BMC Endocrine Disorders

RESEARCH

Open Access

The predictive function of miR-122-5p and its action mechanism by regulating PKM2 in metabolic syndrome

Xinglu Zhou[1†], Rui Wu[2†], Guangfeng Tang[3], Tongtong Shen[4*] and Wei Li[5*]

Abstract

Background Obesity will cause metabolic syndrome (Mets) easily, and its pathogenesis is not completely clear.

Aim To probe into the predictive value of miR-122-5p and its regulatory mechanism in Mets.

Method The predictive effect of miR-122-5p on Mets was evaluated by constructing a Receiver Operating Characteristic (ROC) curve. The target genes of miR-122-5p were predicted using the ENCORI/starBase and TargetScanHuman databases, and pyruvate kinase M2 (PKM2), closely related to Mets, was screened by GO and KEGG analysis. The roles of miR-122-5p/PKM2 in insulin resistance (IR) were explored by treating the human normal liver cells (HLCs) with palmitic acid (PA) to induce the IR model. The effects of miR-122-5p/PKM2 on glucose metabolism (GM) of HLCs were evaluated by detecting the production of pyruvic acid, lactic acid, and ATP.

Results MiR-122-5p was highly expressed in obese people and Mets patients, and its predicted AUC for Mets was 0.876. In HLCs transfected with wild-type PKM2 luciferase vector (PKM2-wt), luciferase activity was attenuated by the miR-122-5p mimic and enhanced by its inhibitor. The expression of PKM2 was inhibited by the miR-122-5p mimic and up-regulated by its inhibitor. The miR-122-5p mimic enhanced PA-induced IR and inhibited the GM of HLCs, which were reversed by overexpression of PKM2. The miR-122-5p inhibitor exerted the opposite effects of its mimic, which were also reversed by silencing of PKM2.

Conclusion MiR-122-5p, a risk factor for Mets, mediated the IR and abnormal glucose metabolism of HLCs by negatively regulating PKM2.

Clinical trial number Not applicable.

Highlights

- As an independent risk factor for Mets, miR-122-5p had a certain value in predicting Mets.
- MiR-122-5p mediated the insulin resistance of HLCs by negatively regulating PKM2.
- MiR-122-5p mediated the abnormal glucose metabolism of HLCs by negatively regulating PKM2.

†Xinglu Zhou and Rui Wu contributed equally to this work.

*Correspondence:
Tongtong Shen
tongtongshen239001@163.com
Wei Li
weili7521@163.com

Full list of author information is available at the end of the article

Keywords Obesity, Metabolic syndrome, miR-122-5p, PKM2, Insulin resistance, Glucose metabolism

Introduction

The incidence of metabolic syndrome (Mets) is rising worldwide. It is estimated that about one-third of the European population and 27% of the Chinese population have Mets [1]. Mets refers to a series of pathological conditions of metabolic disorders in the human body, including the metabolism of carbohydrates, fats, proteins, and other substances, which is a risk factor leading to diabetes and cardiovascular and cerebrovascular diseases [2, 3]. The main manifestations of Mets are obesity, hyperglycemia, hypertension, hyperlipidemia, hyperinsulinemia, and so on [4]. Obesity is a risk factor for Mets, which tends to cause tissue stress and dysfunction, causing metabolic disorders [5]. Abnormal fat accumulation will affect insulin sensitivity. The heart of the Mets pathophysiology is insulin resistance (IR), which is manifested by impaired fasting blood sugar or impaired glucose tolerance [6]. Although Mets is very common worldwide, its cause has not been identified.

MicroRNAs (miRNAs) are evolutionarily conserved non-coding RNA molecules with 18–24 nucleotides in size that are known to be involved in post-transcriptional regulation of protein synthesis [7]. The increasing evidence displays that miRNA plays an important role in a variety of diseases, including Mets. For example, miR-122-5p, miR-21-5p, and miR-146a-5p were significantly up-regulated in Mets patients [8]. Peng et al. demonstrated that miR-377 can cause inflammatory response and IR in obesity by targeting SIRT1 [9]. There were 2 miRNAs that expressed highly and 36 miRNAs that expressed lowly in plasma samples from Mets patients (compared to healthy volunteers), identified by Liu et al. using high-throughput sequencing. Their RT-qPCR data demonstrated that miR-526b-5p and miR-6516-5p were down-regulated in Mets patients [10].

In a systematic review of "microRNAs associated with overweight and obesity in children," miR-122-5p was listed as a good candidate for a biomarker of childhood obesity [11]. A descriptive cross-sectional study showed that miR-122-5p was overexpressed in obese children (compared to normal-weight children) [12], and another study showed that the expression of miR-122-5p in the blood of Mets subjects was significantly higher than that of the healthy group [8]. In a weight-loss intervention assay, circulating miR-122-5p level decreased as subjects lost weight [13]. In a high-fat diet-induced obese rat model of nonalcoholic fatty liver disease, the expression of miR-122-5p in the liver was upregulated. Inhibition of miR-122-5p, induced by swimming exercise and intermittent fasting, could improve the lipid metabolism of the liver in rats [14]. These studies suggest that miR-122-5p is crucial in childhood obesity and may be a potential biomarker for Mets. Based on these, we explored the predictive function of miR-122-5p in Mets, and further probed into the pathogenesis of Mets by mining the downstream genes of miR-122-5p.

Materials and methods

Volunteers and samples

All peripheral blood samples in this study were collected from author's institution, including 150 lean and 112 obese healthy volunteers, and 214 patients with Mets. Body mass index (BMI) < 24 kg/m^2 was considered to be lean, and BMI > 30 kg/m^2 was considered to be obese. The basic information of them was shown in supplementary Table 1. Before the study, we received the informed consent signed by all volunteers. This study was authorized by the Ethics Committee of author's institution.

Real-time quantitative PCR (RT-qPCR)

Total RNA was extracted by the MirPremier MicroRNA Isolation Kit (Sigma-Aldrich, USA), which was subsequently reversely transcribed into cDNA by the miRQuant TaqMan microRNA cDNA Synthesis Kit (Baiao Leibo, China) and the First-Strand cDNA Synthesis Kit (APExBIO, USA), respectively. U6 and GAPDH were used as internal reference genes for miR-122-5p and PKM2, respectively. Primer sequences were shown in supplementary Table 2.

The analysis of miR-122-5p in predicting Mets

The Statistical Package for the Social Sciences (SPSS) software was used to construct the Receiver Operating Characteristic (ROC) curve of miR-122-5p to predict Mets, and perform the multifactorial binary logistic regression analysis of clinical factors to evaluate the predictive value of miR-122-5p in Mets.

Bioinformatics analysis

The downstream genes of miR-122-5p were predicted in the ENCORI/starBase database (https://rnasysu.com/encori/index.php) and the TargetScanHuman database (https://www.targetscan.org/). Bioinformatics (https://www.bioinformatics.com.cn/), an online analysis platform, was used for the GO and KEGG analysis.

Cell transfection

The cell density of RNA transfection was 30–50%, and of DNA transfection was about 90%. The mimic and inhibitor of miR-122-5p, the small interfering RNA (si-PKM2), and the overexpressed plasmid (ov-PKM2) of PKM2 were purchased from MedChemExpress Company (USA), and

they were mixed with Lipofectamine 3000 reagent (Invitrogen, USA) and Opti-MEM medium (Invitrogen, USA) according to the instructions and added to cells pre-inoculated into a 6-well plate. After 8 h, the transfection medium was removed.

Western blotting

Cells were cleaved by RIPA lysate for 30 min. The supernatant (protein mixture) was obtained after centrifugation (4℃, 12000 rpm, 20 min), which then was mixed with loading buffer to incubate for 10 min at 100℃. SDS-PAGE was performed on 50 μg protein per well. The protein was then electrically transferred to the PVDF membrane. The PVDF membrane was incubated with 5% skim milk powder at room temperature for 1.5 h, and then incubated with anti-PKM2 antibody (Abcam, UK) at 4℃ overnight. The next day, after incubation with the second antibody (ZSGB-BIO, China), the protein was checked using the chemiluminescent gel imaging system, after the ECL color-developing solution was added. For the convenience of presentation, only cropped images were shown in the results, please see the supplementary file 1 for the complete images.

Cell culture and treatment

Human normal liver cells (HLCs) purchased from Shanghai Tongwei Biotechnology Co., LTD (China), were cultured with RPMI-1640 medium (10% FBS and 1% penicillin/streptomycin), in a 37℃ sterile incubator with 5% CO_2. The cells, with a density of 80%, were treated with palmitic acid (PA) (0.25 mmol/L, MedChemExpress, USA) for 24 h to build the IR cell model. At 0 and 24 h, the glucose concentration of cell media was measured using the Glucose Oxidase Assay Kit (Applygen, China). The cells were treated with 20 mM of 2-Deoxy-D-glucose (2-DG) (MedChemExpress, USA) for 24 h to inhibit the glycolysis.

Detection of cell GM

The pyruvate concentration of cells was detected by a Pyruvate Assay Kit (Abcam, UK). The lactic acid level in the cell supernatant was determined by a Lactic Acid Detection Kit (KeyGen Biotech, China). The content of ATP was detected by an ATP Assay Kit (Beyotime, China).

Statistical analysis

The results were analyzed by one-way ANOVA or Student's t-test. All results were expressed as mean ± standard deviation (SD), and *p* values below 0.05 were considered statistically significant. All statistical analyses were performed using GraphPad Prism statistical software.

Results

MiR-122-5p was a risk factor for Mets

MiR-122-5p was an up-regulated gene in obese individuals (Fig. 1A). Similarly, miR-122-5p expressed highly in Mets patients (compared to healthy people) (Fig. 1B). ROC analysis showed that miR-122-5p predicted Mets with an AUC of 0.876 (sensitivity = 73.8%, specificity = 88.2%) (Fig. 1C). Multifactorial binary logistic regression analysis confirmed miR-122-5p as an independent risk factor for Mets ($p < 0.001$), and each unit augment of miR-122-5p level elevated the risk of Mets by 2.020-fold (Table 1).

Regulation of PKM2 by miR-122-5p

The downstream genes of miR-122-5p were predicted using the ENCORI/starBase database and the TargetScanHuman database, respectively, among which 104

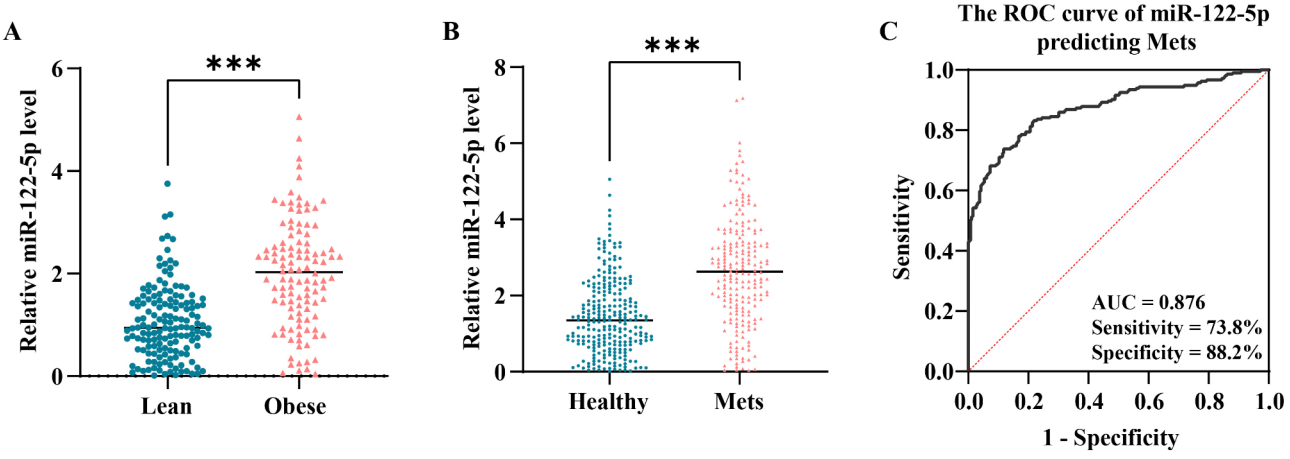

Fig. 1 MiR-122-5p was a risk factor for Mets. The expression of miR-122-5p in obese individuals (**A**), and patients with Mets (**B**). (**C**) The ROC curve of miR-122-5p in predicting Mets. AUC, area under curve. ***$p < 0.001$

Table 1 Multifactorial binary logistic regression analysis of factors predicting Mets

Group	OR	95% CI		*p* value
		Lower	Upper	
miR-122-5p	2.020	1.670	2.443	< 0.001
Gender	1.156	0.754	1.772	0.507
Age	1.190	0.723	1.960	0.494
BMI	1.060	1.025	1.096	0.010
Smoking	1.074	0.703	1.640	0.743
Drinking	1.333	0.870	2.041	0.187
Family history	2.055	0.943	4.478	0.070
Hypertension	1.666	1.066	2.604	0.025
Hyperglycemia	1.997	1.255	3.180	0.004

Notes: Mets, Metabolic Syndrome; OR, Odds Ratio; CI, Confidence Interval; BMI, Body Mass Index

genes were shared (supplementary Fig. 1A). The GO analysis displayed that PKM2 was widely involved in the biological processes related to cell metabolism, such as canonical glycolysis, glucose catabolic process to pyruvate, glycolytic process through glucose-6-phosphate, glucose catabolic process, and so on (Fig. 2A and supplementary Table 3). Moreover, PKM2 was enriched in carbon metabolism, glycolysis/gluconeogenesis, and other metabolism-related signaling pathways (Fig. 2B and supplementary Table 4).

The expression of PKM2 was deficient in obese people and patients with Mets (Fig. 2C-D). According to the binding sequence of miR-122-5p and PKM2 mRNA (supplementary Fig. 1B), wild-type and mutant PKM2 luciferase vectors (PKM2-wt/-mut) were constructed. The miR-122-5p mimic (Fig. 2E) reduced the luciferase activity of HLCs transfected with PKM2-wt and inhibited PKM2 expression (Fig. 2G and I), whereas the miR-122-5p inhibitor (Fig. 2F) had the opposite effects (Fig. 2H and J), indicating that miR-122-5p negatively regulated PKM2 by targeting its mRNA.

The miR-122-5p/PKM2 axis mediated IR

Glucose content in cell cultures was measured to assess IR level. HLCs were treated with 0.25 mmol/L PA for 24 h to induce IR (Fig. 3A). Overexpression of PKM2 weakened PA-induced IR, which was strengthened by the silence of PKM2 in HLCs (Fig. 3B-D). The miR-122-5p mimic enhanced IR induced by PA in HLCs, which was whittled by down-regulation of miR-122-5p (Fig. 3E). Co-transfection of PKM2 plasmid reversed the enhancement effect of miR-122-5p mimic on IR (Fig. 3F). Silencing of PKM2 eliminated the effect of miR-122-5p inhibitor on IR (Fig. 3G).

The miR-122-5p/PKM2 axis mediated GM

The GM of HLCs was evaluated by measuring the content of pyruvate, ATP, and lactic acid. Overexpression of PKM2 promoted the production of pyruvic acid and lactic acid in HLCs, and its knockdown worked oppositely (Fig. 4A and D). Consistent with the effect of 2-DG (the inhibitor of glycolysis), miR-122-5p mimic inhibited the production of pyruvic acid and lactic acid, which was reversed by the overexpression of PKM2 (Fig. 4B and E). The miR-122-5p inhibitor promoted the production of pyruvic acid and lactic acid, which were reversed by the silence of PKM2 (Fig. 4C and F). In addition, the effects of miR-122-5p and PKM2 on ATP production of HLCs were consistent with pyruvic acid and lactic acid (Fig. 4G-I).

Discussion

Mets manifests as a complex set of abnormal metabolisms with extremely complex morbidity. World Health Organization (WHO) defines Mets as: impaired glucose tolerance, impaired fasting blood glucose, or IR; hypertension, blood pressure ≥ 140/90 mmHg; dyslipidemia, triglycerides (TG) ≥ 1.695 mmol/L and high-density lipoprotein cholesterol (HDL-C) ≤ 0.9 mmol/L (male) or 1.0 mmol/L (female); central obesity, waist - hip ratio > 0.90 (men) or 0.85 (women), or BMI > 30 kg/m^2; microalbuminuria, urinary albumin excretion ratio ≥ 20 μg/min or albumin/creatinine ≥ 30 mg/g [15].

There is evidence that miRNA can target the liver, which is a potential target involved in the pathogenesis of Mets. MiR-125b has an anti-inflammatory effect in the liver, which protects the liver from ischemia/reperfusion injury (IRI) by inhibiting the TRAF6 and NF-κB pathways [16], while the up-regulation of miR-22 and miR-450b-5p contributes to the development of hepatic IRI [17, 18]. The circulating miR-122-5p in the blood has been shown to be a biomarker for diagnosis and prognosis of diseases, such as atherosclerosis and cardiogenic shock [19, 20]. In this study, we investigated the predictive value of miR-122-5p in Mets. The ROC curve showed that circulating miR-122-5p was an effective marker of Mets (AUC = 0.876), and it is an independent risk factor for Mets. We further probed into the regulatory mechanism of miR-122-5p in Mets by screening its downstream genes. Our results demonstrated that miR-122-5p promoted the occurrence of IR and blocked the GM in HLCs, by inhibiting the expression of PKM2.

IR refers to the attenuated physiological effects of insulin in the body, which is the typical characteristic of Mets. MiRNAs are considered "key regulators" of multiple biological processes. By regulating gene expression at the post-translational level, miRNAs can broadly regulate cell functions [21]. MiRNA mediates the regulation of IR. MiR-183-5p was over-expressed in PA-treated HepG2 cells and the livers of obese mice fed with a high-fat diet (HFD), and it can directly target the 3'UTR of insulin receptor substrate-1 (IRS-1) to inhibit its expression, restraining insulin signaling and glycogen synthesis

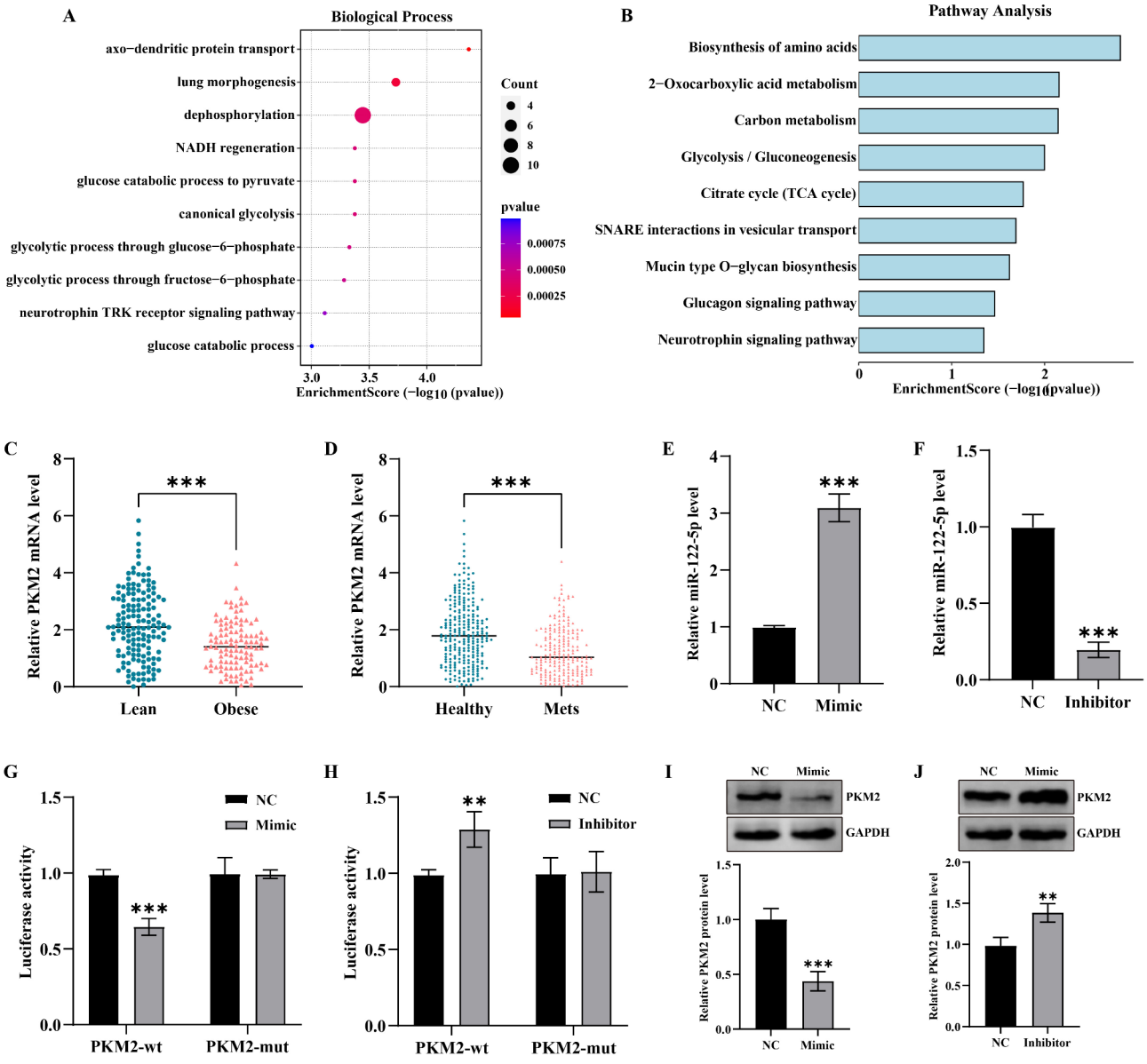

Fig. 2 Regulation of PKM2 by miR-122-5p. The biological processes (**A**) and enrichment signaling pathways (**B**) of 104 genes were obtained by GO and KEGG analysis, respectively. The expression of PKM2 in obese individuals (**C**), and patients with Mets (**D**). The work efficiency of the mimic (**E**) or inhibitor (**F**) of miR-122-5p. The effect of miR-122-5p mimic (**G**) or inhibitor (**H**) on the luciferase activity of HLCs. The effect of miR-122-5p mimic (**I**) or inhibitor (**J**) on the expression of PKM2. $^{**}p < 0.01$, $^{***}p < 0.001$

in hepatocytes [21]. MiRNAs are also important players in GM. MiR-130a, miR-130b, and miR-152 inhibited glycolysis and the production of ATP by decreasing the levels of glucokinase (GCK) and pyruvate dehydrogenase E1 subunit-α1 (PDHA1), and reduced the synthesis and secretion of insulin, in islet β-cells [22]. Pan et al. demonstrated that miR-4431, which expressed highly in the serum of patients with type 2 diabetes, blocked the glucose uptake of HepG2 and L02 cells by down-regulating thyroid hormone receptor interactor 10 (TRIP10) and protein kinase D1 (PRKD1) [23]. Liver and systemic IR are at the heart of Mets. In addition, the liver is an important organ of GM, which can synthesize glucose into liver glycogen which can be broken down into glucose under certain conditions, thereby regulating blood sugar concentration [24]. The exploration of the molecular mechanisms of IR and GM (such as glycolysis) in liver cells is of great significance for understanding the pathogenesis of Mets. Here, we demonstrated that miR-122-5p mediated the obstacle of glucose uptake in HLCs induced by PA, and hindered the glycolysis of HLCs, by negatively regulating PKM2.

PKM2, a key rate-limiting enzyme of glycolysis, can transfer the phosphate group from phosphoenolpyruvate

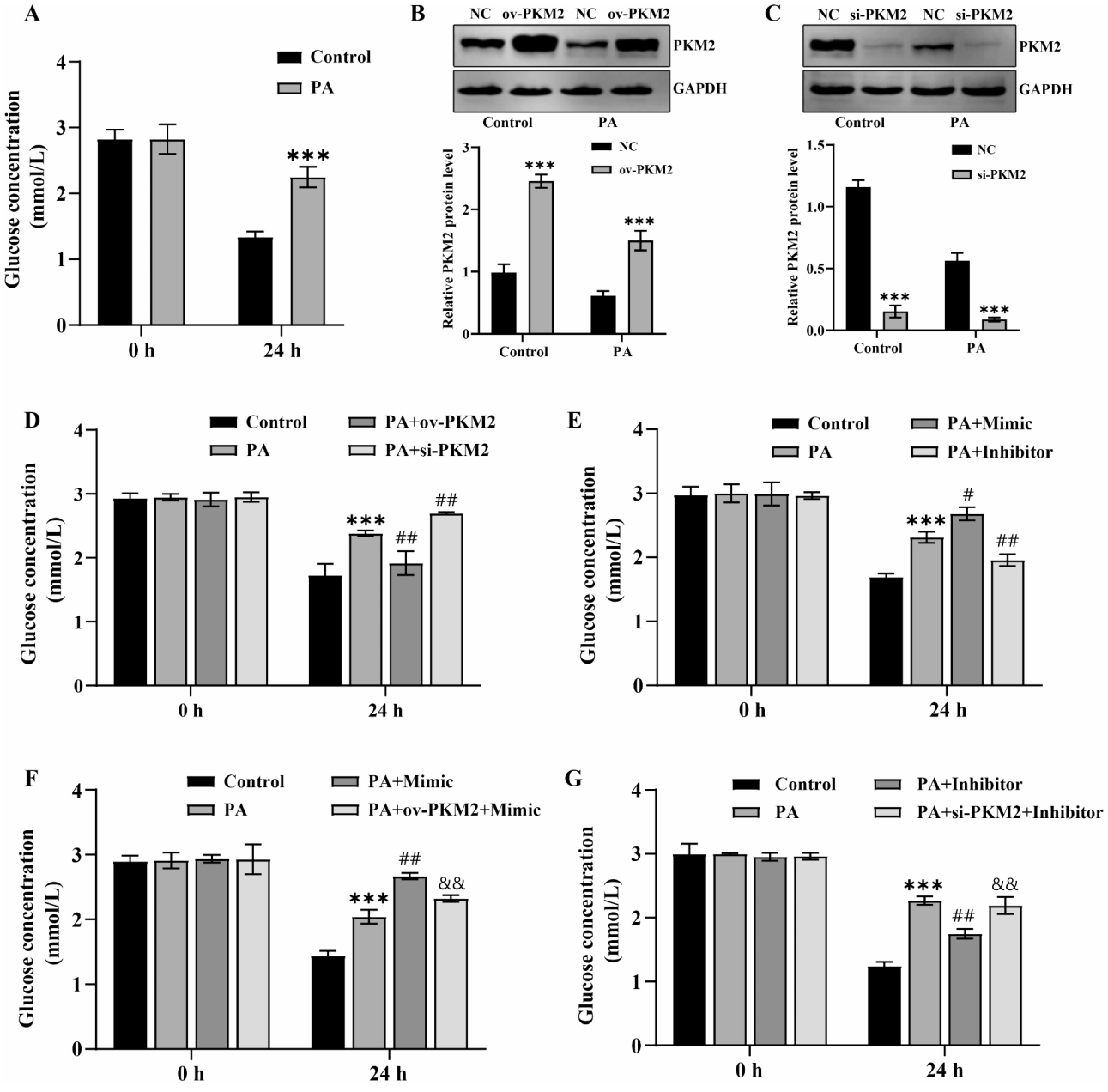

Fig. 3 The miR-122-5p/PKM2 axis mediated IR. (**A**) Effect of 0.25 mmol/L PA on glucose absorption by HLCs. The work efficiency of ov-PKM2 (**B**) and si-PKM2 (**C**). Effect of miR-122-5p (**D**) or PKM2 (**E**) on glucose absorption by HLCs. Effect of overexpression (**F**) or knockdown (**G**) of PKM2 on the role of miR-122-5p in PA-induced IR. $^{\#}p<0.05$, $^{\#\#}p$ and $^{\&\&}p<0.01$, $^{***}p<0.001$

to adenosine diphosphate in glycolysis, producing ATP and pyruvate. Pyruvate is subsequently reduced to lactic acid in the cytoplasm by lactate dehydrogenase, or it is completely oxidized in the mitochondria, producing large amounts of ATP [25]. PKM2 has been shown to play a major role in the development of human diseases and in biological processes through the regulation of metabolism. PKM2 is a key regulator of Warburg effect in tumor cells. Yu et al. showed that OTUB2, a deubiquitinating enzyme, inhibited the ubiquitination of PKM2 by competitively binding to it with Parkin (ubiquitin E3 ligase), which enhanced the activity of PKM2 and promoted glycolysis, promoting the development of colon cancer [26]. Diabetic nephropathy is the second cause of end-stage kidney disease, the activation of PKM2 enhanced the glycolysis process in podocytes, thereby reversing the hyperglycemia-induced elevation of toxic glucose metabolites and mitochondrial dysfunction [27]. The nuclear translocation of PKM2 will lead to a loss of neuronal function, and the inhibition of nuclear

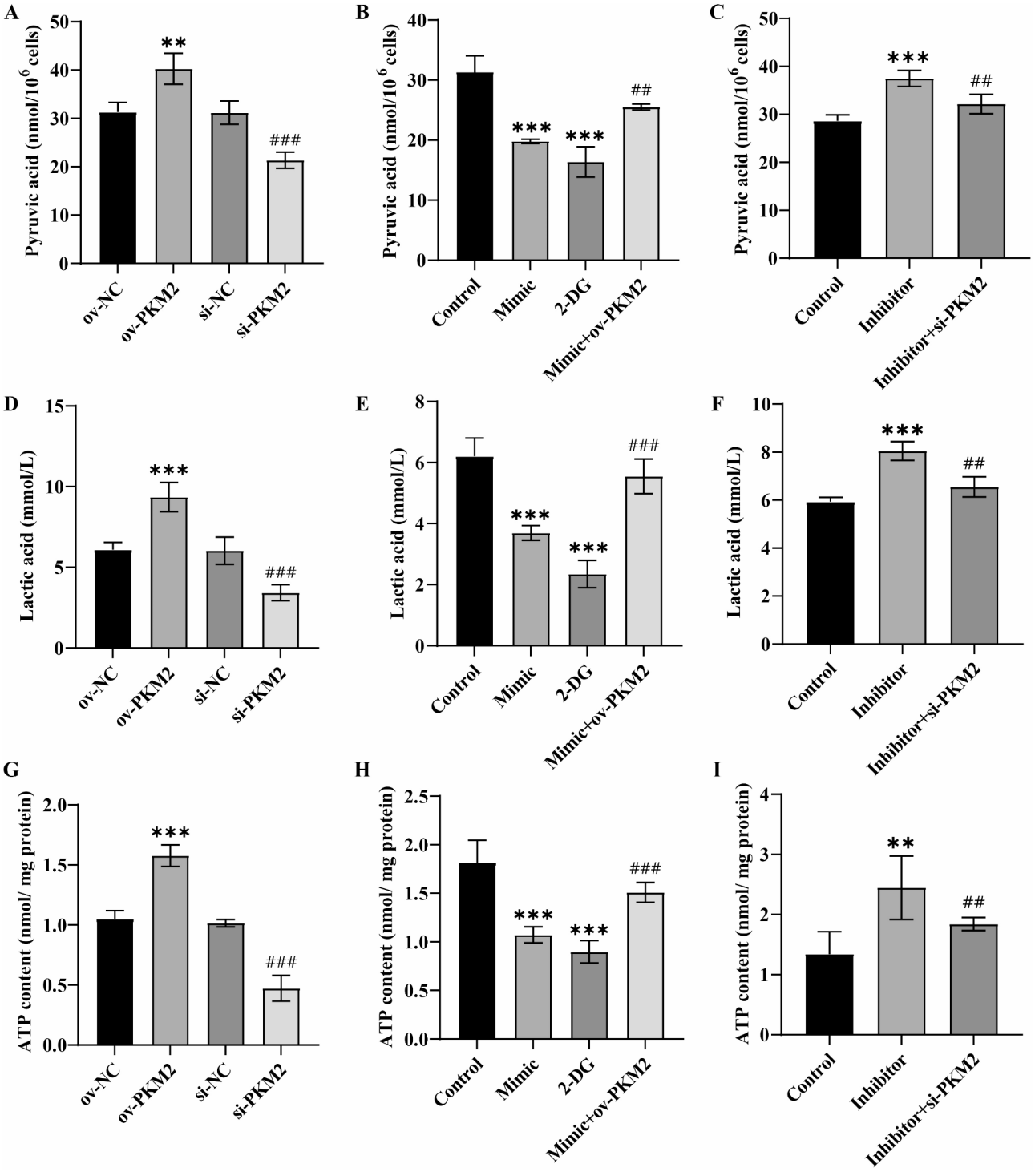

Fig. 4 The miR-122-5p/PKM2 axis mediated GM. Effects of miR-122-5p and PKM2 on the production of pyruvic acid (**A-C**), lactic acid (**D-F**), and ATP (**G-I**) in HLCs. $^{**}p$ and $^{\#\#}p < 0.01$, $^{***}p$ and $^{\#\#\#}p < 0.001$

translocation reversed the changes of specific gene expression in Alzheimer's disease, by restoring neuronal metabolism, which contributed to neuronal activity [28]. PKM2 can coordinate platelet function by promoting the production of lactic acid and metabolic reprogramming [29]. In this study, expression levels of PKM2 in the peripheral blood of patients with Mets, characterized by a range of metabolic disorders, were significantly lower than those in healthy volunteers. In polycystic ovary syndrome (PCOS), which is also characterized by metabolic

disorders, resveratrol alleviated PCOS symptoms in rats by up-regulating PKM2 [30]. These data suggest that PKM2 is a key gene in Mets pathogenesis and may be an important target for Mets treatment.

In conclusion, we revealed the role of miR-122-5p/PKM2 axis in Mets, which will help to understand the pathogenesis of Mets. Circulating miR-122-5p may be able to monitor Mets as a valuable biomarker, and the miR-122-5p/PKM2 axis may be an effective molecular target for Mets treatment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01888-2.

Supplementary Material 1: **Supplementary Figure 1**: (A) The Venn diagram of miR-122-5p target genes predicted by the ENCORI/starBase database and TargetScanHuman database, respectively. (B) The binding sequence of miR-122-5p and PKM2 mRNA predicted by the ENCORI/starBase database.

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7: **Supplementary file 1**: The uncropped western blotting images.

Acknowledgements
Not applicable.

Author contributions
Conceptualization, X.Z., R.W., G.T., T.S. and W.L.; Data curation, X.Z., R.W., G.T. and T.S.; Formal analysis, X.Z., R.W., G.T. and T.S.; Funding acquisition, X.Z.; Investigation, G.T. and T.S.; Methodology, G.T. and T.S.; Project administration, T.S. and W.L.; Resources, G.T. and R.W.; Software, G.T.; Supervision, T.S.; Validation G.T. and T.S.; Visualization, G.T. and T.S.; Roles/Writing - original draft, X.Z. and G.T.; Writing - review & editing, R.W., T.S. and W.L.

Funding
This work was funded by Young Medical Talents Training Program of Pudong Health Bureau of Shanghai (Grant No. PWRq2021-19).

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of The Affiliated Chuzhou Hospital of Anhui Medical University before the study began. The participants' right to be informed about the study was ensured and agreed to participate in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Endocrinology, Shanghai Pudong New Area Gongli Hospital, Shanghai 200135, China
[2]Nursing Department, Geriatric Hospital Affiliated with Wuhan University of Science and Technology, Wuhan 430065, China
[3]Endocrinology Department, The Affiliated Chuzhou Hospital of Anhui Medical University, Chuzhou 239000, China
[4]Cardiovascular Medicine, The Affiliated Chuzhou Hospital of Anhui Medical University, No. 369, West Drunken Weng Road, Nanqiao District, Chuzhou, Anhui 239001, China
[5]Department of Endocrinology, Huanggang Central Hospital Affiliated to Yangtze University, No.6, Qi'an Avenue, Huangzhou District, Huanggang, Hubei Province 438000, China

Received: 5 August 2024 / Accepted: 21 February 2025
Published online: 27 February 2025

References

1. Wlodarski A, Strycharz J, Wroblewski A, Kasznicki J, Drzewoski J, Sliwinska A. The Role of microRNAs in Metabolic Syndrome-Related Oxidative Stress. Int J Mol Sci. 2020; 21(18).
2. Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y et al. Metabolic syndrome: updates on pathophysiology and management in 2021. Int J Mol Sci 2022;23(2).
3. Liu L, Li M, Qin Y, Liu L, Xiao Y. Serum follistatin like 1 in children with obesity and metabolic-associated fatty liver disease. BMC Endocr Disord. 2024;24(1):165.
4. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018;20(2):12.
5. Andersen CJ, Murphy KE, Fernandez ML. Impact of obesity and metabolic syndrome on immunity. Adv Nutr. 2016;7(1):66–75.
6. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech. 2009;2(5–6):231–7.
7. Weiland M, Gao XH, Zhou L, Mi QS. Small RNAs have a large impact: Circulating MicroRNAs as biomarkers for human diseases. RNA Biol. 2012;9(6):850–9.
8. Guo X, Yang Q, Zhang W, Chen Y, Ren J, Gao A. Associations of blood levels of trace elements and heavy metals with metabolic syndrome in Chinese male adults with MicroRNA as mediators involved. Environ Pollut. 2019;248:24866–73.
9. Peng J, Wu Y, Deng Z, Zhou Y, Song T, Yang Y, et al. MiR-377 promotes white adipose tissue inflammation and decreases insulin sensitivity in obesity via suppression of sirtuin-1 (SIRT1). Oncotarget. 2017;8(41):70550–63.
10. Liu G, Lei Y, Luo S, Huang Z, Chen C, Wang K, et al. MicroRNA expression profile and identification of novel MicroRNA biomarkers for metabolic syndrome. Bioengineered. 2021;12(1):3864–72.
11. Florez CAR, Garcia-Perdomo HA, Escudero MM. MicroRNAs associated with overweight and obesity in childhood: A systematic review. Microrna. 2020;9(4):255–65.
12. Rico-Florez CA, Solis-Toro D, Arboleda AM, Hoyos-Quintero A, Bravo-Solarte D, Salazar B, et al. Expression of Circulating MicroRNAs associated with obesity and their relationships with biochemical parameters and Health-related physical fitness in children 6 to 10 years old in Cali, Colombia. Microrna. 2023;12(1):45–62.
13. Hess AL, Larsen LH, Udesen PB, Sanz Y, Larsen TM, Dalgaard LT. Levels of Circulating miR-122 are associated with weight loss and metabolic syndrome. Obes (Silver Spring). 2020;28(3):493–501.
14. Yang K, Liu C, Shao J, Guo L, Wang Q, Meng Z et al. Would combination be better: swimming exercise and intermittent fasting improve High-Fat Diet-Induced nonalcoholic fatty liver disease in obese rats via the miR-122-5p/SREBP-1c/CPT1A pathway. Diabetes Metab Syndr Obes. 2024;17:171675–86.
15. Ahmed M, Kumari N, Mirgani Z, Saeed A, Ramadan A, Ahmed MH, et al. Metabolic syndrome; definition, pathogenesis, elements, and the effects of medicinal plants on it's elements. J Diabetes Metab Disord. 2022;21(1):1011–22.
16. Huang Z, Zheng D, Pu J, Dai J, Zhang Y, Zhang W, et al. MicroRNA-125b protects liver from ischemia/reperfusion injury via inhibiting TRAF6 and NF-kappaB pathway. Biosci Biotechnol Biochem. 2019;83(5):829–35.
17. Huang Z, Mou T, Luo Y, Pu X, Pu J, Wan L, et al. Inhibition of miR-450b-5p ameliorates hepatic ischemia/reperfusion injury via targeting CRYAB. Cell Death Dis. 2020;11(6):455.

18. Huang Z, Pu J, Luo Y, Fan J, Li K, Peng D et al. FAM49B, restrained by miR-22, relieved hepatic ischemia/reperfusion injury by inhibiting TRAF6/IKK signaling pathway in a Rac1-dependent manner. Mol Immunol. 2022;143:143135–46.
19. Hanninen M, Jantti T, Tolppanen H, Segersvard H, Tarvasmaki T, Lassus J et al. Association of miR-21-5p, miR-122-5p, and miR-320a-3p with 90-Day mortality in cardiogenic shock. Int J Mol Sci. 2020;21(21).
20. Singh S, de Ronde MWJ, Kok MGM, Beijk MA, De Winter RJ, van der Wal AC et al. MiR-223-3p and miR-122-5p as Circulating biomarkers for plaque instability. Open Heart 2020;7(1).
21. Nguyen MT, Min KH, Lee W. MiR-183-5p induced by saturated fatty acids hinders insulin signaling by downregulating IRS-1 in hepatocytes. Int J Mol Sci. 2022;23(6).
22. Ofori JK, Salunkhe VA, Bagge A, Vishnu N, Nagao M, Mulder H et al. Elevated miR-130a/miR130b/miR-152 expression reduces intracellular ATP levels in the pancreatic beta cell. Sci Rep. 2017;7:744986.
23. Pan C, Li M, Wang J, Chu X, Xiong J, Yang X, et al. miR-4431 targets TRIP10/PRKD1 and impairs glucose metabolism. J Diabetes Investig. 2022;13(4):617–27.
24. Han HS, Kang G, Kim JS, Choi BH, Koo SH. Regulation of glucose metabolism from a liver-centric perspective. Exp Mol Med. 2016;48(3):e218.
25. Li T, Han J, Jia L, Hu X, Chen L, Wang Y. PKM2 coordinates Glycolysis with mitochondrial fusion and oxidative phosphorylation. Protein Cell. 2019;10(8):583–94.
26. Yu S, Zang W, Qiu Y, Liao L, Zheng X. Deubiquitinase OTUB2 exacerbates the progression of colorectal cancer by promoting PKM2 activity and Glycolysis. Oncogene. 2022;41(1):46–56.
27. Qi W, Keenan HA, Li Q, Ishikado A, Kannt A, Sadowski T, et al. Pyruvate kinase M2 activation May protect against the progression of diabetic glomerular pathology and mitochondrial dysfunction. Nat Med. 2017;23(6):753–62.
28. Traxler L, Herdy JR, Stefanoni D, Eichhorner S, Pelucchi S, Szucs A, et al. Warburg-like metabolic transformation underlies neuronal degeneration in sporadic Alzheimer's disease. Cell Metab. 2022;34(9):1248–63. e6.
29. Nayak MK, Ghatge M, Flora GD, Dhanesha N, Jain M, Markan KR, et al. The metabolic enzyme pyruvate kinase M2 regulates platelet function and arterial thrombosis. Blood. 2021;137(12):1658–68.
30. Huo P, Li M, Le J, Zhu C, Yao J, Zhang S. Resveratrol improves follicular development of PCOS rats via regulating Glycolysis pathway and targeting SIRT1. Syst Biol Reprod Med. 2023;69(2):153–65.

Publisher's note