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Research Article
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The Effect of *PTPRδ* rs17584499 C/T Polymorphism on Therapeutic Efficacy of Metformin in Chinese Patients with Type 2 diabetes

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Abstract

Aim: To investigate whether the protein tyrosine phosphates receptor type delta gene (*PTPRδ*) rs17584499 C/T genetic polymorphism is associated with development of type 2 diabetes mellitus (T2DM) and metformin therapeutic efficacy in Chinese T2DM patients.

Methods: A case-control study of 402 T2DM patients and 171 healthy controls was conducted to identify the genotypes for *PTPRδ* rs17584499 polymorphism using the ABI 3700 automatic sequence assay. 44 first-onset T2DM patients were selected to orally 500 mg metformin daily for 12 consecutive weeks as monotherapy. Serum fasting plasma glucose (FPG), Postprandial Plasma Glucose (PPG), Glycated Hemoglobin (HbA1c), Fasting Serum Insulin (FINS), Postprandial Serum Insulin (PINS), Triglycerol (TG), Cholesterol (CHO), Low-Density Lipoprotein (LDL-c), High-Density Lipoprotein Cholesterol (HDL-c), and Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), Body Mass Index (BMI) were determined before and after metformin treatment.

Results: There were no significant differences in the allelic frequencies of the *PTPRδ* rs17584499 C/T polymorphism between T2DM patients and healthy controls. After metformin treatment, the values of BMI, FPG, PPG, PINS, HbAlc, CHO, and TG in T2DM patients significantly decreased (P <0.01, respectively), while markedly increased FINS (P <0.001). Metformin significantly decreased the levels of PPG (P <0.05) and CHO (P <0.05) of patients with *PTPRδ* rs17584499 CT+TT genotypes compared of individuals with CC genotype.

Conclusion: *PTPRδ* rs17584499 C/T polymorphism may not be associated with the risk of T2DM. But it may affect the PPG, HbAlc, and CHO in Chinese T2DM patients with metformin monotherapy.

Keywords: Genetic polymorphism; Metformin; Protein tyrosine phosphates receptor type delta gene; Type 2 diabetes mellitus; Efficacy

Abbreviations: GWAs: Genome-Wide Association studies; SNPs: Single Nucleotide Polymorphisms; PCR: Polymerase Chain Reaction; T2DM: Type 2 Diabetes Mellitus; PTPRδ: Protein Tyrosine Phosphates Receptor Type Delta; OCTs: Organic Cation Transporters; MATEs: Multidrug and Toxin Extrusions Transporters; PTPs: Protein Tyrosine Phosphates; LAR-PTPs: Leukocyte Common Antigen-related Subfamily of PTPs; BMI: Body Mass Index; WHR: Waist to Hip Ratio; FPG: Fasting Plasma Glucose; PPG: Postprandial Plasma Glucose; HbAlc: Glycated Hemoglobin; FINS: Fasting Serum Insulin; PINS: Postprandial Serum Insulin; HOMA-IR: Homeostasis Model Assessment for Insulin Resistance; TC: Total Cholesterol; LDL-c: Low-density Lipoprotein-cholesterol; HDL-c: High-density Lipoprotein-cholesterol; DV: Differential Value (post-administration minus pre-administration); Pre-: Pre-administration; Post-: Post-administration

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive and complex disorder that is difficult to treat effectively in the long term. The majorities of patients are overweight or obese, and will be unable to maintain long-term glycogenic control without oral antidiabetic agents [1]. Much effort has been devoted to exploring the pathogenesis of T2DM and finding the most effective drugs for T2DM, yet they were still remaining unknown. The disease is considered to be a polygenic disorder in which genetic variants confers a partial and additive effect. Genetic discoveries have provided the new targets for prevention, diagnosis and treatment of T2DM [2,3]. Until now, genome-wide association studies (GWAs) have identified about 40 susceptibility genes associated with T2DM in different population, these discoveries may give some new clues to explore the pathogenesis and the new targets for treatment T2DM [4-7]. Tsai et al. [8] recent reported that protein tyrosine phosphates receptor type delta gene (*PTPRδ*) as a novel susceptibility gene are significantly associated with the development of T2DM in Taiwan population by GWAs analysis. *PTPRδ* rs17584499 located at 9p24 [8]. Protein tyrosine phosphates (PTPs) are key regulators of the insulin receptor signal transduction pathway, expressed in the major human insulin target tissues or cells, such as liver, adipose tissue, skeletal muscle, and endothelial cells [9,10]. Human *PTPRδ* belongs to leukocyte common antigen-related subfamily of PTPs (LAR-PTPs). LAR-PTPs were a major subfamily of PTPs and suggested to be a negative regulator of the insulin receptor tyrosine kinase [11]. *PTPRδ* gene may play an important role in glucose homeostasis and insulin action.

Metformin is regarded as insulin sensitizing drug for T2DM patients with overweight or obesity [12]. Metformin reduced gluconeogensis by increasing hepatic sensitivity to insulin and decreased the hepatic extraction of certain gluconeogensis substrates

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(e.g. lactate) [13,14]. Metformin is negligibly bound to plasma proteins not metabolized in body. It is eliminated in urine via active renal tubular secretion [14]. Metformin is the first-line agent for T2DM patients. However, considerable individual differences in metformin efficacy are reported [15]. Numerous studies showed that Organic cation transporters (OCTs) and Multidrug and toxin extrusions transporters (MATEs) were the major causes of the individual difference of metformin response rather than drug metabolizing enzymes and drug receptors. OCT1 848C/T, 859C/G, 1022 C/T, OCT2 808 G/T, and MATE1, MATE2-K polymorphisms could significantly influence pharmacokinetics of metformin in T2DM patients in different population [15-18]. Our previous studies showed distributive frequency of OCT1 859C/G polymorphism is very low in Chinese population (unpublished data). Toyama K et al. [17] reported that MATEs variants could not influence the disposition of metformin in vivo in Asian. Thus, genetic polymorphisms of OCTs may be the crucial factors for the individual difference of metformin response in Chinese T2DM patients. Metformin efficacy may be affected by gene polymorphisms.

Up to now, there are no reports about the impacts of *PTPRδ* rs17584499 polymorphism on metformin therapeutic efficacy. *PTPRδ* participates in glucose homeostasis and insulin action. Metformin also reduces glucose levels by increasing insulin sensitivity. In this study we explore the association of *PTPRδ* genetic polymorphism with the development of T2DM and assess the effects of *PTPRδ* rs17584499 polymorphism on metformin efficacy in Chinese patients with T2DM.

Materials and Methods

Subjects

A total of 402 unrelated T2DM patients aged ranging from 24 to70 years (mean: 50.65 ± 10.03, 204 female and 198 male) and 171 healthy controls aged ranging from 23 to 72 years (mean: 46.14 ± 10.36, 67 female and 104 male) were enrolled from Xiangya hospital of Center South University, Changsha, Hunan Province, China and Liu-yang Center hospital, LiuYang City, Hunan Province, China during January 2008 to August 2010. All of the T2DM patients were diagnosed according to the diagnosis criteria of the World Health Organization made in 1997 by fasting plasma glucose (FPG≥7.0 mmol/l) and/or postprandial plasma glucose (PPG≥11.1 mmol/l). The criteria for controls were (1) no past diagnostic history of T2DM; (2) HbA1c was ranging from 3.4 to 6; (3) BMI ranging from 18.5-30 kg/m^2. Subjects with type 1 diabetes, gestational diabetes, and maturity-onset diabetes of the young (MODY), history of lactic acidosis, pregnant and lactating women or those with acute myocardial infarction, trauma, kidney and liver disease were excluded from this study. All of T2DM patients and healthy controls in this study were of Han Chinese population; these subjects were local residents in Hunan Province, China. Written informed consents were obtained from all participants before the start of this study. The study protocol was in accordance with the Helsinki Declaration II and was approved by the Ethics Committee of Xiangya School of Medicine, Central South University. A clinical study admission (the registration number: ChiCTR-CCC00000406) was approved by Chinese Clinical Trial Register. In present study, we selected 44 first-onset T2DM patients (33 male, 11 female) with the same OCT1 1022 CC, 848 CC, and OCT2 808 GG homozygous and different genotypes of *PTPRδ* rs17584499 C/T orally 500 mg metformin (ShuangHe, Beijing, China) daily for 12 consecutive weeks and had not administered any anti-diabetes drugs in last three month.

Clinical laboratory tests

After an overnight fast, blood samples for the determination of plasma glucose and insulin level were collected in the fasting state and at 2 h after breakfast; these parameters were measured at the end of weeks 0 and 12 after administration of metformin. Plasma concentrations of FPG, PPG, CHO, TG, and HDL-c were determined by use of an enzymatic colorimetric assay and lipoprotein electrophoresis, respectively. LDL-c concentration was calculated according to Firedewald formula [19]. Plasma insulin and HbA1c levels were measured by use of a radioimmunoassay kit (BNIBT, Beijing, China) and by high-performance liquid chromatography assay (HPLC), respectively. BMI was calculated as weight (kg)/height (m^2). The homeostasis model assessment for insulin resistance (HOMA-IR) value was calculated according to the following formula to estimate the insulin sensitivity. HOMA-IR = fasting serum insulin (mU/l) × fasting blood glucose (mmol/l)/22.5 [20].

Genotyping analysis

The Genomic DNA was extracted from the peripheral blood leukocytes using the Promega DNA purification kit (Promega, USA) according to the manufacturer protocol and then stored at -80°C until use. The primer pairs used in the amplification of *PTPRδ* rs17584499 C/T were forward primer: 5'- TCAGTCCTACACCTCACCCAAG-3', reverse primer: 5'- CCAGGATAACAGGAACAATGAAATAGC-3'. The primer pairs used for *OCT1* 1022C/T, 848C/T, and *OCT2* 808 G/T polymorphisms were forward primer: 5'- TAGATGCTTTCCCTCG-3', reverse primer: 5'- TCACTCCTCGTAAACAAT-3'; forward primer: 5'- CTGCACTGAGCAACAGCATCAC-3', reverse primer: 5'- GCAGGAGGCAACTTCCCATTC-3'; forward primer: 5'-AGGTGGTTGCAGTTCACAGTT-3', reverse primer: 5'-GGAATTGGGCTCTTTGTGAA-3', respectively. The polymerase chain reaction (PCR) amplification were carried out in a total volume of 25 μl containing 2.5 μl 10× PCR buffer, 2 μl dNTP, 1 μl of each primer, approximately 2 μl genomic DNA as a template and 0.2 μl Tag polymerase (above all reagents from Takara, Dalian, China). The PCR conditions for *PTPRδ* rs17584499 polymorphism were as follows: initial denaturizing at 95°C for 5 min, 35 cycles of denaturizing at 95°C for 30 s, annealing at 55.8°C for 30 s, and extension at 72°C for 30 s with a final extension of 5 min at 72°C. The PCR conditions of *OCT1* 1022C/T and 848C/T were the same as follows: first pre denaturing for 1 min at 94°C, then followed by denaturing for 30 s at 94°C, 30 cycles of annealing for 1 min at 62°C and extending for 1 min at 72°C, at last extending for 7 min at 72°C. The PCR conditions of *OCT2* 808 G/T were: first predenaturing for 1 min at 94°C, then followed by denaturing for 30 s at 94°C, 30 cycles of annealing for 1 min at 56.9°C and extending for 1 min at 72°C, at last extending for 7 min at 72°C. The DNA fragments of the five SNPs were amplified on Eppendorf thermal circler (Eppendorf AG, Germany). The fragments of PCR products were sequenced using the ABI 3700 automatic sequencer (ABI 3700, USA) according to the manufacturer's protocols. The sequence data were analyzed by Chromos software (Version 1.62, Australia) to identify the genotypes.

Statistical analysis

All statistical analysis was carried out by SPSS software (version 13.0 for windows, Chicago, USA). Hardy-Weinberg equilibrium and Allelic frequencies in different groups were compared using Pearson-χ^2 test. Baseline characteristics in T2DM patients and health controls were compared with two-sample *t*-test (normally distribution data analyzed) and Mann-Whitney U test (non normally distribution data analyzed). Baseline characteristics among genotypes were compared

with One-way ANOVA. To estimate the effects of metformin on the metabolic parameters among the genotypes, the Paired-Samples T test were used. All data were presented as mean ± standard deviation (SD) and $P<0.05$ was considered statistically significant.

Results

Basic clinical characteristics of subjects

The basic clinical characteristics of 402 T2DM patients and 171 health controls were summarized in Table 1. There were significant differences in gender distribution (P=0.011), age (50.65 ± 10.03 vs 46.14 ± 10.36, years, P<0.001), BMI (24.84 ± 3.09 vs 22.99 ± 2.77, kg/m^2, P<0.001), waist measurement (86.85 ± 8.35 vs 83.78 ± 8.10, cm, P<0.001), hip measurement (95.44 ± 6.89 vs 92.13 ± 7.18, cm, P<0.001), FPG (9.33 ± 3.63 vs 5.07 ± 0.51, mmol/l, P<0.001), TG (3.06 ± 3.06 vs1.53 ± 1.00, mmol/l, P<0.001), and LDL-C (3.11 ± 1.19 vs 2.51 ± 0.70, mmol/l, P<0.001) between T2DM patients and health controls. However, no significant differences in the levels of waist-to-hip ratio and HDL-c were observed in this study.

Genotyping and allelic frequencies

The genotypes of *PTPRδ* rs17584499 C/T polymorphism were determined in 402 T2DM patients and 171 health controls. The allelic frequencies of *PTPRδ* rs17584499 C/T in T2DM patients and health controls showed in Table 2. The T allele frequencies of *PTPRδ* rs17584499 C/T polymorphism were 12.9% in T2DM patients and 9.4% in health controls, The C allele frequencies of *PTPRδ* rs17584499 C/T were 87.1% in T2DM patients and 91.6% in health controls. No significant differences in allelic frequencies of *PTPRδ* rs17584499 C/T between T2DM patients and healthy control. Genotyped frequencies of *PTPRδ* rs17584499 polymorphism were in Hardy-Weinberg equilibrium ($P>0.05$).

Impacts of *PTPRδ* rs17584499 polymorphism on therapeutic efficacy of metformin in patients with T2DM

To exclude the impacts of OCTs polymorphisms on metformin disposition in vivo, we selected 44 first-onset T2DM patients with the same OCT1 1022 CC, 848 CC, and OCT2 808 GG homozygous and different *PTPRδ* rs17584499 genotypes undergo 12 weeks metformin monotherapy. After 12 weeks treatment, metformin significantly decreased the levels of BMI (24.27 ± 2.77 vs 25.54 ± 3.06, kg/m^2, P<0.001), FPG (6.29 ± 0.90 vs 9.13 ± 3.50, mmol/L , P<0.001), PPG (8.80 ± 1.90 vs 18.60 ± 6.26, mmol/L, P<0.001), PINS (34.76 ± 12.35 vs 49.61 ± 24.73, mU/L , P<0.001), HbAlc (6.74 ± 0.99 vs 8.66 ± 2.55, P<0.001), CHO (4.60 ± 0.86 vs 5.19 ± 1.50, mmol/L, P = 0.01), and TG (1.65 ± 1.11 vs 2.98 ± 3.15, mmol/L, P<0.01), while markedly increased FINS (12.98 ± 4.80 vs 7.67 ± 6.27, mU/L, P<0.001) in patients (n=44) (Table 3). Patients with CT+TT genotype (n = 21) of *PTPRδ* rs17584499 polymorphism significantly decreased the levels of PPG (-8.78 ± 5.72 vs -5.68 ± 4.38, mmol/L, $P = 0.049$), HbAlc (-2.86 ± 2.68 vs -1.08 ± 2.02, $P = 0.015$), and CHO (-0.93 ± 1.14 vs -0.27 ± 1.63, mmol/L, $P = 0.023$) compared for patients with the CC genotype (n= 23) (Table 4, Figure 1).

Discussion

Our study is the preliminary work to investigate the influence of *PTPRδ* rs17584499 C/T polymorphism on metformin therapeutic efficacy. In present study, we found that *PTPRδ* rs17584499 C/T genetic polymorphism could influence the therapeutic efficacy of metformin in Chinese T2DM patients, patients with at least one T allele of *PTPRδ* rs17584499 had better therapeutically efficacy of metformin.

PTPRδ gene is relatively high expressed in insulin target tissues and it could attenuate insulin action and acted as key regulators of the insulin receptor signaling pathway [9,10]. *PTPRδ* gene belongs to LAR-PTPs family. LAR-PTPs (mainly containing LAR, PTPRδ and PTPα) are structurally very similar and play the similar roles in the regulation of cell growth, proliferation, differentiation and metabolism [11]. Numerous studies reported that LAR-PTPs confirmed as the new targets of T2DM treatment elevated insulin receptor dephosphorylating activity in adipose tissue from obese subjects [21-23]. Metformin is the first agent for T2DM patients with obese or overweight. Metformin may suppress oxidation of fatty acids and reduce triglyceride levels in T2DM patients by insulin independent manner, the levels of BMI, CHO and LDL-c decreased after metformin treatment [24]. In our study, data showed that metformin could significantly decrease the levels of BMI, FPG, PPG, PINS, HbAlc, TG and CHO in T2DM patients after

Parameters	T2DM patients (n = 402)	Health control (n = 171)	*P* value
Sex male	204 (50.7%)	67 (49.3%)	
Female	198 (39.2%)	104 (60.8%)	0.011*
Age	50.65 ± 10.03	46.14 ± 10.36	0.000***
BMI (kg/m^2)	24.84 ± 3.09	22.99 ± 2.77	0.000***
Waist (cm)	86.85 ± 8.35	83.78 ± 8.10	0.000 ***
Hip (cm)	95.44 ± 6.89	92.13 ± 7.18	0.000 ***
WHR	0.91 ± 0.06	0.91 ± 0.04	0.779

*$P < 0.05$, ***$P < 0.001$

Table 1: Clinical characteristics of T2DM patients and health controls.

Genotype	T2DM patients N = 402 (frequency)	Health controls N = 171 (frequency)	*P* value
PTPRD rs17584499			
CC	305 (75.9%)	139 (81.3%)	
CT	90 (22.4%)	32 (18.7%)	
TT	7 (1.7%)	0 (0.0%)	0.123
Alleles			
C	700 (87.1%)	310 (90.6%)	
T	104 (12.9%)	32 (9.4%)	0.087

P values are determined by Pearson χ2 test

Table 2: Comparison of allelic frequencies of *PTPRD* rs17584499 C/T polymorphism between T2DM patients and healthy controls.

Paremeters	Before	After	*P* value
BMI (kg/m^2)	25.54 ± 3.06	24.27 ± 2.77	0.000***
FPG (mmol/L)	9.13 ± 3.50	6.29 ± 0.90	0.000***
PPG (mmol/L)	18.60 ± 6.26	8.80 ± 1.90	0.000***
FINS (mU/L)	7.67 ± 6.27	12.98 ± 4.80	0.000***
PINS (mU/L)	49.61 ± 24.73	34.76 ± 12.35	0.000***
HOMA-IR	3.48 ± 4.01	3.65 ± 1.42	0.777
HbAlC (%)	8.66 ± 2.55	6.74 ± 0.99	0.000***
TG (mmol/L)	2.98 ± 3.15	1.65 ± 1.11	0.004**
CHO (mmol/L)	5.19 ± 1.50	4.60 ± 0.86	0.010**
LDL-$_C$ (mmol/L)	2.98 ± 1.11	2.91 ± 0.68	0.556
HDL-$_C$ (mmol/L)	1.21 ± 0.32	1.17 ± 0.25	0.248

**$P < 0.01$, *** $P < 0.001$

Table 3: The basic clinical characteristics of all T2DM patients before and after metformin treatment (n=44).

Parameters		*PTPRδ* rs17584499[A]	
	CC (n=23)	CT+TT (n=21)	*P* value
Sex(F/M)	18(5)	15(6)	0.601
BMI (kg/m^2)	-1.69 ± 1.99	-0.81 ± 1.92	0.143
FPG (mmol/L)	-2.17 ± 2.36	-3.56 ± 4.18	0.177
PPG (mmol/L)	-5.68 ± 4.38	-8.78 ± 5.72	0.049 *
FINS (mU/L)	5.68 ± 5.99	4.90 ± 4.81	0.637
PINS (mU/L)	-16.40 ± 8.87	-13.16 ± 29.86	0.667
HOMA-IR	0.57 ± 3.62	-0.27 ± 4.17	0.480
HbAlc(%)	-1.08 ± 2.02	-2.86 ± 2.68	0.015*
TG (mmol/L)	-1.39 ± 2.58	-1.25 ± 3.23	0.880
CHO (mmol/L)	-0.27 ± 1.63	-0.93 ± 1.14	0.023 *
HDL-$_C$ (mmol/L)	0.00 ± 0.26	-0.09 ± 0.19	0.214
LDL-$_C$ (mmol/L)	0.03 ± 0.75	-0.18 ± 0.85	0.380

A: dominant model *$P < 0.05$ for comparison of CC genotypes with CT+TT genotypes of PTPRδ rs17584499 polymorphism

Table 4: The comparisons of different values (postaministration minus preadministration) in T2DM patients with different *PTPRδ* rs17584499 C/T polymorphism before and after metformin treatment (n = 44).

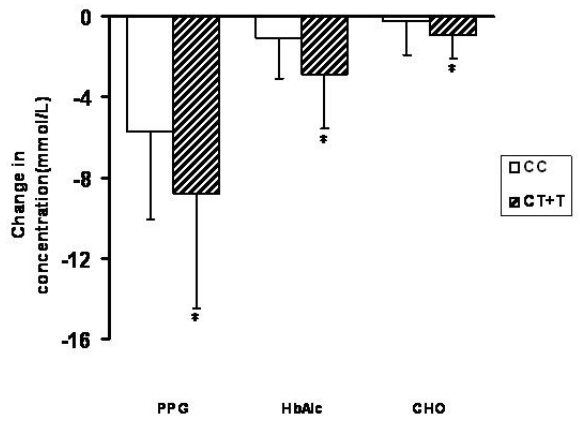

Figure 1: The comparison of differential values (post-administration minus pre-administration) of PPG, HbAlc, and CHO between CC genotype and CT+TT genotypes of *PTPRδ* rs17584499 polymorphism in T2DM patients after 12 weeks metformin treatment. *$P < 0.05$.

12 weeks treatment. They were in accordance with previous reported, whether *PTPRδ* gene is the new target for overweight or obese T2DM patients with metformin treatment need to be further study in biological pathway.

OCTs polymorphisms were the major causes for the individual difference of the pharmacokinetics of metformin in Chinese T2DM patients. Since distributive frequency of OCT1 859C/G polymorphism is very low in Chinese population and MATEs variants could not influence the disposition of metformin in vivo in Asian. The variant allele frequencies of OCT1 848 C/T, 1022 C/T, and OCT2 808 G/T were 0.8%, 11.8% and 13.3% respectively in Chinese population (unpublished data). Therefore, in present study, we excluded the effects of OCTs polymorphisms on metformin response in vivo, and selected the patients with same homozygote of OCT1 848 CC, 1022 CC, and OCT2 808 GG polymorphisms and different *PTPRδ* rs17584499 genotypes orally 12 weeks metformin monotherapy.

Our data also showed patients with CT + TT genotypes of *PTPRδ* rs17584499 polymorphism significantly decreased the level of PPG, HbAlc, and CHO compared of patients with CC genotype after 12 weeks metformin treatment. These results suggested that patients with at least one T allele of *PTPRδ* rs17584499 had better therapeutically efficacy of metformin. The T allele of *PTPRδ* rs17584499 may also beneficial for T2DM patients who need treatment with metformin. Further data analysis is necessary to be replicated in larger samples.

In summary, the genetic polymorphism of *PTPRδ* rs17584499 C/T was not associated with the susceptibility of T2DM. *PTPRδ* rs17584499 polymorphism could influence the therapeutically efficacy of metformin. Moreover, patients with at least one T allele of *PTPRδ* rs17584499 seem to be more sensitive to metformin treatment compared for individuals with the CC genotype. Therefore, we think that prior genotyping analysis for *PTPRδ* rs17584499 polymorphism may be beneficial for T2DM patients who need treatment with metformin. These findings need to be replicated in larger populations with a longer follow up visit. Our study also suggested that susceptibility genes of T2DM development need be detected in different populations may confer different risks and different drug response, which lead to a better understanding of the molecular pathogenesis of T2DM and provide the new targets for prevention, diagnosis and treatment in T2DM.

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