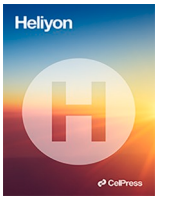
Heliyon 10 (2024) e37909

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Increased nuclear receptor subfamily 2, group E, member 1 (NR2E1) concentrations of PBMCs are associated with chronic inflammation in overweight/obesity

Mingqing He [b,1], Qiyuan Cui [b,1], Yun Zheng [b], Bin Feng [a,**], Zheng Liu [a,*]

[a] Department of Endocrinology, The First Affiliated Hospital of Soochow University, No.188 Shizi Street, Suzhou, Jiangsu, 215006, China
[b] Department of Geriatrics, The First Affiliated Hospital of Soochow University, No.188 Shizi Street, Suzhou, Jiangsu, 215006, China

ARTICLE INFO

Keywords:
NR2E1
Overweight/obese
Chronic inflammation
Proinflammatory factor

ABSTRACT

Background: Chronic inflammation plays a crucial role in the pathogenesis of overweight/obesity. Nuclear receptor subfamily 2, group E, member 1 (NR2E1) is one of the nuclear receptor family proteins that play crucial roles in regulating numerous life processes. In this study, we attempted to detect NR2E1 levels in peripheral blood mononuclear cells (PBMCs) of overweight/obese people and preliminarily elucidate the regulatory role of NR2E1 in obesity-related chronic inflammation.

Methods: We conducted a cross-sectional analysis of the clinical and biochemical data from 62 overweight/obese people and 70 control subjects. PBMCs of the participants were collected for detection of NR2E1 levels. PBMCs isolated from the control subjects were treated with different concentrations of palmitic acid (PA). We also transfected p-EGFP-N1-NR2E1 plasmids into PBMCs and treated them with PA, then detected TNF-α and IL-6 concentrations in the supernatant of PBMCs.

Results: The NR2E1 mRNA and protein levels in overweight/obese people were both significantly higher than those in normal-BMI people ($p < 0.01$). NR2E1 mRNA levels in PBMCs of overweight/obese people were positively related with TC, FFA, IL-6, TNF-α ($r = 0.387, 0.440, 0.610, 0.530$, $p < 0.01$) and LDL-c ($r = 0.290$, $p < 0.05$). A similar correlation was also found between NR2E1 protein levels and these parameters. The expression of NR2E1 in PBMCs from the control subjects increased apparently with the treatment of PA in a concentration-depend manner *in vitro*. Overexpression of NR2E1 in PBMCs decreased TNF-α and IL-6 expression induced by PA ($p < 0.01$).

Conclusion: NR2E1 levels are increased in overweight/obese people and have a positive relationship with TC, FFA, LDL-C, TNF-α and IL-6. Overexpression of NR2E1 could alleviate PA-induced chronic inflammation. NR2E1 may be a potential target for regulating chronic inflammation in obesity.

* Corresponding author.
** Corresponding author.
E-mail addresses: njufengbin@163.com (B. Feng), liuzheng06@suda.edu.cn (Z. Liu).
[1] Mingqing He and Qiyuan Cui contributed equally to this study and should be regarded as the co-first authors.

https://doi.org/10.1016/j.heliyon.2024.e37909
Received 17 March 2024; Received in revised form 2 September 2024; Accepted 12 September 2024
Available online 16 September 2024

1. Introduction

Overweight and obesity have become a huge threat to human health worldwide, with over 710 million obese people, accounting for 4.0 million deaths every year according to the recent epidemiological data [1]. Chronic inflammation, as indicated by various studies, plays a crucial role in the pathogenesis of obesity [2]. Accumulated studies have implied that in overweight/obesity, adipose tissue is infiltrated by immune cells [3,4]. Proinflammatory factors such as TNF-α, IL-6, and MCP-1, which are secreted by adipose tissue and immune cells, not only affect adipose tissue, but also affect muscles, pancreas, liver, kidneys and other organs through the circulatory system [5]. Obesity-related chronic inflammation causes insulin resistance throughout the body [6], and further leads to metabolic diseases such as type 2 diabetes and atherosclerosis [7]. Peripheral blood mononuclear cells (PBMCs), as the main source of inflammatory cells in adipose tissue, are often used to evaluate the chronic inflammatory status of obesity [8,9].

The nuclear receptors (NRs) are the most abundant transcription factors involved in regulating development, metabolism and inflammation [10,11]. Nuclear receptor subfamily 2, group E, member 1 (NR2E1), is a ubiquitously expressed nuclear receptor, not only expressed in nervous system, but also expressed in other tissues and organs, such as islet, adrenal gland, blood cells and so on. NR2E1-knockout mice showed impaired liver glucolipid metabolism and lower weight and fat pad content compared to the control mice [12]. NR2E1 deficiency aggravated insulin resistance [13] in a diet-induced obese mice model. Knockdown of NR2E1 resulted in increased sensitivity to lipotoxicity and oxidative stress in beta cells [14]. It was reported that NR2E1 was closely related to subclinical inflammation of type 2 diabetes mellitus [15], and reduced the inflammatory response of islet cells [16]. However, the association between NR2E1 and chronic inflammation in overweight/obesity is still unknown. Therefore, in this study we aimed to detect NR2E1 levels in PBMCs of overweight/obese people, analyze the correlation between NR2E1 and metabolic indicators as well as proinflammatory factors. Besides, we overexpressed NR2E1 in PBMCs *in vitro*, and investigated its effect on PA-induced inflammation.

2. Material and methods

2.1. Subject

62 overweight/obese people recruited by the First Affiliated Hospital of Soochow University from December 2019 to April 2021, and 70 individuals with BMI below 24 kg m^{-2} were enrolled as a control group in the study. The age of the participants was between 18 and 60 years old. Overweight and obesity are defined as body mass index (BMI) $\geq$ 24 kg m^{-2} and $\geq$28 kg m^{-2}, respectively, according to the Consensus of Chinese Experts on Adult Obesity Prevention and Control (2011). BMI of all the subjects was above 24 kg m^{-2}, including 47 people with BMI exceeding 28 kg m^{-2}. All the enrolled subjects received 75 g glucose oral glucose tolerance test (OGTT) to make sure they were free from diabetes. Exclusion criteria included: (1) pathological overweight/obesity caused by the hypothalamus, pituitary, thyroid and other diseases; (2) acute infection, stress status, hypertension, severe liver, kidney or other systemic diseases; (3) taking medicines that may affect liver function, blood lipid level or endocrine metabolism; (4) pregnant or lactating women. The study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Soochow University (Approval number: 2019079). All the subjects signed written informed consent.

2.2. Anthropometric and biochemical measurements

The basic information of the subjects was obtained by questionnaire. Height, body weight and waist circumference (WC) were measured by professionals. BMI was calculated as body weight (kg) divided by height (m) squared. All subjects were fasting for more than 12 h before drawn venous blood the next morning. Triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL-c), high-density lipoprotein (HDL-c), free fatty acid (FFA), fasting blood glucose (FBG) and alanine aminotransferase (ALT) were measured by an autoanalyzer (Hitachi 7600, Hitachi, Ltd., Japan). An automated immunoassay analyzer (AIA-2000ST, TOSOH company, Japan) was used to detect fasting insulin (FIN). Insulin resistance index was measured by homeostasis model assessment of insulin resistance (HOMA-IR) as FIN (μU/mL) × FBG (mmol/L)/22.5.

2.3. Separation of PBMCs

2 mL fasting venous blood was mixed with equal amount of Hank's solution thoroughly, then 2 mL PBMCs separation reagent (Haoyang biotech company of Tianjin, China) was added. After centrifuged at 2000 rpm for 25 min, PBMCs were collected from the third layer from the bottom up. Washed PBMCs by Hank's solution for several times, and centrifuged again. Then collected PBMCs for detection and further experiments.

2.4. Cell culture and transfection of PBMCs

RPMI1640 medium (Thermo Fisher Scientific, American) containing 10 % fetal bovine serum (Thermo Fisher Scientific, American) was used to culture PBMCs at 37 °C and 5 % CO_2 in a humidified cell incubator. Divided PBMCs into control group and O-NR2E1 group using random number method, and transfected negative control plasmids and p-EGFP-N1-NR2E1 plasmids according to the instructions of Lipofectamine3000. Then continued to culture for 72 h at 37 °C and 5 % CO_2. Treated the cells with RPMI1640 medium and 500 μM palmitic acid (PA) for 6 h. Centrifuged at room temperature for 5 min with 2000 rpm and discarded the supernatant. Then collected PBMCs and the supernatant separately for detection.

2.5. Real-time PCR analysis

The RNA from PBMCs was extracted by RNA extraction kit (Beijing SBS Genetech, China) and reversely transcribed into cDNA for RT-PCR by reverse transcription kit (Promega, USA). Primer sequences: NR2E1: F 5′-GCACAACCAATAGCCACCTG-3′, R 5′-AAATGCGGCTTGTTGATCCG-3'. β-actin: F 5′-CCTGGCACCCAGCACAAT-3′, R 5′GGGCCGGACTCGTCATAC-3'. Reaction condition: pre-denaturation at 95 °C for 2 min, denaturation at 95 °C for 15 s, denaturation at 60 °C for 34 s, extension at 72 °C for 30 s, cycle for 40 times, and extension at 72 °C for 10 min. The relative quantification method ($2^{-\triangle\triangle CT}$) was used to detect the relative content of NR2E1.

2.6. Western blotting

The total protein was extracted by lysing PBMCs with RIPA buffer. The concentration of the proteins was detected by the BCA kit. After routine SDS-PAGE electrophoresis, the membrane was immersed in TBST with 5 % skim milk powder for 2 h, and incubated with primary antibody against NR2E1 (1:500), β-actin (1:10000) at 4 °C overnight. All the primary antibodies were bought from Cell Signaling Technology, Boston, USA. After washed for 3 times, added HRP-labeled secondary antibody (1:10000 goat anti-rabbit, Abcam, Cambridge, UK) and incubated at room temperature for 1 h. Then washed for 3 times, the protein membrane was fully contacted with the mixture chemiluminescence reagent for 5 min. The optical density values were analyzed by Image Pro Plus 6.0 software.

2.7. ELISA

The concentrations of TNF-α and IL-6 from the plasma and the supernatant of PBMCs were detected by ELISA kits (Wuhan Boster Biotech, China).

2.8. Statistical analysis

SPSS 21.0 (IBM, USA) software was adopted for statistical analysis. Normal distribution of the data was analyzed by Shapiro-Wilk test. Data were presented as mean ± standard deviation (for normally distributed data) or median (interquartile range) (for non-normally distributed data). The distribution of sex between the two groups was assessed by χ^2 test. Normally distributed variables and variables showed to be normally distributed after logarithmic transformed were compared by independent sample *t*-test. Non-normally distributed variables were compared by Mann-Whitney *U* test. Spearman correlation analysis was used to analyze the correlation between NR2E1 and each clinical index. Multiple linear regression analysis was used to evaluate the independent impact of NR2E1 levels on inflammatory factors. The statistical differences between the expression of NR2E1 in PBMCs treated with different concentrations of PA *in-vitro* were analyzed by one-way ANOVA and Bonferroni test. $P < 0.05$ was regarded significant difference.

Table 1
Clinical characteristics and laboratory parameters of the study subjects.

Variables	Overweight/Obese group	Control group	*P* value
Sex (M/F)	36/26	36/34	NS ($p = 0.445$)
Age (years)	38.35 ± 13.40	36.81 ± 11.54	NS ($p = 0.601$)
BMI (kg/m^2)	29.07 (2.61)	22.12 (2.66)	$p < 0.01$
WC (cm)	98.79 ± 6.83	77.15 ± 4.92	$p < 0.01$
TC (mmol/L)	5.00 (0.95)	4.62 (0.83)	$p < 0.01$
TG (mmol/L)	1.99 (1.55)	1.03 (0.82)	$p < 0.01$
HDL-c (mmol/L)	0.92 ± 0.18	1.08 ± 0.23	$p < 0.01$
LDL-c (mmol/L)	2.90 (0.92)	2.72 (0.88)	$p < 0.01$
FFA (μmol/L)	597.09 ± 224.06	453.82 ± 187.21	$p < 0.05$
ALT (U/L)	28.80 (30.23)	23.83 (19.62)	NS ($p = 0.071$)
FBG (mmol/L)	5.19 (1.24)	4.69 (0.72)	NS ($p = 0.165$)
FIN (μU/mL)	13.46 ± 4.13	5.56 ± 1.67	$p < 0.01$
HOMA-IR	3.08 ± 0.96	1.27 ± 0.45	$p < 0.01$
TNF-α (pg/mL)	73.86 ± 23.82	55.85 ± 15.66	$p < 0.01$
IL-6 (pg/mL)	14.97 ± 2.66	10.13 ± 4.93	$p < 0.01$

M = male; F = female; ns = not significant.
Normal distributed variables were presented as mean ± standard deviation and compared by two independent sample *t*-test; non-normal distributed variables were presented as median (interquartile range) and compared by Mann-Whitney *U* test. Sex between the two groups was compared by χ^2 test.

3. Results

3.1. Clinical characteristics and laboratory parameters of the two groups

The two groups did not show any statistically significant differences in gender, age, ALT or FBG ($p > 0.05$; Table 1). The overweight/obese participants were apparently higher than the control subjects in BMI, WC, TC, TG, LDL-c, FFA, FIN, HOMA-IR, TNF-α and IL-6, but lower in HDL-c ($p < 0.05$; Table 1).

3.2. The comparison of NR2E1 levels in PBMCs of the two groups

The abundance of NR2E1 mRNA in PBMCs of overweight/obese people was significantly higher than that of control subjects (1.90 ± 1.06 vs 1.27 ± 0.46, $p < 0.01$; Fig. 1A). The expression of NR2E1 protein in PBMCs of overweight/obesity subjects was also higher than that of the controls (0.153 ± 0.090 vs 0.100 ± 0.059, $p < 0.01$; Fig. 1B and C).

3.3. Statistical analysis of NR2E1 and other parameters in overweight/obese subjects

According to Spearman correlation analysis, the abundance of NR2E1 mRNA had a positive correlation with TC ($r = 0.387$, $p < 0.01$), FFA ($r = 0.440$, $p < 0.01$), LDL-c ($r = 0.290$, $p < 0.05$), TNF-α ($r = 0.530$, $p < 0.01$) and IL-6 ($r = 0.610$, $p < 0.01$) (Fig. 2A–E). A similar correlation was seen between NR2E1 protein levels and TC, FFA, LDL-c, TNF-α and IL-6 ($r = 0.486, 0.439, 0.480, 0.527, 0.584$, $p < 0.01$). The details of the Spearman correlation about NR2E1 mRNA, NR2E1 protein levels and other parameters were separately shown in Supplementary Table 1 and Supplementary Table 2.

In order to evaluate the independent impact of NR2E1 levels on inflammatory factors TNF-α and IL-6, we performed multiple linear regression analysis. Taken TNF-α or IL-6 as the dependent variable, taken variables which were statistically correlated to TNF-α or IL-6 according to Spearman correlation analysis as independent variables, then we found NR2E1 ($\beta = 0.368$, $p < 0.01$ for TNF-α; $\beta = 0.383$, $p < 0.01$ for IL-6) was an independent impact factor of inflammatory factors TNF-α and IL-6. The details of the multiple linear regression analysis for the independent factors influencing TNF-α and IL-6 concentration were separately shown in Supplementary Table 3 and Supplementary Table 4.

3.4. The expression of NR2E1 in PBMCs treated by PA in vitro

The PBMCs from the control subjects were treated with 0 μM, 250 μM, 500 μM and 1000 μM PA for 24 h. The expression of NR2E1 increased apparently with the treatment of PA in a concentration-depend manner. Though PBMCs treated with 1000 μM PA had higher expression of NR2E1 compared to PBMCs treated with 500 μM PA, there was no significant difference ($p > 0.05$; Fig. 3). So, in the following experiment we used 500 μM PA to treat PBMCs.

3.5. Expression of NR2E1 in PBMCs transfected with p-EGFP-N1-NR2E1 plasmids

Real-time PCR and Western Blotting were used to detect the expression of NR2E1 in PBMCs that transfected with p-EGFP-N1-NR2E1 plasmids and the negative controls. The mRNA and protein of NR2E1 were both up-regulated in O-NR2E1 group compared to the negative control group (5.47 ± 0.30 vs 0.72 ± 0.19, $p < 0.01$; 0.37 ± 0.04 vs 0.21 ± 0.04, $p < 0.01$) (Fig. 4A–C).

3.6. Expression of proinflammatory factors in PBMCs treated with PA

We used 500 μM PA to stimulate PBMCs in O-NR2E1 group and negative control group to induce an inflammatory response, and detected the expression of proinflammatory factor TNF-α, IL-6. We found that compared to the negative control group, the expression of TNF-α and IL-6 decreased significantly in O-NR2E1 group (Fig. 4D). This result suggested that overexpression of NR2E1 in PBMCs could alleviate PA-induced inflammation.

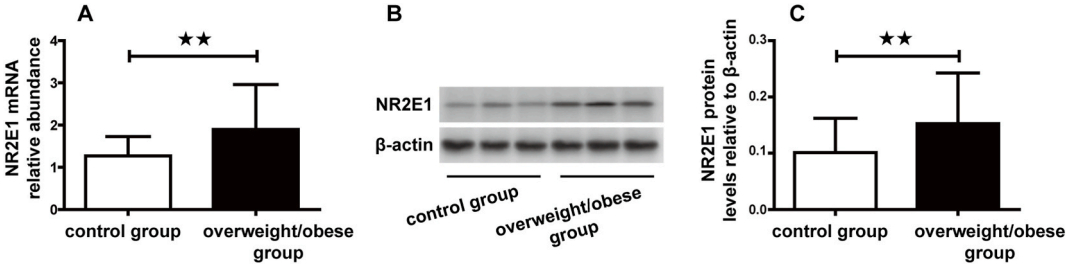


Fig. 1. NR2E1 levels in the PBMCs of the overweight/obese people and the controls. (A) the relative abundance of NR2E1 mRNA. (B) representative Western blot images of NR2E1 protein in PBMCs. (C) the NR2E1 protein levels relative to β-actin. ★★$p < 0.01$.

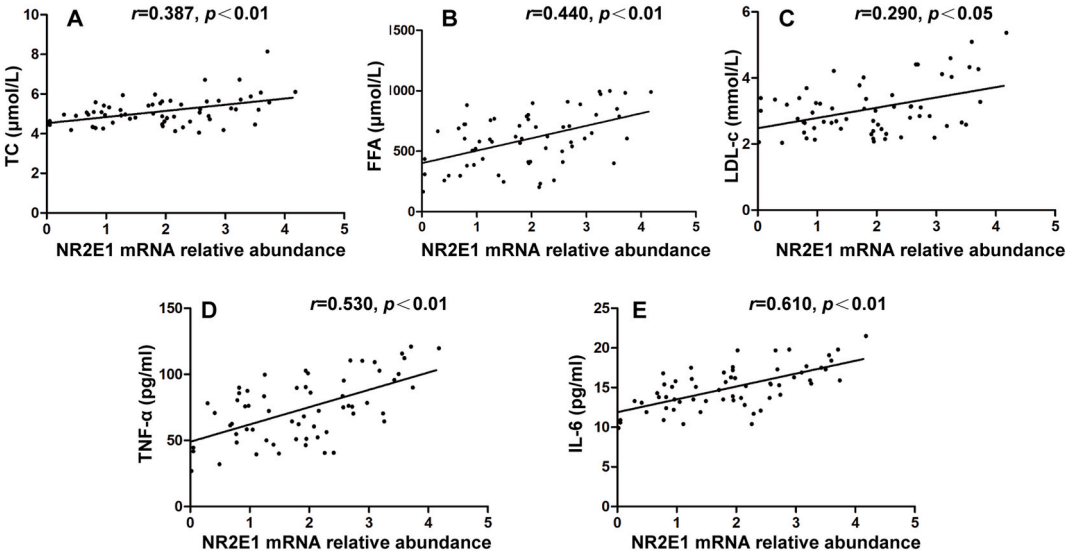


Fig. 2. Scatter plots showing the correlation between NR2E1 mRNA relative abundance and (A) TC, (B) FFA, (C) LDL-c, (D) TNF-α, (E) IL-6 in the overweight/obese subjects. TC = total cholesterol; FFA = free fatty acid; LDL-c = high-density lipoprotein; TNF-α = tumor necrosis factor alpha; IL-6 = interleukin- 6.

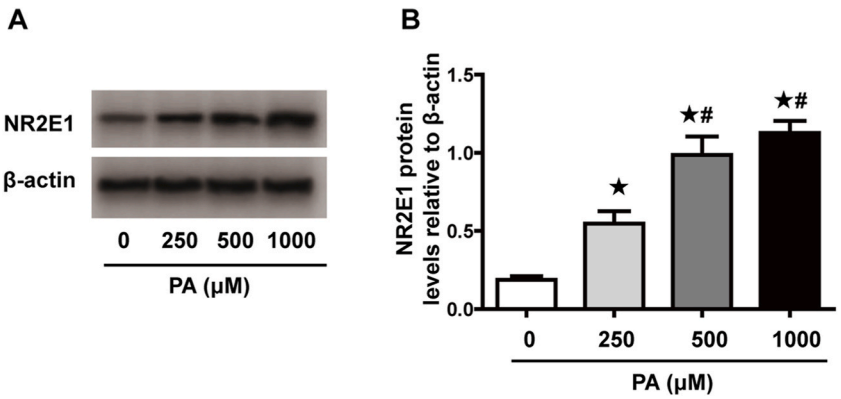


Fig. 3. The expression of NR2E1 protein in PBMCs treated with different concentrations of palmitic acid (PA). (A–B) Western blot image and representative bands showed the expression of NR2E1 treated with 0 μM, 250 μM, 500 μM and 1000 μM PA for 24 h. $^{\star}p < 0.01$ vs. 0 μM PA group, $^{\#}p < 0.01$ vs. 250 μM PA group.

4. Discussion

Overweight and obesity have a significant impact on people's health. Chronic inflammation, which is closely associated with obesity, serves as a common molecular pathomechanism that triggers various metabolic diseases [17]. In obese condition, dysfunctional adipocytes release chemokines, leading to the migration of PBMCs to adipose tissue where they differentiate into macrophages. This process further results in the infiltration of inflammatory cells such as neutrophils, eosinophils, and mast cells [18]. These inflammatory cells then release proinflammatory factors, such as TNF-α, IL-6 and MCP-1, which trigger chronic inflammation [2]. Additionally, impaired adipose tissue function leads to a decline in lipid storage capacity. Excessive free fatty acids promote ectopic lipid deposition, insulin resistance, as well as vascular and cardiac dysfunction [19].

Accumulated evidences have implicated that NR2E1, a transcription factor, plays a crucial role in cell proliferation, differentiation, and self-renewal [20]. The current research on NR2E1 mainly focused on neural stem cells and retinal precursor cells [21–23]. It was found that NR2E1 directly inhibits p21 and PTEN through transcriptional regulation to maintain undifferentiated proliferation of neural stem cells and retinal progenitor cells in the embryonic and adult brain [21]. Besides neuronal pathologies, scientists also found that NR2E1 could play a role in metabolic disorders. Knocking out NR2E1 in mice increased serum cholesterol and triglyceride levels, and caused more lipid deposition in the liver. Furthermore, knocking out NR2E1 in mice also increased the expression of inflammatory genes, and high-fat diets amplified the damage [12]. NR2E1 deletion affected the expression of insulin signaling and aggravated insulin resistance [13]. NR2E1 was reported closely related to subclinical inflammation of type 2 diabetes mellitus [15], and could

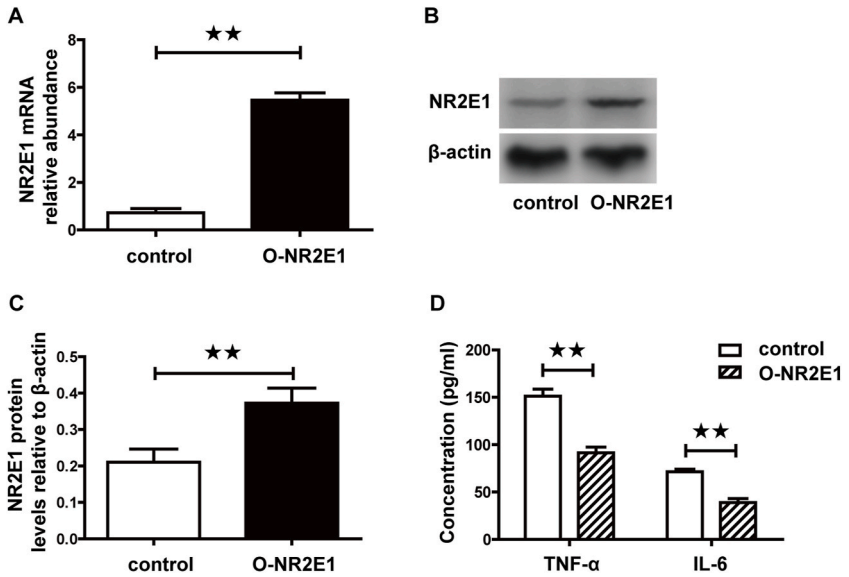


Fig. 4. Comparation of NR2E1, TNF-α and IL-6 concentrations between O-NR2E1 and negative control group. (A) the abundance of NR2E1 mRNA and (B–C) the expression of NR2E1 protein in PBMCs transduced with p-EGFP-N1-NR2E1 plasmids (O-NR2E1) and the negative controls. Comparation of TNF-α and IL-6 concentrations in supernatant of PBMCs between O-NR2E1 and negative control group. $^{\star\star}p < 0.01$ vs. control group.

reduce the apoptosis of pancreatic β cells by inhibiting oxidative stress and inflammatory response [14,16]. However, there are few studies on NR2E1 in overweight/obese patients, and the correlation between NR2E1 and obesity-related chronic inflammation has not been reported. In our study, for the first time, we found the expression of NR2E1 in overweight/obese patients was significantly higher than that in the control group, and was positively correlated with TC, FFA, LDL-C, TNF-α and IL-6, suggesting that NR2E1 might be closely related to lipid metabolism and obesity-related chronic inflammation.

As a metabolic syndrome, obesity is closely related to insulin resistance, metabolic dysfunction-associated steatotic liver disease (MASLD), hypertension and lipid abnormalities [24]. One of the key factors linking obesity to obesity-associated metabolic syndrome is FFA [25]. Among FFA, saturated fatty acids have the most prominent effect on chronic inflammation in the body [26]. In both mice and human, PA is the main saturated fatty acid found in the circulatory system. Therefore, in our study we treated PBMCs from the control subjects with PA *in vitro*. Upon treatment of PA, the expression of NR2E1 was apparently increased in a concentration-depend manner. Furthermore, we overexpressed NR2E1 in PBMCs from the control subjects and treated them with PA. Then we observed a significant decrease in TNF-α and IL-6 levels compared to the negative control group. This result suggested that NR2E1 could alleviate PA-induced inflammation. This finding seemed to contradict the results of our clinical trial, in which NR2E1 levels were positive correlated with TNF-α and IL-6. But in fact, we should not ignore an important fact that due to the nature of cross-sectional study, it is impossible to determine the causality between NR2E1 and pro-inflammatory cytokines. It is possible that the positive correlation between NR2E1 and inflammatory factors is only a concomitant phenomenon. So, based on the finding *in vivo*, a reasonable explain was that the increased expression of NR2E1 in overweight/obese individuals could be a compensatory response to maintain homeostasis by mitigating chronic inflammation under metabolic stress, which meant that if without a compensatory increase of NR2E1, pro-inflammatory cytokines in overweight/obese people could increase even more. The study by Xiong etc. [12] could to some extent support our speculation, where they found that NR2E1 ablation amplified liver inflammation in high-fat diet-induced mice. Although it seemed that the compensatory phenomenon alone was insufficient to inhibit the changes observed in the parameters evaluated in the blood of overweight/obese individuals, it also gave us clues about the potential role of NR2E1 in obesity-associated chronic inflammation. To prove our speculation and figure out whether other factors are involved in the process, further animal studies are needed. In the future, we will knock out NR2E1 in obese mice and compare the pro-inflammatory cytokines and other metabolic parameters between NR2E1-knock out mice and the control obese mice.

Due to the ability of NRs to bind to small molecules, they are excellent targets for drug design. Therefore, research on NRs have always been an important field in functional genomics and translational medicine. Our findings suggested that NR2E1 might be a promising target for regulating chronic inflammation in obesity and drug design of obesity-associated diseases.

There are several limitations to our present study. Firstly, the hospital-based cross-sectional study in our research was conducted at a single center with a relatively small sample size, multiple centers and larger samples are required in the future. Secondly, our study only gave crude evidences about the role of NR2E1 in regulating chronic inflammation in obesity. The mechanism of how NR2E1 alleviated inflammation needs to be further studied in the future.

5. Conclusion

In summary, our findings, for the first time, provided novel evidences that the concentrations of NR2E1 were elevated in overweight/obese subjects and had a positive relationship with TC, FFA, LDL-C, TNF-α and IL-6. Overexpression of NR2E1 could alleviate PA-induced chronic inflammation. Taken together, these findings suggest that NR2E1 may serve as a promising target for regulating chronic inflammation in obesity.

Funding

This work was financially supported by the National Natural Science Foundation of China (81900794, 81901262), the Science and Technology Plan Projects of Suzhou (Grant No. SKY2023164), and Jiangsu Provincial Government Scholarship for Overseas Studies.

Data availability statement

Data that associated with our study has not been deposited into a publicly available repository. Data will be available from the corresponding author, upon reasonable request.

Ethics statement

This study was reviewed and approved by the Medical Ethics Committee of the First Affiliated Hospital of Soochow University with the approval number 2019079, dated September 17, 2019. All participants provided written informed consent to participate in the study and for their data to be published.

CRediT authorship contribution statement

Mingqing He: Writing – review & editing, Writing – original draft, Resources, Funding acquisition, Conceptualization. **Qiyuan Cui:** Writing – review & editing, Resources, Formal analysis, Data curation. **Yun Zheng:** Software, Project administration, Methodology, Formal analysis. **Bin Feng:** Writing – review & editing, Writing – original draft, Project administration, Formal analysis, Data curation, Conceptualization. **Zheng Liu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37909.

References

[1] A. Afshin, M.H. Forouzanfar, M.B. Reitsma, et al., Health effects of overweight and obesity in 195 countries over 25 years, N. Engl. J. Med. 377 (2017) 13–27.
[2] T. Kawai, M.V. Autieri, R. Scalia, Adipose tissue inflammation and metabolic dysfunction in obesity, Am. J. Physiol. Cell Physiol. 320 (2021) C375–c391.
[3] T. Chavakis, V.I. Alexaki, A.W. Ferrante Jr., Macrophage function in adipose tissue homeostasis and metabolic inflammation, Nat. Immunol. 24 (2023) 757–766.
[4] Y.S. Lee, J. Olefsky, Chronic tissue inflammation and metabolic disease, Genes Dev. 35 (2021) 307–328.
[5] A. Asghar, N. Sheikh, Role of immune cells in obesity induced low grade inflammation and insulin resistance, Cell. Immunol. 315 (2017) 18–26.
[6] H. Li, Y. Meng, S. He, et al., Macrophages, chronic inflammation, and insulin resistance, Cells 11 (2022) 31–55.
[7] T.V. Rohm, D.T. Meier, J.M. Olefsky, et al., Inflammation in obesity, diabetes, and related disorders, Immunity 55 (2022) 31–55.
[8] S. Liqiang, L. Fang-Hui, Q. Minghui, et al., Free fatty acids and peripheral blood mononuclear cells (PBMC) are correlated with chronic inflammation in obesity, Lipids Health Dis. 22 (2023) 93.
[9] V. Catalán, J. Gómez-Ambrosi, A. Rodríguez, et al., Peripheral mononuclear blood cells contribute to the obesity-associated inflammatory state independently of glycemic status: involvement of the novel proinflammatory adipokines chemerin, chitinase-3-like protein 1, lipocalin-2 and osteopontin, Genes & nutrition 10 (2015) 460.
[10] A.A. Walth-Hummel, S. Herzig, M. Rohm, Nuclear receptors in energy metabolism, Adv. Exp. Med. Biol. 1390 (2022) 61–82.
[11] D.E. Frigo, M. Bondesson, C. Williams, Nuclear receptors: from molecular mechanisms to therapeutics, Essays Biochem. 65 (2021) 847–856.
[12] Q. Xiong, Y. Wu, M. Yang, et al., Nr2e1 ablation impairs liver glucolipid metabolism and induces inflammation, high-fat diets amplify the damage, Biomed. Pharmacother. 120 (2019) 109503.

[13] G. He, J. Gu, H. Wang, et al., Nr2e1 deficiency aggravates insulin resistance and chronic inflammation of visceral adipose tissues in a diet-induced obese mice model, Life Sci. 278 (2021) 119562.
[14] X. Shi, H. Deng, Z. Dai, et al., Nr2e1 Deficiency Augments Palmitate-Induced Oxidative Stress in Beta Cells, Oxid. Med. Cell. Longev. 2016 (2016) 9648769.
[15] L. Sun, H. Deng, L. He, et al., The relationship between NR2E1 and subclinical inflammation in newly diagnosed type 2 diabetic patients, J. Diabet. Complicat. 29 (2015) 589–594.
[16] X. Shi, X. Xiong, Z. Dai, et al., Nuclear orphan receptor TLX affects gene expression, proliferation and cell apoptosis in beta cells, Biochem. Biophys. Res. Commun. 468 (2015) 387–393.
[17] C. Kessler, Pathophysiology of obesity, Nurs. Clin. 56 (2021) 465–478.
[18] M.W. Schleh, H.L. Caslin, J.N. Garcia, Metaflammation in obesity and its therapeutic targeting, Sci. Transl. Med. 15 (2023) eadf9382.
[19] G.C. Henderson, Plasma free fatty acid concentration as a modifiable risk factor for metabolic disease, Nutrients 13 (2021) 2590.
[20] J.D. O'Leary, O.F. O'Leary, J.F. Cryan, et al., Regulation of behaviour by the nuclear receptor TLX, Gene Brain Behav. 17 (2018) e12357.
[21] A.T. Nelson, Y. Wang, E.R. Nelson, TLX, an orphan nuclear receptor with emerging roles in physiology and disease, Endocrinology 162 (2021) bqab184.
[22] P.K. Sobhan, K. Funa, TLX-its Emerging Role for Neurogenesis in Health and Disease, vol. 54, 2017, pp. 272–280.
[23] X. Corso-Díaz, E.M. Simpson, Nr2e1 regulates retinal lamination and the development of Müller glia, S-cones, and glycineric amacrine cells during retinogenesis, Mol. Brain 8 (2015) 37.
[24] J. Gutiérrez-Cuevas, A. Santos, J. Armendariz-Borunda, Pathophysiological molecular mechanisms of obesity: a link between mafld and nash with cardiovascular, Diseases 22 (2021) 11629.
[25] A.P. Isaeva, K.V. Gapparova, Y.G. Chekhonina, et al., Characteristics of free fatty acid metabolism in pathogenesis of obesity: current view, Vopr. Pitan. 87 (2018) 18–27.
[26] A.B. Engin, What is lipotoxicity? Adv. Exp. Med. Biol. 960 (2017) 197–220.