org/）数据库对靶基因进行通路研究。随后，用 R 语言的 GOplot 包对靶基因功能结果进行可视化绘图。其中，GO 功能分析包括生物学过程（biological process，BP）、分子功能（molecular function，MF）和细胞组成成分（cell component，CC）。以 $P<0.05$ 表示差异具有统计学意义。

1.3 蛋白 - 蛋白相互作用网络的构建和模型的选择

为鉴别中枢基因并筛选模型，将靶基因集上传至 STRING（version 10.5；http://www.string-db.org/）数据库进行在线分析，建立蛋白 - 蛋白相互作用（protein- protein interaction，PPI）网络[7]，并通过 Cytoscape 软件（version 3.5.1；www.cytoscape.org）及 Cytohubba 插件对 PPI 网络进行绘制。Cytohubba 插件共包含 11 种分析参数，本研究以连接度（Degree）作为参数标准，对 PPI 网络中的区域进行连接度分析，筛选排名前 30 位的中枢基因。同时，使用 MCODE 插件筛选评分排名前 3 位的子模块，实现聚类结果的可视化。随后，通过 DAVID 数据库对模块中的中枢基因进行 KEGG 通路分析，检验其通路富集情况。

1.4 DM 相关中枢基因的筛选

为进一步缩小 hsa-miR-223-3p 靶基因的范围并提高预测的准确性，将 Cytohubba 插件获得的中枢基因集与经 KEGG 通路分析获得的胰岛素分泌通路涉及的基因集绘制 Venn 图，以筛选与 DM 相关的中枢基因。

2 结果

2.1 Hsa-miR-223-3p 相关文献检索及其靶基因筛选

经 PubMed 检索后发现，hsa-miR-223-3p 在结肠癌[8]、肾细胞癌（renal cell carcinoma，RCC）[9]、卵巢癌[10]、睾丸生殖细胞瘤（testicular germ cell tumor，TGCT）[11]等疾病中表达上调，在口腔鳞状细胞癌（oral squamous cell carcinoma，OSCC）[12]、骨肉瘤[13]等疾病中表达下调。此外，其还参与了肺动脉高压（pulmonary arterial hypertension，PAH）[14]、糖尿病肾病[15]、视网膜色素上皮炎性损伤[16]、脊髓损伤（spinal cord injury，SCI）[17]、低氧损伤[18]、骨关节炎[19]等过程（表 1）。随后，采用 starBase 靶基因预测数据库的 7 种算法中至少 2 种算法同时预测基因与 hsa-miR-223-3p 靶向结合，共得到 1 094 个 mRNA。去除重复基因后，最终获得 870 个靶基因。

表 1 Hsa-miR-223-3p 靶基因参与部分疾病的发生与发展
Tab 1 Hsa-miR-223-3p target genes involved in the occurrence and development of some diseases

Target gene	Disease	Biological effect	Hsa-miR-223-3p expression
ITGB3	PAH	Inhibit proliferation and decrease α-SMA expression in pulmonary arterial smooth muscle cells	Downregulated
SHOX2	OSCC	Inhibit the proliferation and migration, promote the apoptosis of OSCC cells	Downregulated
FBXW7	Diabetic retinopathy	Promote cell migration and proliferation	Upregulated
PRDM1	Colon cancer	Promote the proliferation, invasion and migration of colon cancer cells	Upregulated
NLRP3	Retinal pigment epithelial inflammatory damage	Inhibit the expression of NLRP3-related inflammatory cytokines	Downregulated

Continued Tab

Target gene	Disease	Biological effect	Hsa-miR-223-3p expression
RIP3	SCI	Inhibit H_2O_2-induced necroptosis	Downregulated
SLC4A4	RCC	Promote cell proliferation and metastasis	Upregulated
KLF15	Hypoxia-induced injury	Promote cardiomyocyte apoptosis and oxidative stress	Upregulated
CDH6	Human osteosarcoma	Inhibit cell invasion, migration, growth, and proliferation	Downregulated
SOX11	Ovarian cancer	Promote ovarian cancer cell proliferation, migration and invasion	Upregulated
SDF1	Osteoarthritis	Inhibit IL-1β induced ECM degradation in chondrocytes	Downregulated
FBXW7	TGCT	Promote TGCT cells proliferation and inhibit cells apoptosis	Upregulated

Note: *ITGB3*—integrin subunit β 3; *SHOX2*—short stature homeobox 2; *FBXW7*—F-box and WD repeat domain containing 7; *PRDM1*—PR/SET domain 1; *NLRP3*—NLR family pyrin domain containing 3; *RIP3*—receptor interacting protein 3; *SLC4A4*—solute carrier family 4 member 4; *KLF15*—Kruppel like factor 15; *CDH6*—cadherin 6; *SOX11*—SRY-box transcription factor 11; *SDF1*—stromal cell-derived factor 1; α-SMA—α-smooth muscle actin; IL-1β—interleukin-1β; ECM—extracellular matrix.

2.2 Hsa-miR-223-3p 靶基因的 GO、KEGG 和 Reactome 分析

GO 功能分析显示，hsa-miR-223-3p 靶基因主要存在于胞浆和核浆中，显著富集于蛋白质结合、RNA 结合、连接酶活性等方面，参与 RNA 聚合酶Ⅱ启动子的调节、细胞对胰岛素刺激的反应、基因转录和翻译的调控等过程（图 1）。KEGG 通路分析显示，hsa-miR-223-3p 靶基因主要参与泛素介导的蛋白水解、癌症的转录失调、减数分裂、甲状腺激素信号传导、胰岛素分泌等通路（图 2）。Reactome 通路分析显示，hsa-miR-223-3p 靶基因主要富集在雌激素依赖型基因表达、人类免疫缺陷病毒蛋白 R（Vpr）介导的前嵌合复合体入核、来源于无内含子转录本的成熟 mRNA 的转运等生物学反应中，其中排名前 10 位的通路总结如表 2。

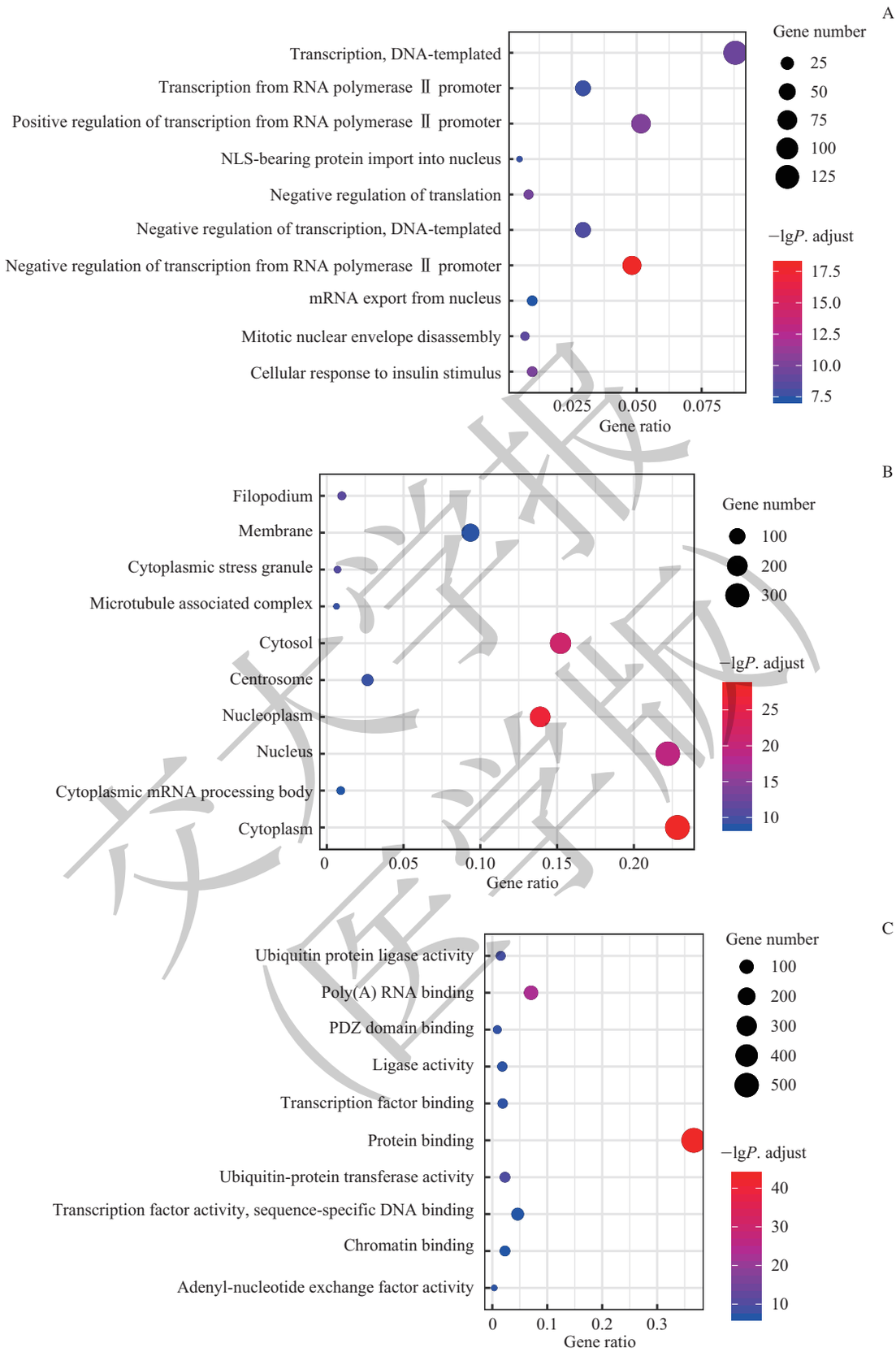
表 2 Hsa-miR-223-3p 靶基因富集排名前 10 位的通路
Tab 2 Top 10 pathways of hsa-miR-223-3p target genes enrichment

ID	Pathway name	Count	*P* value
R-HSA-9018519	Estrogen-dependent gene expression	17	6.77×10^{-4}
R-HSA-180910	Vpr-mediated nuclear import of PICs	9	1.24×10^{-3}
R-HSA-159231	Transport of mature mRNA derived from an intronless transcript	9	1.71×10^{-3}
R-HSA-8953750	Transcriptional regulation by E2F6	7	1.71×10^{-3}
R-HSA-168276	NS1 mediated effects on host pathways	9	1.71×10^{-3}
R-HSA-159227	Transport of the SLBP independent mature mRNA	8	1.93×10^{-3}
R-HSA-159234	Transport of mature mRNAs derived from intronless transcripts	9	2.00×10^{-3}
R-HSA-176033	Transport of mature mRNAs derived from intronless transcripts	9	2.00×10^{-3}
R-HSA-2122947	Interactions of Vpr with host cellular proteins	8	2.26×10^{-3}
R-HSA-159230	NOTCH1 intracellular domain regulates transcription	8	2.28×10^{-3}

Note: PIC—pre-integration complex; NS1—non-structural protein 1; SLBP—stem-loop binding protein; NOTCH1—Notch receptor 1.

2.3 Hsa-miR-223-3p 靶基因的 PPI 网络构建及模块分析

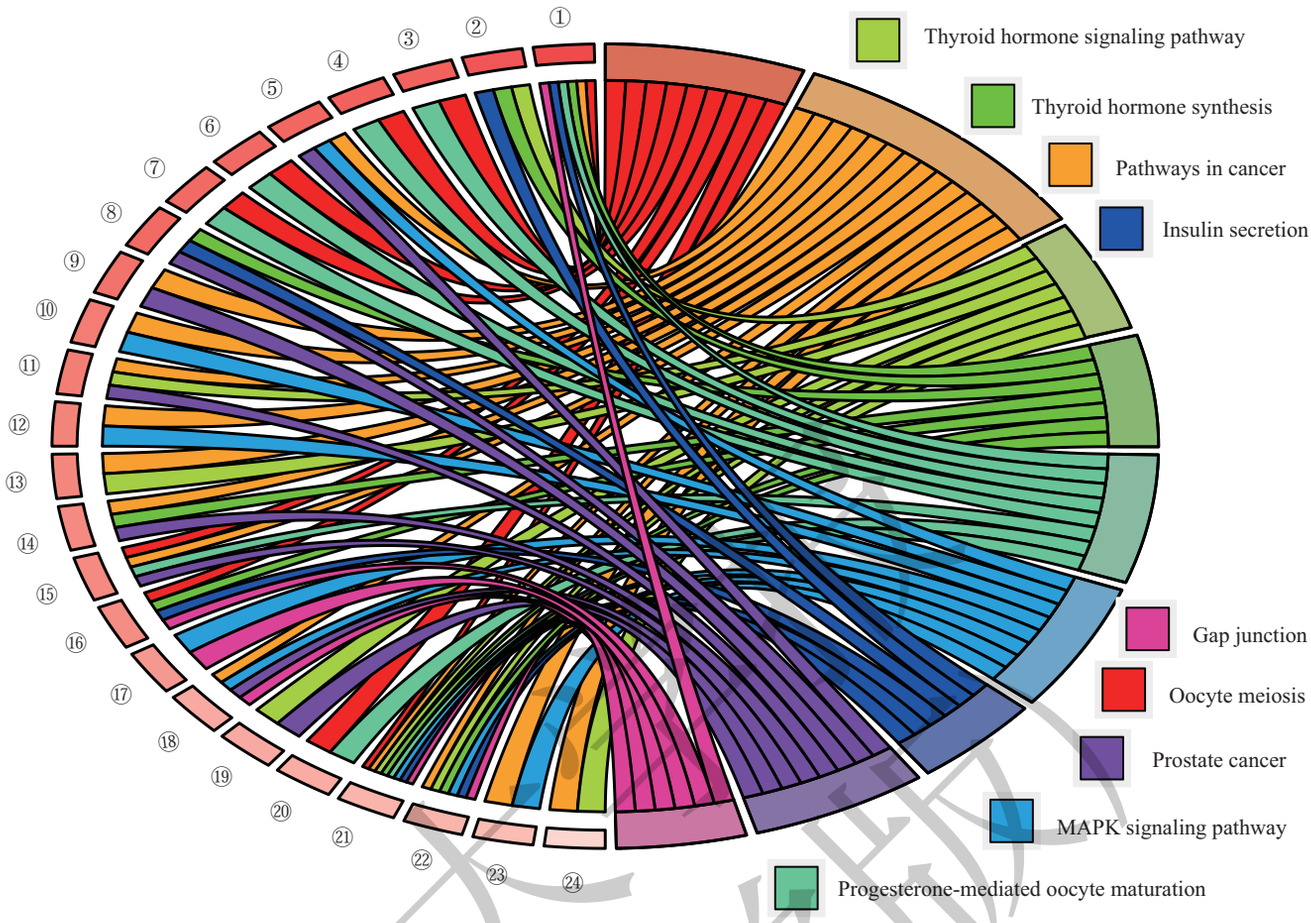
将预测得到的靶基因数据上传到 STRING 数据库中，获得靶基因对应的 PPI 网络。研究 [20] 显示，2 个或 2 个以上的蛋白质会通过非共价键形成蛋白复合体，且蛋白质之间的相互作用越多则该蛋白质越重要。利用 STRING 构建 PPI 网络后，将 PPI 评分 >0.9 作为阈值条件，通过 Cytohubba 插件筛选出连接度排名前 30 的节点。由于第 30 和第 31 个节点的连接度均为 21，故最终纳入连接度 ≥ 21 的 31 个节点为中枢基因。利用 MCODE 插件筛选出 PPI 中评分排名前 3 位的子模块（图 3），并通过 DAVID 数据库对模块中的中枢基因进行 KEGG 通路分析，结果显示模块 1 的靶基因主要富集于泛素介导的蛋白水解作用，模块 2 的靶基因主要参与 RNA 转运和细胞周期，模块 3 的靶基因主要参与内吞作用（表 3）。



Note: A. Biological process. B. Cell component. C. Molecular function. NLS—nuclear localization signal.

图 1 Hsa-miR-223-3p 靶基因的 GO 功能分析

Fig 1 GO function analysis of hsa-miR-223-3p target genes

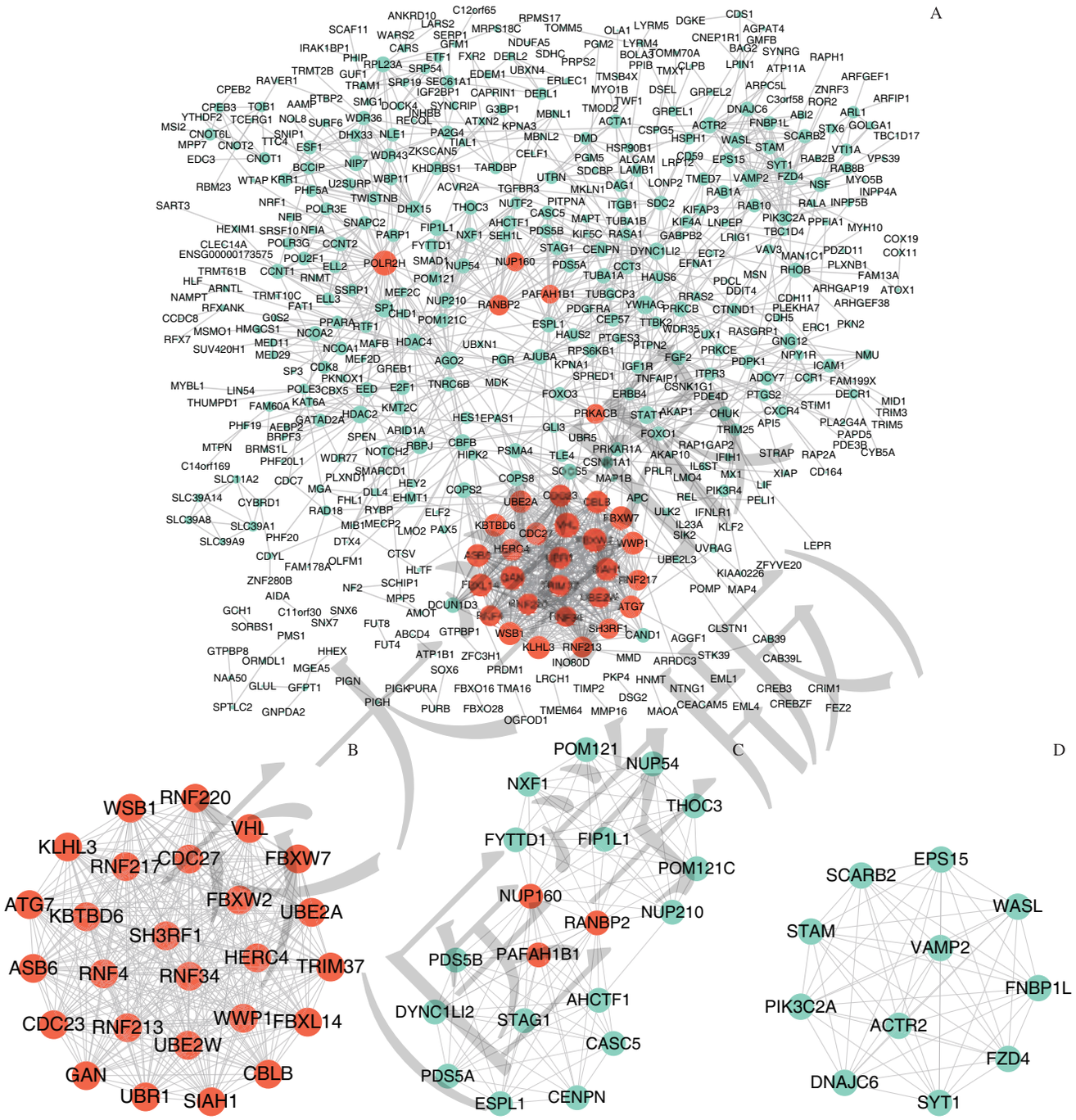


Note: ① *ADCY7*—adenylate cyclase 7; ② *ATP1B1*—ATPase Na^+/K^+ transporting subunit β 1; ③ *CDC23*—cell division cycle 23; ④ *CDC27*; ⑤ *CHUK*—conserved helix-loop-helix ubiquitous kinase; ⑥ *CPEB2*—cytoplasmic polyadenylation element binding protein 2; ⑦ *CPEB3*—cytoplasmic polyadenylation element binding protein 3; ⑧ *CREB3*—cAMP responsive element binding protein 3; ⑨ *E2F1*—E2F transcription factor 1; ⑩ *FGF2*—fibroblast growth factor 2; ⑪ *FOXO1*—forkhead box O1; ⑫ *GNG12*—G protein subunit γ 12; ⑬ *HDAC2*—histone deacetylase 2; ⑭ *HSP90B1*—heat shock protein 90 β family member 1; ⑮ *IGF1R*—insulin like growth factor 1 receptor; ⑯ *ITPR3*—inositol 1, 4, 5-trisphosphate receptor type 3; ⑰ *MAP3K2*—mitogen-activated protein kinase kinase kinase 2; ⑱ *PDGFRA*—platelet derived growth factor receptor α; ⑲ *PDPK1*—3-phosphoinositide dependent protein kinase 1; ⑳ *PGR*—progesterone receptor; ㉑ *PRKACB*—protein kinase cAMP-activated catalytic subunit β; ㉒ *PRKCB*—protein kinase C; ㉓ *RASGRP1*—RAS guanyl releasing protein 1; ㉔ *STAT1*—signal transducer and activator of transcription 1. MAPK—mitogen-activated protein kinase.

图 2 Hsa-miR-223-3p 靶基因的 KEGG 通路分析
Fig 2 KEGG pathway analysis of hsa-miR-223-3p target genes

表 3 排名前 3 位的子模块中中枢基因的 KEGG 通路分析
Tab 3 KEGG pathway analysis of hub genes in top 3 modules

Module	Pathway	Count	*P* value	Gene
Module 1	Ubiquitin mediated proteolysis	11	1.39×10^{-16}	*TRIM37, CBLB, UBE2A, FBXW7, VHL, WWP1, HERC4, CDC23, UBE2W, SIAH1, CDC27*
Module 2	RNA transport	5	1.42×10^{-4}	*POM121*, *NUP210*, *RANBP2*, *NUP54*, *NXF1*
	Cell cycle	2	3.00×10^{-2}	*ESPL1*, *STAG1*
Module 3	Endocytosis	4	2.00×10^{-3}	*EPS15*, *DNAJC6, STAM*, *WASL*



Note: A. PPI network. B. Module 1（score=26）. C. Module 2（score=11.11）. D. Module 3（score=11）. The circular nodes represent target genes. The edges/lines stand for the association between two nodes. The top 31 hub genes are highlighted with red circles. POLR2H—NA polymerase Ⅱ subunit H; GAN—gigaxonin; KLHL3—kelch like family member 3; WSB1—WD repeat and SOCS box containing 1; KBTBD6—kelch repeat and BTB domain containing 6; ASB6—ankyrin repeat and SOCS box containing 6; ATG7—autophagy related gene 7; FBXL14—F-box and leucine rich repeat protein 14; RNF213—ring finger protein 213; UBR1—ubiquitin protein ligase E3 component n-recognin 1; SH3RF1—SH3 domain containing ring finger 1; PAFAH1B1—platelet activating factor acetylhydrolase 1b regulatory subunit 1; RANBP2—RAN binding protein 2; NUP160—ucleoporin 160; UBE2A—ubiquitin conjugating enzyme E2A; VHL—von Hippel-Lindau tumor suppressor; TRIM37—tripartite motif containing 37; CBLB—Cbl proto-oncogene B; WWP1—WW domain containing E3 ubiquitin protein ligase 1; SIAH1—siah E3 ubiquitin protein ligase 1; HERC4—HECT and RLD domain containing E3 ubiquitin protein ligase 4; POM121—POM121 transmembrane nucleoporin; NXF1—nuclear RNA export factor 1; THOC3—THO complex 3; FYTTD1—forty-two-three domain containing 1; FIP1L1—factor interacting with PAPOLA and CPSF1; PDS5B—PDS5 cohesin associated factor B; DYNC1LI2—dynein cytoplasmic 1 light intermediate chain 2; AHCTF1—AT-hook containing transcription factor 1; STAG1—stromal antigen 1; CASC5—cancer susceptibility candidate 5; ESPL1—extra spindle pole bodies like 1; CENPN—centromere protein N; SCARB2—scavenger receptor class B member 2; EPS15—epidermal growth factor receptor pathway substrate 15; WASL—WASP like actin nucleation promoting factor; STAM—signal transducing adaptor molecule; VAMP2—vesicle associated membrane protein 2; FNBP1L—formin binding protein 1 like; PIK3C2A—phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 α; ACTR2—actin related protein 2; FZD4—frizzled class receptor 4; DNAJC6—DnaJ heat shock protein family（Hsp40）member C6; SYT1—synaptotagmin 1.

图 3 Hsa-miR-223-3p 靶基因的 PPI 网络及其模块

Fig 3 PPI network and its modules of hsa-miR-223-3p target genes

2.4 DM 相关中枢基因的获取

将 Cytohubba 插件获得的 31 个中枢基因集和 KEGG 分析获得的胰岛素分泌通路中的基因集数据制作 Venn 图，得到两者交集的靶基因为 *PRKACB*（图 4）。因此，我们预测在 DM 发病过程中，*PRKACB* 可能作为 hsa-miR-223-3p 的靶基因对胰岛素分泌通路发挥调控作用。

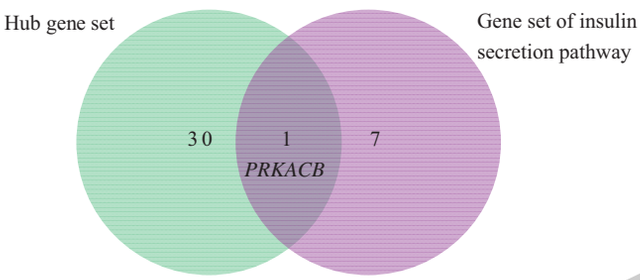


图 4 DM 相关中枢基因的筛选
Fig 4 Screening of DM-related hub genes

3 讨论

DM 分子机制的识别对靶向诊断和治疗十分重要。近年来有文献报道显示，miR-124a 和 miR-96 可以调节胰岛素分泌细胞相关蛋白的表达[21]；miR-133a 能诱导 DM 患者发生心肌肥大[22]；miR-223 和 miR-23a 在妊娠期 DM 中可上调表达，并被认为是早期妊娠期 DM 诊断的分子标志物[23]。上述结果表明，miRNA 不仅可作为疾病诊断、预后的分子指标，还可在临床疾病靶向基因治疗中发挥作用。既往研究显示 hsa-miR-223-3p 与多种疾病密切相关，因此我们猜测其可能参与了 DM 的发病过程。

本研究通过 starBase 靶基因预测库建立了一个包含 870 个 hsa-miR-223-3p 靶基因的数据集。这些靶基因主要存在于胞浆和核浆中，在 RNA 聚合酶Ⅱ启动子的调节、基因转录和翻译、细胞对胰岛素的应答等生物过程中发挥作用，同时还主要参与泛素介导的蛋白水解、减数分裂、甲状腺激素信号传导、胰岛素分泌等通路。利用 Cytohubba 插件筛选出连接度排名前 31 的中枢基因，依次为 *POLR2H*、*VHL*、*GAN*、*FBXW2*、*KLHL3*、*WSB1*、*FBXW7*、*KBTBD6*、*ASB6*、*ATG7*、*WWP1*、*FBXL14*、*CBLB*、*UBE2A*、*SIAH1*、*CDC23*、*CDC27*、*RNF213*、*HERC4*、*RNF4*、*UBR1*、*TRIM37*、*RNF220*、*RNF34*、*RNF217*、*UBE2W*、*SH3RF1*、*RANBP2*、*PRKACB*、*PAFAH1B1*、*NUP160*。目前，已有学者探索了其中部分中枢基因与血糖及 DM 间的联系。例如有研究[24]发现，*VHL* 是维持第一时相胰岛素分泌以及血糖稳态的调节因子之一。β 细胞中 *VHL* 的缺失会激活缺氧诱导因子（hypoxia-inducible factor，HIF），并使葡萄糖诱导的胰岛素分泌能力受损，从而导致葡萄糖耐受不良[25]。FBXW7 可直接与胎球蛋白 A 结合，诱导其泛素化和蛋白酶体降解，从而升高血糖，增加 DM 的发生风险[26]。ASB6 作为胰岛素受体信号复合体中的一分子，主要表达于脂肪细胞，其可通过使含 PH 和 SH2 结构域衔接蛋白（adapter protein with a pleckstrin homology and SH2 domain，APS）及其复合物泛素化，使 APS 失去传导胰岛素信号的作用[27]。在 DM 患者中，其 ATG7 的表达水平较低使得由 ATG7 介导的细胞自噬作用对胰岛素的反应性下降，从而导致血糖维持较高的状态[28]。WWP1 可能通过与腺苷酸活化蛋白激酶亚型 2（AMP-activated，α 2 catalytic subunit，AMPKa2）的相互作用下调其表达，参与胰岛素抵抗，导致血糖升高[29]。CBLB 通过影响 T 细胞激活途径参与 1 型 DM 等自身免疫疾病[30]。DM 中高密度脂蛋白可通过上调参与 HIF 稳定性的 SIAH1 等关键调节因子，修复 DM 中受损的血管新生能力[31]。然而在 31 个中枢基因中，仍有许多靶基因与 DM 的关系未被探索。如，*FBWXW2* 被证实能降解 β- 连环素，降低细胞迁移能力，且肺癌细胞的迁移和侵袭能力的提高均与 *FBWXW2* 表达下调密切相关[32]，但尚未有文献研究 *FBXW2* 在 DM 中的作用。

PRKACB 属于丝氨酸 / 苏氨酸蛋白激酶家族，是 cAMP 依赖性蛋白激酶 A（protein kinase A，PKA）的催化亚基之一[33]。PKA 可通过与 cAMP 的相互作用调节信号传导，参与细胞周期、细胞增殖和分化等细胞反应。目前，已有文献就 *PRKACB* 与 miRNAs 之间的相互作用进行报道。在急性髓性白血病中，miR-496 的表达被抑制，而其靶基因 *PRKACB* 的表达增加，从而促进细胞增殖并抑制细胞凋亡[34]；在肝癌中，miR-302-3p 通过抑制 PRKACB 蛋白的表达，抑制类固醇受体辅助活化因子（steroid receptor coactivator，Src）和 CREB（环磷腺苷反应元件结合蛋白）的磷酸化水平，从而抑制肿瘤细胞的增殖和迁移[35]；在阿尔茨海默病中，miR-200-3p 通过靶向 *PRKACB* 抑制 tau 蛋白的过磷酸化，发挥神经保护作用[33]；miR-200c 可直接作用于靶基因 *PRKACB*，通过抑制 cofilin 蛋白的磷酸化达到抑制癌细胞转移的效果[36]。同时，*PRKACB* 还可通过其他方式参与到人类疾病中，如在肝外胆管癌中发现 *PRKACB* 可与成纤维细胞生长因子受体（fibroblast growth factor receptor 2，*FGFR2*）发生基因融合[37]。但有关 *PRKACB* 与 DM 之间的关系，仍尚未见报道。根据本研究获得的 Venn 图，我们预测在 DM 的发病过程中，hsa-miRNA-223-3p 的靶基因 *PRKACB* 可能通

过胰岛素分泌通路发挥作用，未来其或可成为干预 DM 病程发展的一个新靶点。由于本研究仅为初步预测，尚缺乏临床标本和细胞实验的验证，就 hsa-miR-223-3p 对靶基因的调控作用还需更深入的研究加以证实。

综上，本研究通过生物信息学方法对 hsa-miR-223-3p 进行靶基因预测、GO 功能分析、KEGG 及 Reactome 通路分析，结果显示 hsa-miR-223-3p 可能通过调控多个靶基因参与信号通路的调节，在机体的多种生理与病理过程中发挥重要作用；同时，我们初步预测 hsa-miR-223-3p 可能通过 *PRKACB* 调控胰岛素分泌，对其进一步深入研究可为我们后续探索 DM 发病机制及治疗新靶点提供理论指导，还可为今后 DM 的机制研究与治疗提供更多新的思路。

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