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## 小儿扩张型心肌病血清蛋白及 microRNA 表达谱的生物信息学分析和发病机制

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**[摘要]** 目的: 对小儿扩张型心肌病(pediatric dilated cardiomyopathy, PDCM)血清蛋白及microRNA(miRNA)表达谱进行生物信息学分析, 探讨其发病机制。方法: 对PDCM血清蛋白芯片数据进行差异分析及基因本体论(Gene Ontology, GO)和京都基因与基因组百科全书(Kyoto Encyclopedia of Genes and Genomes, KEGG)通路富集分析。对PDCM miRNA表达谱挑选部分差异表达miRNA, 预测靶基因, 与差异血清蛋白/基因取交集, 获取共享基因, 构建miRNA-mRNA关系对, 并行GO和KEGG通路富集分析。结果: PDCM差异血清蛋白富集到细胞黏附调节、免疫调控、含胶原的细胞外基质等GO子集中。差异蛋白主要参与趋化因子信号通路、肾素分泌、肾素-血管紧张素系统、细胞因子-细胞因子受体相互作用、扩张型心肌病(dilated cardiomyopathy, DCM)、醛固酮的合成和分泌、病毒蛋白与细胞因子及细胞因子受体的相互作用等10条信号通路中。4个下调miRNA行靶基因预测后与差异血清蛋白/基因取交集, 共8个共享基因, 即HSPD1、LIFR、RPS7、ANXA2、PDPK1、EIF4G2、AGT和PRKCA。共享基因显著富集到心肌肥厚正调控等GO子集中; 及醛固酮的合成和分泌及调节钠重吸收、心肌细胞中的肾上腺素能信号和蛋白激酶B-哺乳动物雷帕霉素靶蛋白(Akt-mammalian target of rapamycin, Akt-mTOR)通路等13条通路中。结论: 通过分析PDCM血清蛋白及miRNA表达谱, 有助于进一步了解该病发病机制, 为临床诊疗提供思路。

**[关键词]** 扩张型心肌病; microRNA; 差异表达基因; 生物信息学; 富集分析

## Bioinformatics analyses of serum proteins and microRNAs expression profiles and pathogenesis of pediatric dilated cardiomyopathy

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**Abstract** **Objective:** To implement bioinformatics analyses of the serum proteins and microRNA (miRNA) expression

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profiles about pediatric dilated cardiomyopathy (PDCM), to explore the pathogenesis. **Methods:** Differential analyses, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways enrichment analyses were performed on serum proteins microarray data of PDCM. Partial differentially expressed miRNAs were selected from miRNA expression profile of PDCM, followed by target genes prediction, and shared genes acquisition by overlapping with differential serum proteins/genes to construct miRNA-mRNA matching relation. GO and KEGG pathways enrichment analyses of common genes were also carried out. **Results:** Differential proteins of PDCM were enriched to multiple GO terms, including regulation of cell adhesion and immune process, collagen-containing extracellular matrix, and etc. Differential proteins were enriched to 10 signal pathways, including chemokine signaling pathway, renin secretion, renin-angiotensin system, cytokine-cytokine receptor interaction, dilated cardiomyopathy, aldosterone synthesis and secretion and viral protein interaction with cytokine and cytokine receptor, etc. predicted target genes of 4 down-regulated miRNAs were overlapped with differential serum proteins/genes, and then 8 common genes were obtained, namely *HSPD1*, *LIFR*, *RPS7*, *ANXA2*, *PDPK1*, *EIF4G2*, *AGT*, and *PRKCA*. Eight common genes were enriched to multiple GO terms, including positive regulation of cardiac muscle hypertrophy, etc. and 13 signal pathways, such as aldosterone-regulated sodium reabsorption, aldosterone synthesis and secretion, adrenergic signaling in cardiomyocytes, mTOR signaling pathway, etc. **Conclusion:** Bioinformatics analyses of the serum proteins and miRNAs expression profiles about PDCM will benefit our further understanding the pathogenesis of the disease and provide clues for clinical diagnosis and treatment.

**Keywords** dilated cardiomyopathy; microRNA; differentially expressed genes; bioinformatics; enrichment analysis

小儿扩张型心肌病(pediatric dilated cardiomyopathy, PDCM)是儿童最常见的心肌病<sup>[1-2]</sup>, 是小儿进行性心力衰竭及死亡的主要原因<sup>[3]</sup>, 也是儿童心脏移植的主要指征<sup>[4-5]</sup>。该病预后较差, 造成严重的社会经济问题。其发病机制涉及病毒感染、免疫、遗传和环境等多方面, 且尚未清晰阐明, 因此探讨其发病机制, 对提升临床诊疗效果具有积极的推动作用。

内源性非编码microRNA(miRNA)作为由18~25个核苷酸组成的小RNA分子, 可通过直接降解靶基因mRNA或阻断蛋白质翻译<sup>[6-7]</sup>来调控基因表达, 从而参与细胞增殖、分化、凋亡等许多生物学过程(biological processes, BP)<sup>[8]</sup>。研究<sup>[9]</sup>表明miRNA的失调与扩张型心肌病(dilated cardiomyopathy, DCM)的发生和发展密切相关。

本研究基于基因表达公共数据库(Gene Expression Omnibus, GEO)中的PDCM血清蛋白及miRNA表达谱进行整合生物信息学分析, 探讨其发病机制, 从而为分子机制研究及临床诊疗的探索提供参考。

## 1 数据与方法

### 1.1 数据下载及预处理

本研究流程图如图1所示。以“pediatric dilated cardiomyopathy”为搜索词, 进入GEO数据库(<https://www.ncbi.nlm.nih.gov/>)<sup>[10-11]</sup>搜索已公布的PDCM芯片, 获取蛋白芯片数据集GSE181091和miRNA相关数据集GSE181048, 均来源于美国科罗拉多大学药理学儿科心脏病中心。GSE181091以PDCM患者血清蛋白为研究对象(8例), 无DCM小儿血清蛋白为对照组(4例)。对各个样本数据进行预处理, 如存在缺失值自动补全或蛋白/基因对应多个探针取均值等, 随后进行背景校正、标准化, 并进行蛋白/基因名称转化。GSE181048以PDCM患儿血清为研究对象(32例), 正常小儿血清为对照组(12例), 通过实时定量聚合酶链反应测定血清miRNA含量, 并统计分析得到miRNA差异表达谱。

### 1.2 差异表达分析

采用统计软件R 3.5.0和limma包对GSE181091蛋白芯片进行差异分析。差异表达基因(differentially

expressed genes, DEGs)的筛选条件为 $|\log \text{fold change}| \geq 1, P < 0.05$ 。运用R语言pheatmap包绘制热图, 以可视化DEGs。

### 1.3 GO 和 KEGG 通路富集分析

对DEGs实施基因本体论(Gene Ontology, GO)和京都基因与基因组百科全书(Kyoto Encyclopedia of Genes and Genomes, KEGG)通路富集分析<sup>[12-13]</sup>, 利用R语言clusterProfiler包<sup>[14]</sup>实现, 在BP、细胞组分(cellular component, CC)和分子功能(molecular function, MF)(<http://www.geneontology.org>)方面

对蛋白/基因进行功能注释, 并探讨DEGs显著富集的信号通路。采用R语言ggplot2包进行可视化呈现。 $P < 0.05$ 被认为有统计学意义。

### 1.4 差异表达 miRNA 预测下游靶基因

GSE181048数据集提供miRNA差异表达谱, 选取 $|\log \text{fold change}| \geq 1$ 且 $P < 0.05$ 的miRNA, 以分组比较和点图形式展示其差异表达, 并使用在线数据库miRNet(<https://www.mirnet.ca/miRNet/Secure/MirNetView.xhtml>)进行下游靶基因(mRNA)的预测。

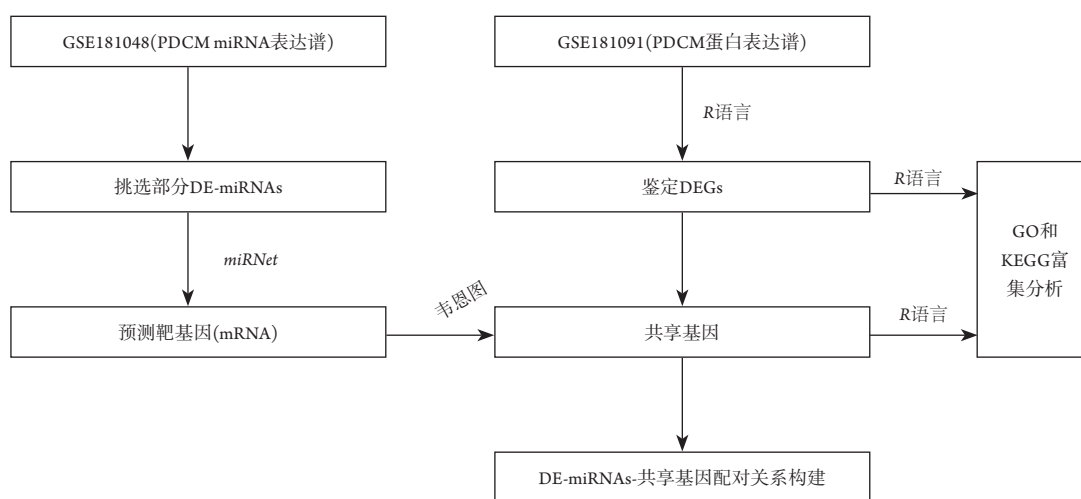


图1 本研究流程图

Figure 1 Workflow of the current study

### 1.5 MiRNA靶基因与DEGs共享基因的获取及GO和KEGG富集分析

为了进一步探讨血清miRNA对PDCM的影响, 我们将miRNA预测的靶基因与GSE181091数据集差异蛋白对应的mRNA取交集, 通过在线平台‘VennDiagram’(<https://cran.r-project.org/web/packages/VennDiagram/>)获取二者共享基因, 构建miRNA-mRNA关系对, 并对共享基因进行GO和KEGG通路富集分析(方法同1.3)。

### 2.2 差异蛋白 GO 和 KEGG 富集分析

GO分析发现差异蛋白富集到945个不同的GO子集中, 主要涉及细胞黏附调节、免疫调控, 含胶原的细胞外基质, 受体配体活性等。KEGG通路富集分析发现DEGs主要参与趋化因子信号通路、肾素分泌、肾素-血管紧张素系统、细胞因子-细胞因子受体相互作用、DCM、醛固酮的合成和分泌、病毒蛋白与细胞因子及细胞因子受体的相互作用10条信号通路中。BP、CC、MF各子集排名前10( $P$ 值升序)及KEGG通路富集分析如图3、4所示。

## 2 结果

### 2.1 差异表达分析

PDCM血清蛋白中40个蛋白质差异有统计学意义, 其中32个上调, 8个下调。差异表达分析如表1所示, 热图可视化展示如图2。

### 2.3 差异表达 miRNA 靶基因预测

选取 $|\log \text{fold change}| \geq 1$ 且 $P < 0.05$ 的miRNA, 其差异表达见图5。这4个miRNA(hsa-miR-145-5p、hsa-miR-133a-3p、hsa-miR-125b-5p和hsa-miR-125a-5p)的靶基因预测, 共2 957个(图6, 表2)。

表1 小儿扩张型心肌病血清蛋白/基因差异分析

Table 1 Difference analyses of serum proteins/genes from pediatric dilated cardiomyopathy patients and controls

蛋白/基因	LogFC	平均表达值	<i>t</i>	<i>P</i>	<i>B</i>	上调/下调
SFRP1	2.50	10.31	5.44	0.00	1.32	上调
FER	1.63	6.61	5.13	0.00	0.86	上调
EIF4G2	2.23	8.35	4.92	0.00	0.56	上调
FABP3	1.35	9.92	4.62	0.00	0.09	上调
PDE5A	1.28	11.80	4.25	0.00	-0.50	上调
SEMA3E	-1.46	9.92	-4.14	0.00	-0.69	下调
GNS	1.35	11.27	4.11	0.00	-0.73	上调
PDPK1	1.66	8.09	3.93	0.00	-1.04	上调
LYN	1.68	10.59	3.91	0.00	-1.06	上调
ADRBK1	1.57	11.08	3.89	0.00	-1.10	上调
CCL25	2.58	10.66	3.82	0.00	-1.23	上调
PRKCA	1.57	11.00	3.66	0.00	-1.49	上调
METAP1	1.05	8.92	3.45	0.00	-1.85	上调
IGFBP1	1.36	10.84	3.25	0.01	-2.18	上调
CA1	-1.05	16.08	-3.17	0.01	-2.32	下调
CCL21	1.35	13.54	3.15	0.01	-2.37	上调
APOB	-1.93	12.32	-2.92	0.01	-2.75	下调
ANXA1	1.98	12.84	2.86	0.01	-2.85	上调
SIGLEC9	3.15	11.04	2.71	0.02	-3.10	上调
AGT	-2.08	10.28	-2.71	0.02	-3.11	下调
CCL28	1.64	13.64	2.66	0.02	-3.18	上调
REN	2.26	10.79	2.66	0.02	-3.19	上调
AK1	-1.02	15.90	-2.66	0.02	-3.19	下调
HSPD1	1.18	11.09	2.65	0.02	-3.20	上调
LIFR	1.08	7.73	2.64	0.02	-3.22	上调
PRKACA	1.42	7.48	2.54	0.03	-3.39	上调
PRL	1.05	11.10	2.51	0.03	-3.43	上调
RPS7	1.17	10.04	2.48	0.03	-3.49	上调
PGLYRP1	1.21	9.84	2.41	0.03	-3.60	上调
HTRA2	1.11	10.88	2.37	0.03	-3.67	上调
ACP1	-1.05	12.22	-2.36	0.04	-3.68	下调
UFC1	1.11	12.35	2.35	0.04	-3.71	上调
ANXA2	1.12	12.27	2.34	0.04	-3.71	上调
MDK	2.29	14.65	2.33	0.04	-3.74	上调
TPSB2	-1.08	9.97	-2.30	0.04	-3.78	下调
TNNI3	1.44	8.72	2.29	0.04	-3.79	上调
DCTPP1	1.89	12.22	2.25	0.04	-3.86	上调
XPNPEP1	1.06	10.15	2.23	0.04	-3.88	上调
CSK	1.03	10.37	2.22	0.04	-3.90	上调
OMD	-1.11	14.23	-2.19	0.04	-3.95	下调

“LogFC”是两组表达值间以2为底对数化的变化倍数；“B”为贝叶斯检验后得到的标准差的对数化值。

“LogFC” is the base-2 logarithmic fold change between the 2 groups of expression values; “B” is the logarithmic value of the standard deviation obtained after Bayesian test.

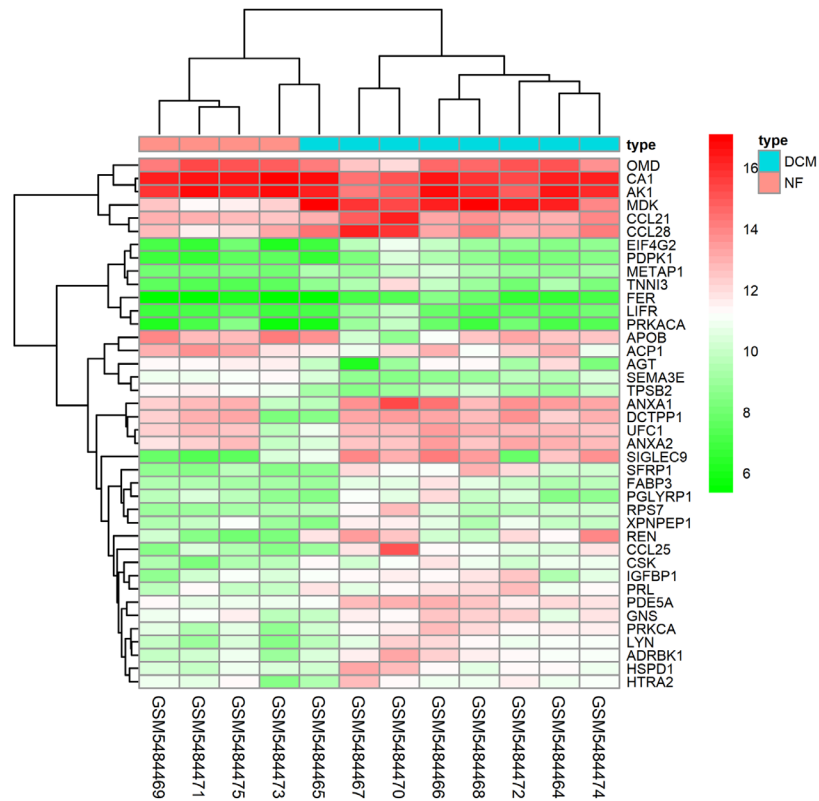


图2 血清蛋白/基因差异分析热图

Figure 2 Heatmap of difference analyses of serum proteins/genes

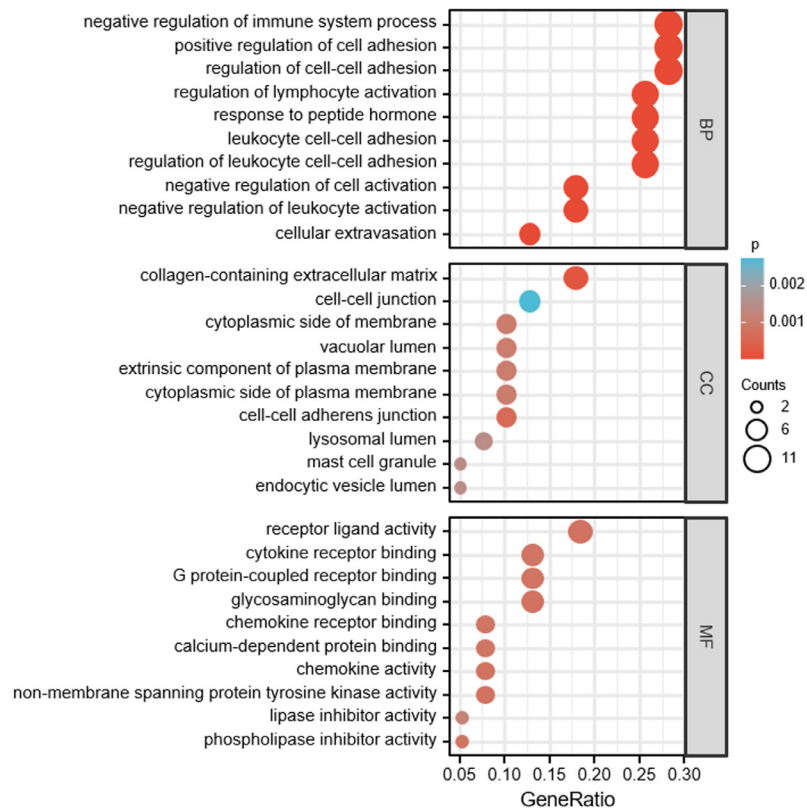


图3 差异蛋白GO富集分析部分可视化

Figure 3 Partial visualization for GO enrichment analyses of differential proteins

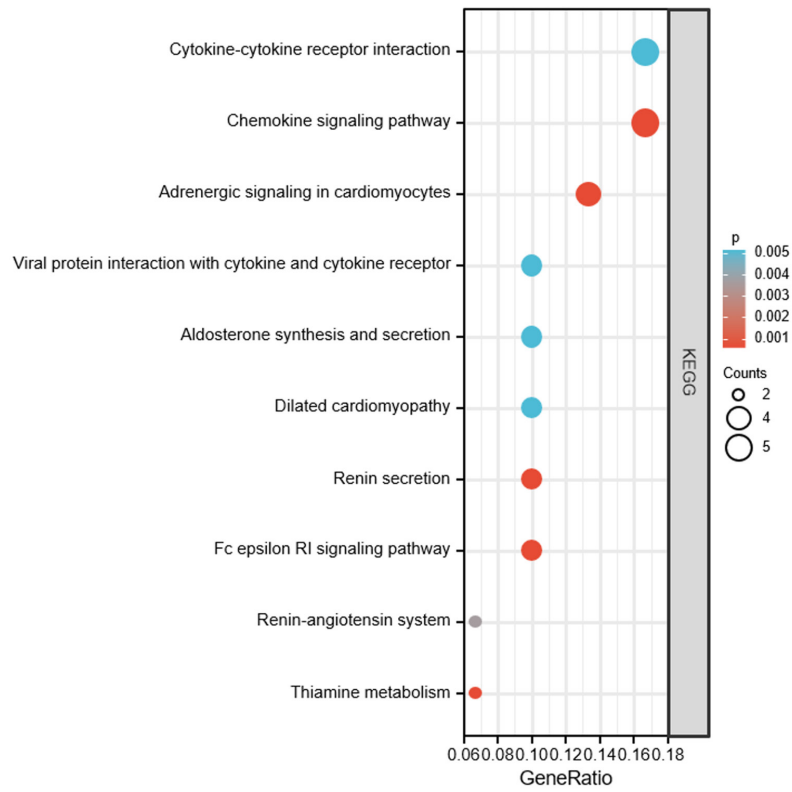


图4 差异蛋白KEGG富集分析部分可视化

Figure 4 Partial visualization for KEGG enrichment analyses of differential proteins

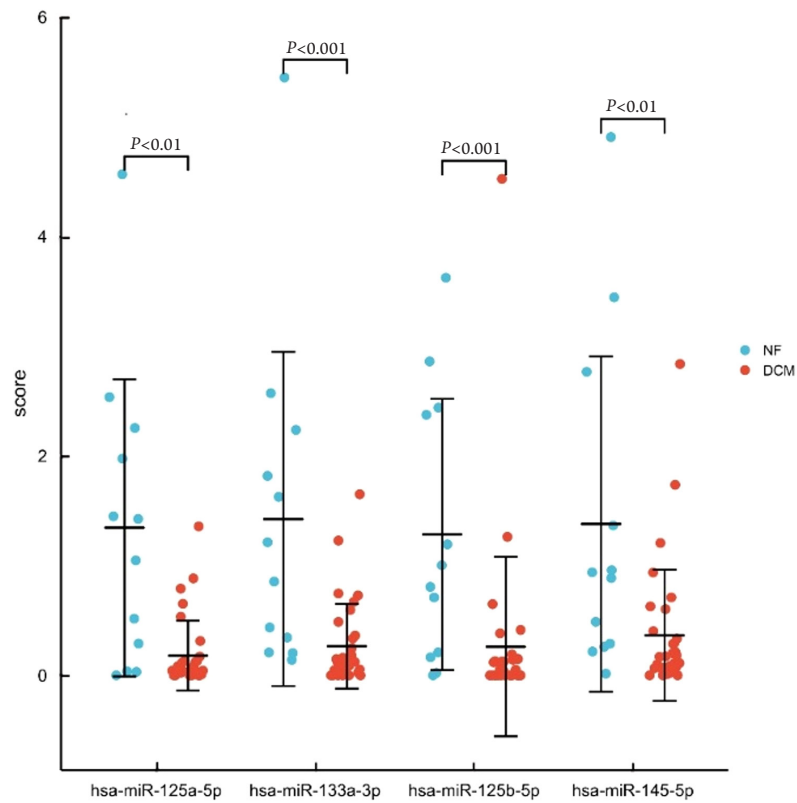


图5 差异表达miRNA分组比较图可视化

Figure 5 Visualization of group comparison chart for differential miRNAs

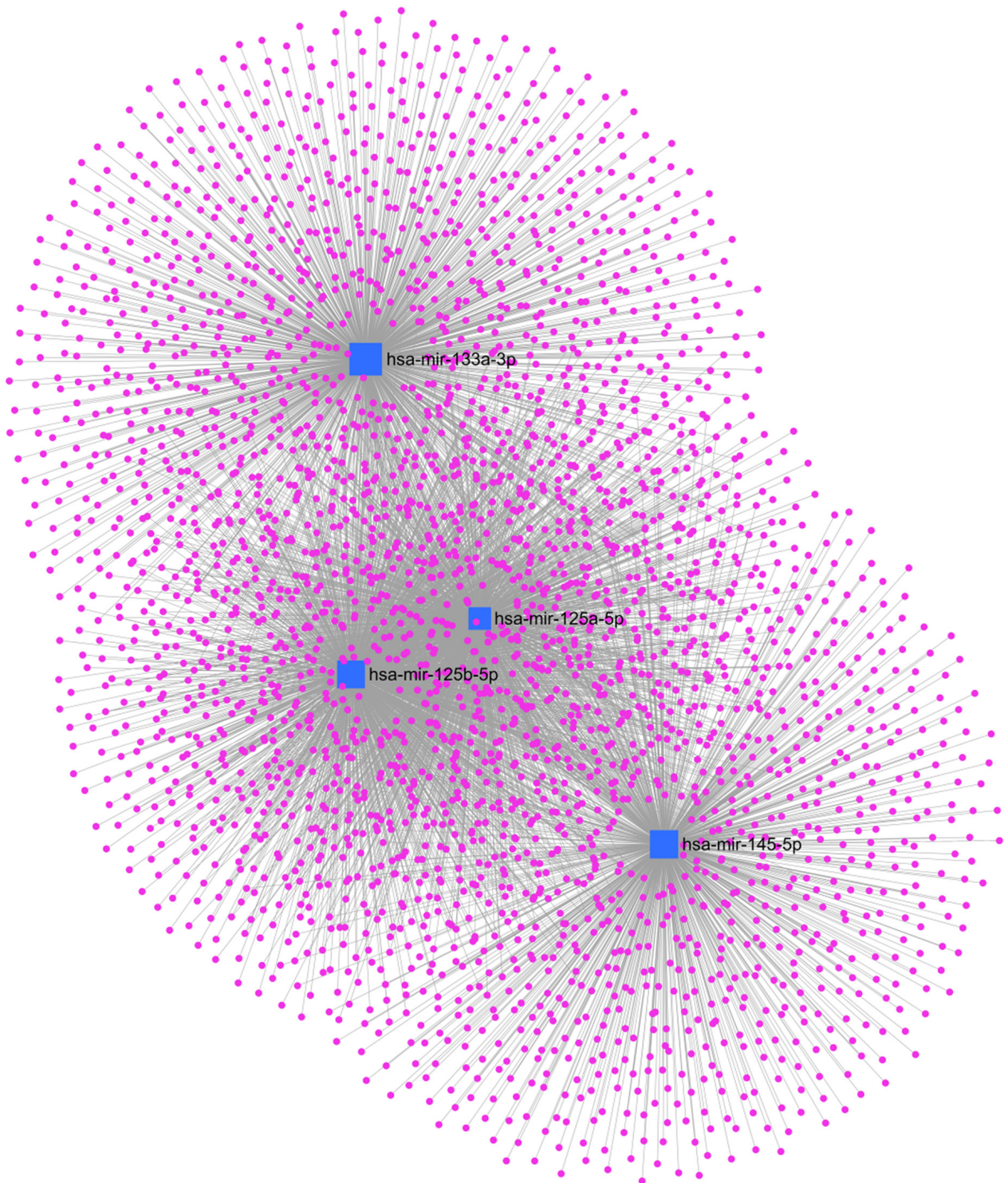


图6 差异表达miRNA靶基因预测(方形, miRNA; 圆形, 靶基因)

Figure 6 Prediction of target genes for differential miRNAs (square, miRNA; circle, target gene)

表2 差异表达miRNA靶基因预测

Table 2 Prediction of target genes for differential miRNAs

下调的miRNA	靶基因(mRNA)数目/个
hsa-miR-145-5p	1 056
hsa-miR-133a-3p	1 209
hsa-miR-125b-5p	1 555
hsa-miR-125a-5p	1 338
总计(去除重叠)	2 957

#### 2.4 miRNA 靶基因与 DEGs 共享基因获取

用R语言及在线平台‘VennDiagram’对2 957个靶基因和40个差异蛋白/基因进行取交集，得到韦恩

图(图7)。获取8个共享基因，即：*HSPD1*、*LIFR*、*RPS7*、*ANXA2*、*PDPK1*、*EIF4G2*、*AGT*和*PRKCA*。差异表达miRNA与共享基因配对关系见表3。

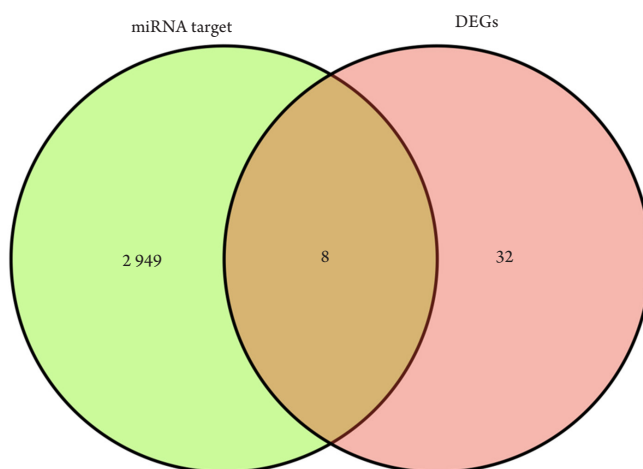


图7 miRNA靶基因与差异表达基因韦恩图

Figure 7 Venn diagram for miRNAs' target genes and DEGs

表3 差异表达miRNA与共享基因配对关系

Table 3 Matching relation of miRNAs and common genes

miRNA	靶基因
hsa-miR-145-5p	<i>AGT</i> , <i>PRKCA</i>
hsa-miR-133a-3p	<i>LIFR</i> , <i>ANXA2</i>
hsa-miR-125b-5p	<i>LIFR</i> , <i>PRKCA</i> , <i>EIF4G2</i> , <i>HSPD1</i> , <i>RPS7</i>
hsa-miR-125a-5p	<i>LIFR</i> , <i>PRKCA</i> , <i>EIF4G2</i> , <i>PDPK1</i>

#### 2.6 miRNA 靶基因与 DEGs 共享基因富集分析

富集分析发现共享基因参与心肌肥厚正调控等多个GO子集，并参与醛固酮的合成和分泌及调节钠重吸收、心肌细胞中的肾上腺素能信号、蛋

白激酶B-哺乳动物雷帕霉素靶蛋白(Akt-mammalian target of rapamycin, Akt-mTOR)通路等13条通路中。BP、CC、MF各子集排名前10(P值升序)及KEGG通路富集分析见图8、9所示。



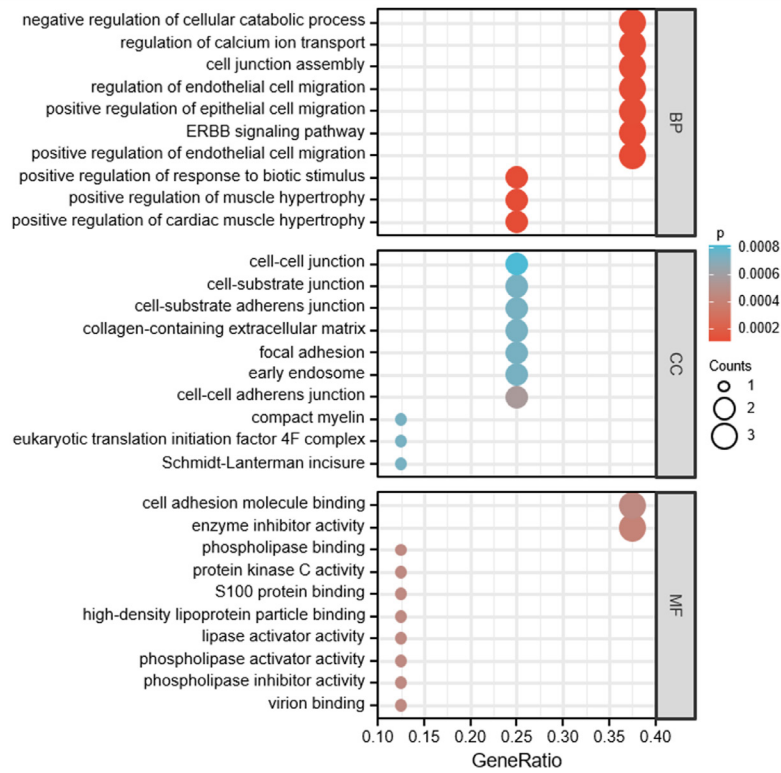


图8 共享基因GO富集分析部分可视化

Figure 8 Partial visualization for GO enrichment analyses of common genes

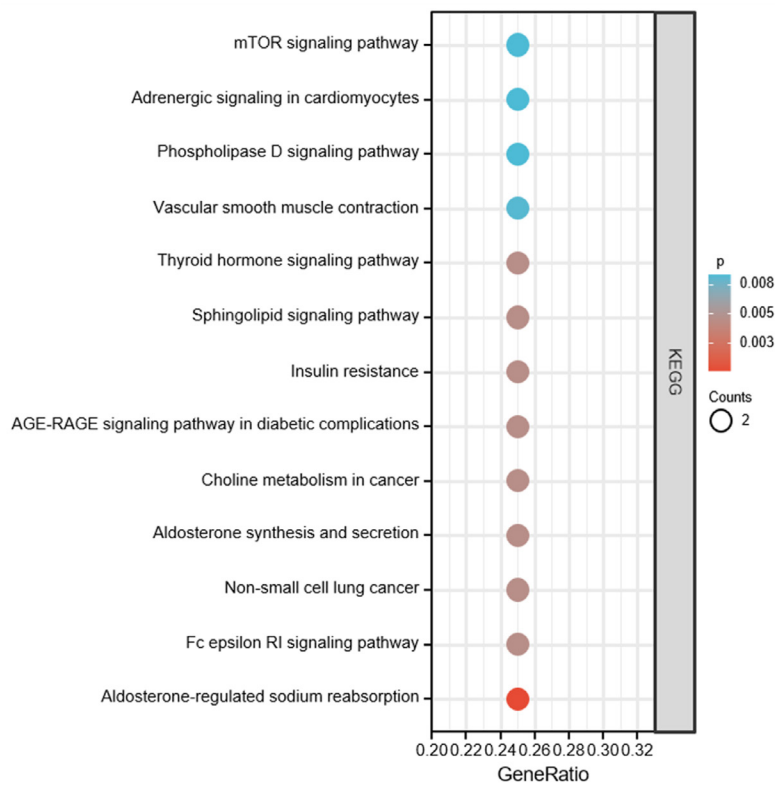


图9 共享基因KEGG富集分析部分可视化

Figure 9 Partial visualization for KEGG enrichment analyses of common genes

### 3 讨论

PDCM多与病毒感染、遗传因素和环境等因素有关,是造成儿童心力衰竭及死亡的主要原因,成为儿童心脏移植的主要指征。非编码miRNA的失调与DCM的致病机制密切相关。本研究基于GEO数据库芯片分析,探讨其对疾病发生发展的作用。

我们发现PDCM血清差异蛋白质显著富集于细胞黏附调节、免疫调控;含胶原的细胞外基质等GO子集中。DCM与心肌及间质急性慢性炎症相关,免疫细胞及其调控过程贯穿疾病始末,并涉及细胞外基质的重塑,GO富集结果与之符合。差异蛋白质参与趋化因子信号通路、肾素分泌、肾素血管紧张素系统、细胞因子-细胞因子受体相互作用、DCM、醛固酮的合成和分泌、病毒蛋白与细胞因子及细胞因子受体的相互作用10条信号通路。趋化因子及其受体是正常免疫及病毒性心肌炎等多种炎症性疾病过程中白细胞募集的关键调节因子,参与免疫反应、心脏纤维化及重塑<sup>[15]</sup>。高血清C-C基序趋化因子21(C-C motif chemokine 21, CCL21)水平与心肌梗死后心力衰竭患者的病死率独立相关<sup>[16]</sup>;CCL21与慢性心力衰竭患者的全因病死率和心血管病死率相关<sup>[17]</sup>。本研究中CCL21、CCL25和CCL28等以上调的方式参与到趋化因子及其受体和病毒蛋白与细胞因子及细胞因子受体的相互作用通路中,提示其在PDCM的发病过程中起重要作用。肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system, RAAS)激活,在心力衰竭早期发挥代偿作用,后期可引起心脏扩张和心肌纤维化,引发心力衰竭。有研究<sup>[18]</sup>发现PDCM左室组织RAAS中的肾素原受体、肾素、血管紧张素转化酶的表达量高于成人,相关抑制剂的研发为PDCM的治疗提供了线索。也有研究<sup>[19]</sup>提及,醛固酮可直接促使外周血液中单核细胞参与炎症反应,其拮抗剂(螺内酯)能抑制炎症反应。我们发现差异蛋白血管紧张素原(angiotensinogen, AGT)、环磷酸腺苷依赖性蛋白激酶催化亚基 $\alpha$ (cAMP-dependent protein kinase catalytic subunit alpha, PRKACA)、肾素(renin, REN)、蛋白激酶C $\alpha$ 型(protein kinase C alpha type, PRKCA)等参与肾素分泌、肾素血管紧张素系统和醛固酮的合成和分泌通路中,提示这些蛋白质在PDCM中扮演着重要角色。

为进一步了解差异表达miRNA对PDCM可能的影响,我们挑选部分显著差异下调的miRNA进

行靶基因预测,并与DEGs取交集,再对共享基因进行富集分析,从而深入探讨差异表达的miRNAs是如何通过DEGs影响PDCM。4个下调的miRNA调控的8个共享基因显著富集到心肌肥厚正调控、醛固酮的合成和分泌及调节钠重吸收、心肌细胞中的肾上腺素能信号和mTOR信号通路等信号通路中。

其中,共享基因/蛋白3-磷酸肌醇依赖性蛋白激酶1(3-phosphoinositide-dependent protein kinase 1, PDK1)、AGT和PRKCA涉及的GO子集及信号通路,可能与PDCM密切相关。据文献<sup>[20]</sup>报道,PDK1以磷酸化方式激活Akt-mTOR通路,参与心肌细胞肥大、自噬及凋亡。AGT是RAAS关键组分。其基因多态性与捷克人群中DCM和缺血性心力衰竭风险增加相关<sup>[21]</sup>。AGT的全身或心脏特异性过表达可提升心脏血管紧张素II的浓度,促进心肌肥大<sup>[22]</sup>。在体外用血管紧张素II处理心脏成纤维细胞可刺激外泌体的分泌,上调AGT的表达,激活培养的心肌细胞中的RAAS,促进心肌细胞肥大<sup>[23]</sup>。PRKCA参与细胞增殖、分化、迁移、凋亡、心脏肥大和炎症<sup>[24]</sup>。PRKCA是肾上腺素 $\beta$ -1受体的关键下游信号分子,在心脏中PRKCA调控变异的激活有可能影响心力衰竭中 $\beta$ -阻断剂的治疗效果<sup>[25]</sup>。

总而言之,上述差异蛋白质和显著下调的miRNA及其靶向作用的共享差异基因参与的功能集与信号通路可能在PDCM的发生发展中发挥着关键作用,可能对发病机制及临床诊疗的探索提供参考价值。本研究也存在一定的局限性,目前研究结果仅基于公共数据集的生物信息学分析,后期仍需开展并逐步扩大临床样本的收集与检测,以进一步佐证我们的结果。同时,在DCM发病机制中涉及到的多个关键分子及信号通路也值得进一步深度挖掘。

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