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ORIGINAL ARTICLE

A gene expression study suggests the possible involvement of IGF2BP2-related ncRNA network in Type 2 Diabetes

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Abstract

Aims Genome-wide association studies (GWAS) have identified the IGF2BP2 (Insulin-like Growth Factor 2 mRNA binding protein 2) gene as a susceptibility locus for Type 2 diabetes mellitus (T2D). This study aimed to evaluate the IGF2BP2 mRNA levels in the blood of a cohort of T2D patients and to quantify the expression levels of non-coding RNAs (ncRNAs) that are predicted to interact with it.

Methods We extracted RNA from peripheral blood mononuclear cells of 50 T2D patients and 30 healthy controls (CTRL) and quantified, by qPCR, the IGF2BP2 expression levels. Using bioinformatics tools, we predicted its main ncRNAs target and quantified it.

Results The expression study showed a significantly higher IGF2BP2 level in T2D subjects than in CTRL. In silico analysis identified hsa-let7b-5p as a potential microRNA regulator of IGF2BP2, with reduced expression levels observed in T2D patients. Additionally, three lncRNAs (SNHG5, HOTAIR, and MEG3) were predicted as potential targets of IGF2BP2. Their expression levels were significantly elevated in T2D patients. In vitro assays demonstrated that inhibiting hsa-let7b-5p in HeLa cells resulted in increased expression of IGF2BP2 and the three lncRNAs.

Conclusion These findings highlight a potential regulatory network involving IGF2BP2, hsa-let7b-5p, and lncRNAs. This network may contribute to dysregulation of insulin/IGF signaling and glucose metabolism pathways, providing insights into T2D pathogenesis.

Keywords Type 2 diabetes · IGF2BP2 · lncRNAs

Introduction

Type 2 diabetes mellitus (T2D) is a complex metabolic disease characterized by elevated blood glucose levels due to pancreatic beta-cell dysfunction and insulin resistance. The etiology of T2D is multifactorial with a complex interplay of genetic and environmental factors contributing to the onset of this condition [1]. Genome-wide association Studies (GWAS) and meta-analyses have identified numerous susceptibility loci, helping to understand better the genetic background underlying T2D [2].

Among these identified loci, variants in the IGF2BP2 (Insulin-like Growth Factor 2 mRNA binding protein 2) gene have been described as risk factors for T2D by two independent GWAS [3–5]. In particular, the single nucleotide variants (SNVs) rs4402960 and rs1470579, located in the second intron of this gene, have been extensively studied and are susceptibility factors to T2D in different ethnic populations [6]. Furthermore, the variant allele of the SNV rs4402960 has also been described in association with lower insulin levels, impaired β-cell function [7], and gestational diabetes mellitus [8]. IGF2BP2 gene encodes an RNA binding protein (RBP) that plays a key role in the

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post-transcriptional regulation of numerous genes involved in metabolic processes [9]. In particular, several studies have demonstrated that IGF2BP2 participates in the modulation of insulin/IGF signaling pathways binding to the mRNA of the growth factor IGF2 [9, 10]; indeed, altered levels of IGF2BP2 mRNA have been detected in pancreatic islets of T2D patients [11].

It is known that non-coding RNAs (ncRNAs) contribute to gene expression regulation and could also influence IGF2BP2 mRNA levels. For instance, microRNAs (miRNAs) can suppress IGF2BP2 expression binding to its 3' UTR. On the other hand, IGF2BP2 interacts with several classes of RNA and modulates their expression, including ncRNAs. In particular, growing evidence shows that IGF2BP2 can modulate biological functions by binding and stabilizing lncRNAs, a class of ncRNAs longer than 200nt [12]. lncRNAs have recently emerged for their involvement in diabetes pathogenesis and alterations in IGF2BP2 could therefore influence the levels of its lncRNAs targets, modulating different pathways underlying the development of T2D [13, 14].

Based on this knowledge, we aimed to investigate the mRNA expression levels of IGF2BP2 in a cohort of T2D patients' blood and quantify the expression levels of ncRNAs bioinformatically predicted to interact with it.

Materials and methods

Patients recruitment

We collected blood samples from 50 patients with T2D attending the Diabetes Clinic of the Policlinico Tor Vergata in Rome (Italy). Patients were eligible for inclusion if they had a clinical diagnosis of type 2 diabetes and were aged between 18 and 80 years. Individuals were excluded in case of a history of malignancies, autoimmune disorders, renal failure (defined as serum creatinine $\geq$2 mg/dL), or severe hepatic disease. Anthropometric and clinical characteristics of the study population have reported in Table S1.

At the time of blood sampling, the following measurements were obtained: casual blood pressure, height, weight, waist circumference, and blood glucose levels. Individuals who reported smoking at least one cigarette per day on a regular basis were categorized as current smokers. Alcohol intake was also recorded. Subjects who engaged in at least one hour per week of leisure-time physical activity were considered physically active, while those who did not meet this criterion were classified as sedentary. A comprehensive clinical history was collected for each patient, including family history of metabolic and cardiovascular diseases in first-degree relatives, the presence of any relevant active medical conditions, and current pharmacological treatments. Coronary artery disease (CAD) was defined as a history of myocardial infarction, angina, coronary revascularization procedures (such as angioplasty or bypass surgery), or documented evidence of clinically significant myocardial ischemia. Asymptomatic patients—those without typical or atypical cardiac symptoms or abnormal resting electrocardiogram—did not undergo screening for silent CAD. The definition of cardiovascular disease included both coronary and non-coronary forms of atherosclerotic disease, specifically one or more of the following: CAD, peripheral artery disease, carotid artery disease (defined as $\geq$50% stenosis of a carotid artery), or a history of cerebrovascular events such as transient ischemic attack or stroke. Peripheral artery disease was diagnosed based on the presence of claudication and/or absence of palpable dorsalis pedis or posterior tibial pulses, or documented by instrumental methods (e.g., Doppler ultrasound or magnetic resonance angiography). Data on prior ischemic foot ulcers, lower limb amputations, or revascularization procedures were also collected. Routine laboratory evaluations included glycated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, serum creatinine, and 24-hour urinary albumin excretion. Microalbuminuria and macroalbuminuria were defined as a 24-hour urinary albumin excretion between 30 and 299 mg and $\geq$300 mg, respectively. The presence of non-proliferative or proliferative diabetic retinopathy was assessed through ophthalmoscopic examination. Diabetic neuropathy was diagnosed when at least two neurological tests revealed abnormalities.

Thirty age-, sex-, and ethnicity-matched healthy subjects were also enrolled as controls. The study was approved by the Ethics Committee of the University Hospital of Rome Tor Vergata (approval number 2936/2017). All participants gave their written informed consent.

Expression study

PBMCs were isolated using the standard Ficoll-Histopaque density gradient centrifugation method (Sigma-Aldrich). Total RNA was extracted from PBMCs using TRIzol reagent (Ambion, CA, USA), and subsequently reverse transcribed into complementary DNA (cDNA) using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Waltham, MA, USA). Gene expression analysis was carried out by quantitative reverse transcription polymerase chain reaction (RT-qPCR) using the SYBR Green Assay (Applied Biosystems).

For miRNA expression analysis, cDNA was synthesized using the TaqMan™ Advanced miRNA cDNA Synthesis Kit (Life Technologies–Applied Biosystems, CA, USA).

The expression of hsa-let-7b-5p was assessed using the TaqMan Advanced miRNA Assay (Applied Biosystems). All quantitative real-time PCR (qRT-PCR) were per-formed on a 7500 Real-Time PCR System (Applied Biosystems, Foster City, CA, USA).

The expression levels of IGFBP2 and ncRNAs were also investigated in HeLa cells treated with the mirVana® miRNA inhibitor of has-let-7b-5p, as described in a previous study [15]. In particular, HeLa cell line (ATCC) was cultured in complete medium DMEM supplemented with 10% Fetal Bovine Serum (FBS), 1X L-glutamine at 37 °C and 5% CO2. The cells were seeded at a 250,000 cell/well density and grown in complete culture medium. To inhibit the microRNA has-let7b-5p, HeLa cells were transiently transfected with mirVana® miRNA inhibitor (Thermofisher Scentistic). For transfection, we used a final concentration of 45 pmol of inhibitor and 5 µl of Lipofectamine™ RNAiMAX Transfection Reagent (Invitrogen) following the manufacturer's instructions. Cells were harvested 24, 48 and 72 h after transfection and suspended in 500 µl of TRIzol (Ambion) until RNA extraction.

All qRT-PCR were performed in triplicate and in each assay an endogenous control was run to standardize the results (β-actina and GADPH). Relative expression levels were calculated using the 2-ΔΔCt method.

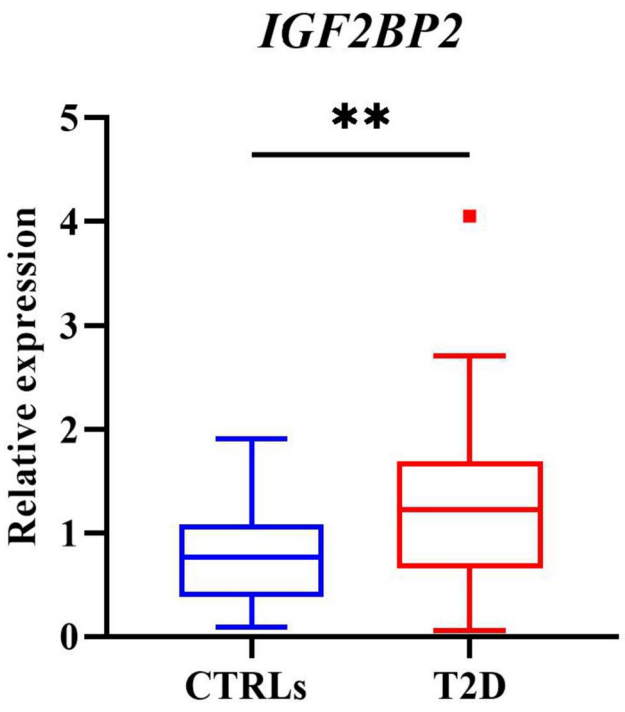


Fig. 1 Comparison of IGF2BP2 expression levels between CTRLs and T2D subjects. T2D patients showed a significant increase in IGF2BP2 expression levels compared to CTRLs. ** P-value = 0.002, calculated by Mann-Whitney test

In silico prediction analysis

A first in silico analysis was conducted using the TargetScanHuman 8.0 (https://www.targetscan.org/vert_80/) to predict potential miRNAs binding to the 3'UTR region of IGF2BP2 transcript. A second in silico analysis was performed to identify putative lncRNAs targets of IGF2BP2. This analysis was carried out by using RNAinter (http://www.rnainter.org/) and the results obtained from this bioinfo rmatic analysis were subsequently confirmed with another bionformatic tool, Encori (https://rnasysu.com/encori/).

Statistical analysis

Statistical analyses were achieved using the SPSS statistical software package v.26 (IBM Corp, Armonk, NY, USA), while all graphs were performed by GraphPad Prism 9 (GraphPad Software, USA). The normal distribution of expression data from qRT-PCR assays was first evaluated using the Kolmogorov-Smirnov test. Accordingly, statistical significance was assessed using Mann-Whitney or ANOVA tests. A post hoc power analysis ($\alpha = 0.05$) based on the observed difference in IGF2BP2 expression levels between T2D patients and controls has been performed. Pearson correlation analysis was used to evaluate a possible linear relationship among gene expression levels. The receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of the genes differentially expressed, to discriminate the patients and control group. Data are shown as mean ± standard deviation. For all analyses, differences were considered as significant at $P < 0.05$. The main steps of the study, from sample collection to data analysis, are summarized in the methodological flowchart diagram (Figure S1).

Results

In this study, we recruited 50 participants with T2D (34 men), with a mean age of 62.1 ± 6.8 years, a T2D duration of 12.3 ± 9.1 years, a body mass index (BMI) of 31.6 ± 6.2 kg/m2, and HbA1c of 7.2 ± 1.5% (55.3 ± 16.5 mmol/mol). IGF2BP2 expression levels were analyzed in peripheral blood mononuclear cells (PBMCs) of all T2D patients and 30 age-, sex-, and ethnicity-matched healthy controls (CTRLs). T2D patients showed a significant increase in IGF2BP2 expression levels compared to CTRLs ($P = 0.002$), as shown in Fig. 1. The post hoc power calculation based on IGF2BP2 expression differences indicated a power value of 93.4% ($\alpha = 0.05$), supporting the robustness of the observed association.

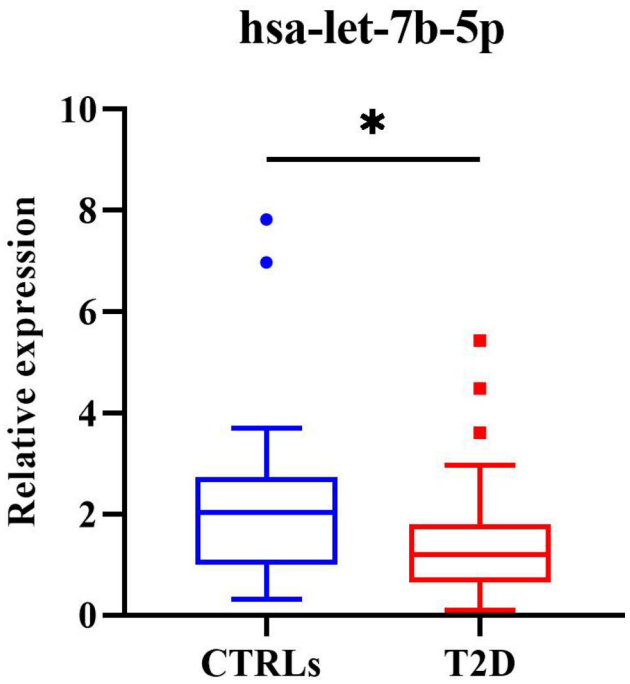


Fig. 2 Comparison of hsa-let-7b-5p expression levels between CTRLs and T2D subjects. T2D patients showed a significant decrease in hsa-let-7b-5p expression levels compared to CTRLs. * P-value = 0.04, calculated by Mann-Whitney test

Since it is known that IGF2BP2 interacts with several classes of RNAs, we performed an in-silico analysis to identify potential miRNAs that interact with IGF2BP2 mRNA and regulate its expression. Bioinformatic analysis, using TargetScanHuman 8.0, showed that hsa-let-7b-5p is the miRNA with the highest interaction score (context++score= −0.39) and the best predicted binding affinity (relative KD= −5.08) with the IGF2BP2 transcript (Table S2). The putative binding site is located at position 1304–1311 of the IGF2BP2 3' UTR and lies on a site widely conserved among vertebrates.

Therefore, we analyzed the expression levels of hsa-let-7b-5p in T2D patients and CTRLs. As shown in Fig. 2, T2D patients showed a significant decrease of this miRNA compared to CTRLs ($P = 0.04$).

Then, we performed a second in silico analysis to predict potential lncRNAs targets of IGF2BP2 using an online software (RNAInter). This predictive analysis identified several potential lncRNAs targets of IGF2BP2. Based on interaction scores and literature data, we selected three of them as potentially involved in the mechanisms underlying T2D: SNHG5 (Small Nucleolar RNA Host Gene 5) [score = 0.4772], HOTAIR (HOX Transcript Antisense RNA) [score = 0.3973] and MEG3 (Maternally Expressed Gene 3) [score = 0.1229]. Subsequently, the predicted interactions were validated by another bioinformatic tool, ENCORI, which provides a specific section for predicting RBP-lncRNAs interaction. Moreover, according to the bioinformatic findings, the interactions between SNHG5/HOTAIR and IGF2BP2 are also supported by strong experimental evidence [16, 17]. On the contrary, the interaction between MEG3 and IGF2BP2 is only computationally predicted.

Therefore, we analyzed the expression levels of these three lncRNAs in T2D patients and CTRLs. Expression levels analyses showed an increase of all three selected lncRNAs in T2D subjects compared to CTRLs ($P < 0.0001$ for MEG3; $P = 0.0017$ for HOTAIR; $P < 0.0001$ for SNHG5) (Fig. 3).

Since all three lncRNAs showed significant increase in expression levels in T2D patients, we performed the ROC curve analysis, to evaluate the capacity of these molecules to identify the subjects more likely to develop T2D. The results demonstrated that the area under the ROC curve (AUC) for the model including the three lncRNAs was 0.84 with 83% sensitivity and 72% specificity (Fig. 4). Moreover, statistical analysis highlighted a positive correlation between IGF2BP2 mRNA levels and the three lncRNAs

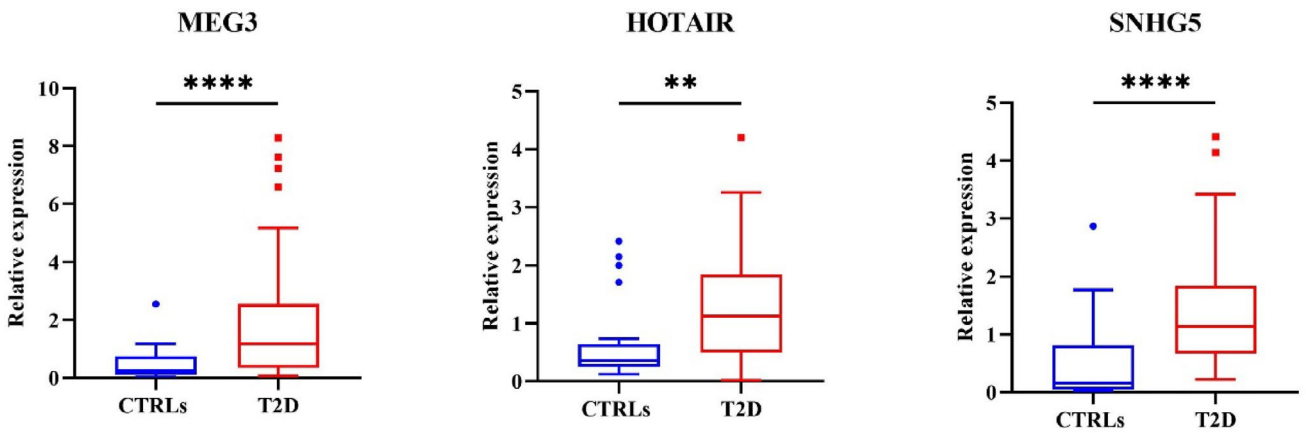
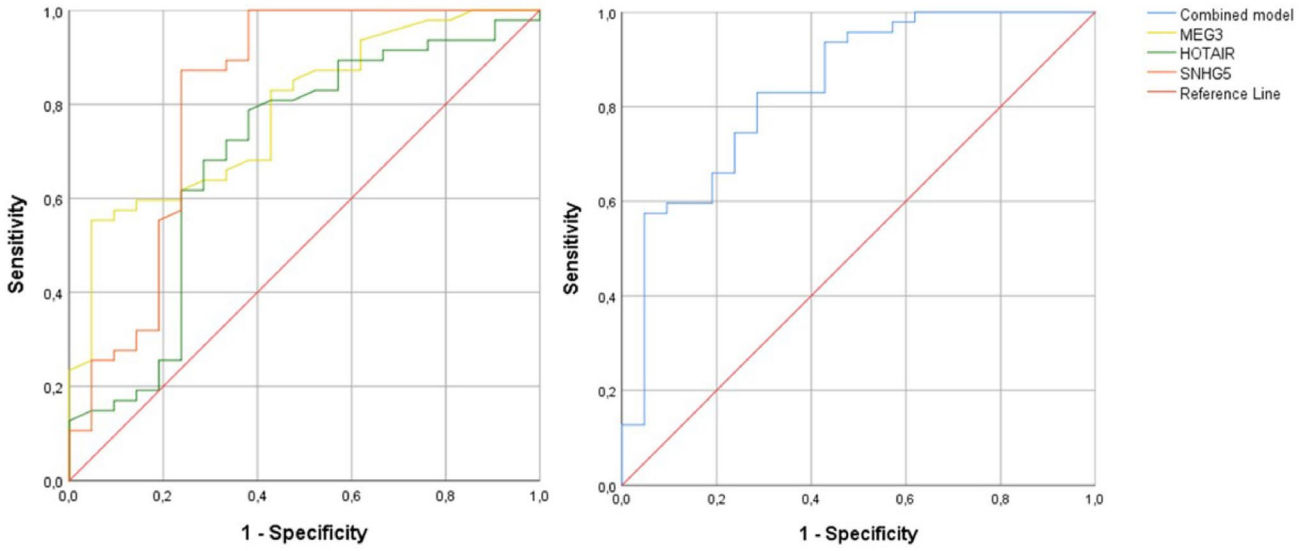


Fig. 3 Comparison of lncRNAs expression levels between CTRLs and T2D subjects. T2D patients showed a significant increase in MEG3, HOTAIR and SNHG5 expression levels compared to CTRLs. **** P-value < 0.0001; **P-value = 0.0017, calculated by Mann-Whitney test



	AUC	95% CI	Std. error
MEG3	0.784	0.671-0.896	0.057
HOTAIR	0.694	0.547-0.840	0.075
SNHG5	0.817	0.685-0.949	0.067
Combined model	0.839	0.733-0.945	0.054

Fig. 4 Receiver operator characteristic (ROC) curves for diabetic subjects. ROC curve analysis evaluating the predictive ability of the combined lncRNA panel (MEG3, HOTAIR, and SNHG5) for T2S. The model including all three lncRNAs showed an AUC of 0.84, with 83% sensitivity and 72% specificity. *AUC* Area under the curve, *CI* Confidential interval, *Std* Standard deviation

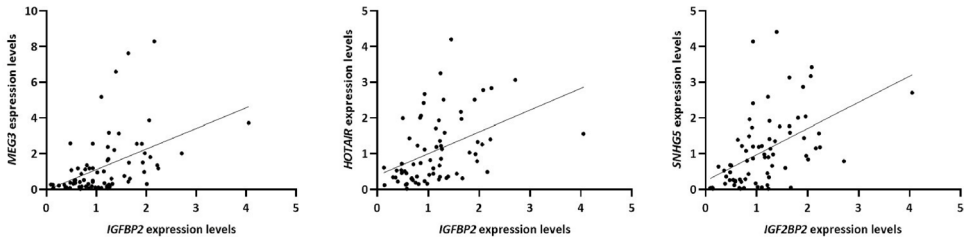


Fig. 5 Correlation analysis between IGF2BP2 expression levels and the three predicted lncRNAs. Correlation analyses revealed a significant positive association between IGF2BP2 mRNA expression levels and each of the three lncRNAs (MEG3: $P<0.0001$, $R=0.459$; HOTAIR: $P=0.0002$, $R=0.438$; SNHG5: $P<0.0001$, $R=0.488$)

($P<0.0001$ $R=0.459$ for MEG3; $P=0.0002$ $R=0.438$ for HOTAIR; $P<0.0001$ $R=0.488$ for SNHG5), as we expected (Fig. 5).

Subsequently, we have explored possible associations between the expression levels of these genes and patients' clinical characteristics, including the micro- and macrovascular complications. We observed that patients with microalbuminuria showed a higher expression level of IGF2BP2 ($p=0.015$).

To verify the hypothesis that, in T2D subjects, the decrease of hsa-let-7b-5p has an effect on IGF2BP2 and its putative lncRNAs targets, we performed in vitro functional assays. In a previous study, we treated Hela cells with hsa-let-7b-5p inhibitor and verified that this miRNA was decreased compared to untreated cells [15]. In those same cells, we evaluated the expression levels of IGF2BP2 and of three predicted lncRNAs. As expected, in HeLa cells treated with the hsa-let-7b-5p inhibitor, we observed a progressive increase in IGF2BP2 mRNA levels compared to untreated cells (Fig. 6).

In agreement, even the expression levels of MEG3, SNHG5 and HOTAIR increased in the treated HeLa cells. In particular, the change of expression levels reached statistical significance after 24 h of treatment for HOTAIR and after 48 h for MEG3 and SNHG5.

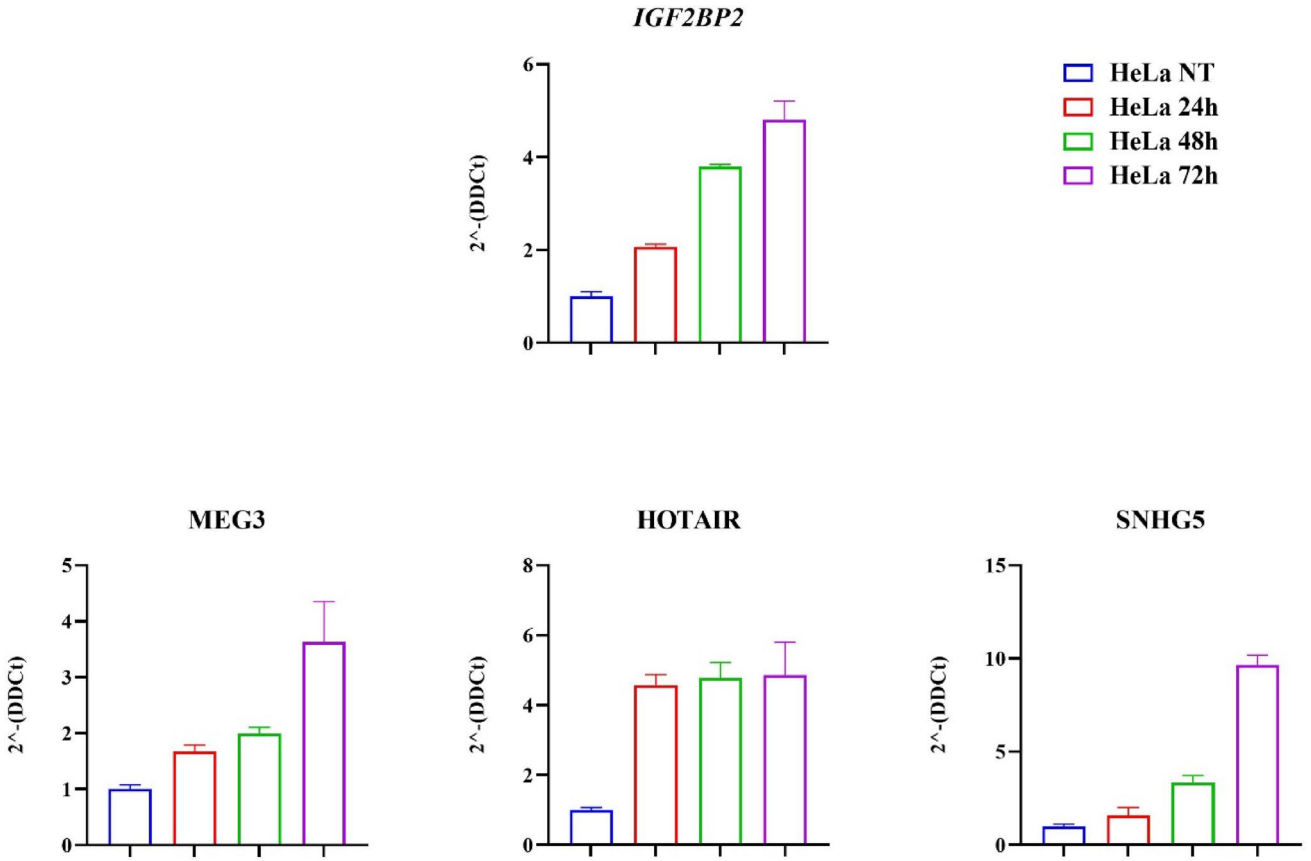


Fig. 6 Effect of hsa-let-7b-5p inhibition on IGF2BP2 and lncRNAs mRNA levels in HeLa cell line at three different time points (24, 48 and 72 h). Inhibition of hsa-let-7b-5p resulted in a progressive increase in IGF2BP2 mRNA and lncRNAs expression compared to untreated cells, supporting the hypothesis that reduced hsa-let-7b-5p levels contribute to IGF2BP2 upregulation

Discussion

T2D is characterized by alterations in insulin secretion and sensitivity and elevated insulin and blood glucose levels. Genetic factors play a central role in the development and pathogenesis of this condition and many susceptibility loci have been identified. Three independent GWAS found a strong association between genetic variants in the IGF2BP2 gene and T2D [3–5] and replication studies have reported that several SNVs are associated with reduced insulin sensitivity or low glucose levels [18]. However, few studies have been conducted on the expression levels of this gene, and specific data on PBMCs blood sample from subjects with T2D are lacking.

In this study, we observed an increase of IGF2BP2 levels in PBMCs of T2D patients compared to CTRLs. Consistent with these data, higher levels of IGF2BP2 were also detected in adipose tissue and in the pancreatic islets from T2D patients compared to those from healthy individuals [19, 20]. An in-vivo study has also demonstrated that IGF2BP2-deficient mice presented improved glucose tolerance and insulin sensitivity [21], suggesting the crucial role of this gene in regulating glucose homeostasis. IGF2BP2 may contribute to T2D development by binding to the 5'-UTR of IGF2 (Insulin-like growth factor 2) mRNA and promoting its translation. It has been demonstrated that IGF2 overexpression plays an important role in the predisposition to T2D by causing β-cell dysfunction and making islets more vulnerable to β-cell damage and immune attack [22].

Interestingly, in our cohort, IGF2BP2 expression levels were higher in patients with microalbuminuria compared to those without renal involvement. This finding is consistent with emerging evidence linking IGF2BP2 to early renal injury in diabetes. For example, an expression study on the kidney of diabetic mice found elevated IGF2BP2 mRNA levels at 5 weeks compared with controls [23]. Although direct human data are limited, these findings support our hypothesis that IGF2BP2 up-regulation in PBMCs may reflect early microvascular stress in the kidney.

Our prediction analysis has shown let-7b-5p as a possible miRNA interacting with the 3'-UTR region of the IGF2BP2 transcript. It is known that miRNAs can modulate the gene expression binding to the 3' UTR region of

mRNAs, so a reduction of let-7b-5p could be one of the factors that induces an increase in IGF2BP2 in T2D patients. As hypothesized, we found a decrease in the expression levels of let-7b-5p in our cohort of T2D patients compared to CTRLs. The involvement of let-7b-5p in T2D pathogenesis has also been reported in a previous study, describing decreased levels of this miRNA in T2D patients and a negative association between the expression levels of let-7b-5p and serum insulin levels [24].

Most studies have indicated that IGF2BP2 helps promote gene expression. Indeed, IGF2BP2 is structurally featured with tandem repeats of the RNA recognition motif at the N-terminal and heterogeneous nuclear ribonucleoprotein K homology domains at the C-terminal, that cooperate to recognize and bind to hundreds of target transcripts, to improve their stability, and translation [25]. In addition to mRNAs, IGF2BP2 can also recognize ncRNAs. For this reason, we performed an in-silico prediction analysis and identified SNHG5, HOTAIR and MEG3 as potential lncRNAs targets of IGF2BP2. Expression analyses highlighted an increase of all three selected lncRNAs in T2D subjects compared to CTRLs and their positive correlation with IGF2BP2 mRNA levels. The interaction of IGF2BP2 with SNHG5 [16] and HOTAIR [17] had also been demonstrated through functional studies.

These three lncRNAs have already been investigated in T2D patients. Indeed, in a recent study, circulating levels of HOTAIR were reported to be higher in T2D and pre-diabetes patients than healthy subjects, suggesting its potential role as a biomarker to distinguish these groups [26]. Similarly, Alrefai et al., have shown that MEG3 could be a possible biomarker able to discriminate T2D towards pre-diabetes patients [27]. In addition, overexpression of MEG3 has been observed in PBMCs of T2D patients [28] and in subcutaneous adipose tissue of obese women [29]; moreover, its upregulation enhances hepatic insulin resistance, a major feature of T2D [30]. Finally, a significant positive correlation was found between HbA1c and the expression levels of HOTAIR [26] and MEG3 [31], while elevated SNHG5 serum levels were detected mainly in nephropathic patients [32]. These results suggest that increased levels of these lncRNAs could participate in the mechanisms underlying T2D and, if appropriately confirmed in larger and validated cohorts, they could represent easily accessible biomarkers to identify subjects at high risk of developing this condition.

Our in vitro results also confirmed that acting on the levels of let7b-5p, it is possible to modulate the levels of IGF2BP2 and the three lncRNAs targets. In fact, by inhibiting the expression levels of this miRNA in the cell line, we observed a significant increase in IGF2BP2, HOTAIR, SNHG5 and MEG3 levels. This increase could therefore emulate what we observed in T2D patients, where we confirmed the decrease in let7b-5p. Therefore, this miRNA seems to play a key role in the regulation of the IGF2BP2–lncRNAs axis. Given the cross-sectional nature of our study, we cannot determine if the dysregulation of this axis contributes to the development of T2D or is a consequence of the disease. However, our in vitro data support the hypothesis that reduced let-7b-5p levels may increase IGF2BP2 expression and its lncRNA targets, establishing a regulatory loop potentially relevant in T2D. (Figure S2).

This study has some limitations. Functional assays were performed in HeLa cells due to their high transfection efficiency, although they have no metabolic relevance. Future studies should validate these findings in disease-relevant models such as hepatocytes or pancreatic β-cells. A further limitation is the lack of protein material, which prevented the assessment of IGF2BP2 protein levels, because this analysis was not included in the original study design at the time of patient recruitment. Moreover, we did not perform luciferase assays to confirm our hypothesis. However, the interaction between hsa-let-7b-5p and IGF2BP2 has already been validated through functional assays [33]. Similarly, IGF2BP2 binding to HOTAIR and SNHG5 lncRNAs has been experimentally demonstrated [16, 17]. Our expression data and correlation analysis are therefore consistent with these previous findings.

Conclusions

In conclusion, our results highlight a significant upregulation of IGF2BP2 mRNA levels in T2D patients, supporting its potential role in T2D pathogenesis. Both in silico analysis and experimental data suggest a complex interaction network involving IGF2BP2 and specific ncRNAs. In particular, our findings showed the existence of a regulatory axis where decreased hsa-let-7b-5p levels may lead to increased IGF2BP2 expression, which, in turn, could influence the expression of its lncRNAs targets. Although it is not possible to identify a causal relationship between alterations in this axis and disease, these findings provide insight into the molecular interactions that potentially contribute to the deregulation of insulin secretion and sensitivity observed in T2D patients. Overall, our data support the existence of an IGF2BP2-related ncRNA network that may play a role in the complex pathogenesis of type 2 diabetes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00592-025-02640-x.

Author contributions Conceptualization, A.L. and C.C.; formal analysis, A.L., G.D.B. and C.M.; investigation, A.L., G.D.B. and C.M.; resources, F.A. and D.L; writing—original draft preparation, A.L.; C.M. and C.C.; writing—review and editing, V.S. and P.B.; visualization,

G.D.B.; supervision, V.S. and P.B.; project administration, G.N.; funding acquisition, G.N. All authors have read and agreed to the published version of the manuscript.

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Declarations

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

Ethical approval The study was approved by Ethics Committee of the University Hospital of Rome Tor Vergata (Approval No. 2936/2017).

Informed consent Informed consent was acquired from the patients.

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