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FPS-ZM1 attenuates the deposition of lipid in the liver of diabetic mice by sterol regulatory element binding protein-1c

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Abstract

Background Nonalcoholic fatty liver disease (NAFLD) shares common pathogenic mechanisms of type 2 diabetes mellitus (T2DM) with upregulated advanced glycation end products (AGEs). Here, we aim to investigate the effect of FPS-ZM1, an inhibitor for receptor for AGEs (RAGE), on lipid deposition in the liver of mice.

Methods KK-Ay mice were used as models of T2DM with NAFLD, while C57BL/6j mice were controls. Additionally, KK-Ay mice were treated with DMSO (with a concentration of 1%), with or without FPS-ZM1 (3 mg/kg/day, i.p). Lipid deposition in hepatocytes was observed using oil red O stain. Levels of AGEs and RAGE were measured. Sterol regulatory element-binding protein-1c (SREBP-1c), as well as nuclear factor κB p65 (p65 nfκb) and mitogen-activated protein kinase p38 (p38 MAPK), were also detected.

Results Lipid deposition is increased in the hepatocytes of KK-Ay mice compared to C57BL/6j mice. In addition, not only were the levels of AGEs elevated in plasma, but also the levels of RAGE in liver tissue. Although total SREBP-1c levels did not change in the liver of diabetic mice, mature SREBP-1c increased in KK-Ay mice with diabetes mellitus. Moreover, diabetic mice showed increased levels of phosphorylated-p65 nfκb (p-p65 nfκb) and phosphorylated-p38 MAPK (p-p38 MAPK). On the contrary, FPS-ZM1 decreased lipid deposition in liver cells, as well as mature SREBP-1c, p-p65 nfκb and p-p38 MAPK levels in liver tissue.

Conclusion Generally, FPS-ZM1 may attenuate lipid deposition in hepatocytes of diabetic mice via SREBP-1c down-regulation. This may depend on the downregulation of p65 nfκb and p38 MAPK phosphorylation.

Keywords Nonalcoholic fatty liver, Type 2 diabetes mellitus, Advanced glycation end products, Sterol regulatory element binding protein-1c

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Background

The global prevalence of diabetes is estimated to be 9.3% (more than 400 million people) in 2019 among the 20-79-year-old population [1]. Additionally, the prevalence of diabetes, using the WHO criteria, was 11.2% in China [2]. T2DM is the most common kind of diabetes, characterized by chronic hyperglycemia [3]. Additionally, AGEs are formed through non-enzymatic reactions under conditions of chronic hyperglycemia, and they are involved in a variety of diabetes-related complications [4–10]. NAFLD is one of the most important complications in T2DM patients with obesity and dyslipidemia [11]. In fact, in our previous study, a high-fat diet (HFD) induced NAFLD in C57BL/6j mice, with significant lipid deposition in hepatocytes and hyperlipidemia [12]. However, further investigation is required to elucidate the precise involvement of AGEs in the hepatic accumulation of lipids in diabetic mice.

Recent research has shown that lipid content and SREBP-1c are significantly increased in HFD rats. Additionally, transfection with siRNA-SREBP-1c resulted in a significant amelioration of lipid accumulation induced by palmitic acid in HK2 cells [13]. The aforementioned study suggests that SREBP-1c may be involved in lipid deposition in the kidney. However, further investigation is needed to determine the impact of SREBP-1c on lipid deposition in the liver, particularly in the context of NAFLD in diabetic mice. The AMP-activated protein kinase-mediated SREBP signaling pathway has been shown to play a significant role in the development of NAFLD in KK-Ay mice with diabetes [14]. Upon activation, SREBPs are translocated from the endoplasmic reticulum to the Golgi, where they are cleaved into active mature forms of SREBPs. These mature forms of SREBPs then translocate into the nucleus and act as transcription factors involved in lipid metabolism [15, 16]. The KK-Ay mouse is a well-established model for T2DM, characterized not only by chronic hyperglycemia but also by significant obesity and dyslipidemia. Further animal experiments have shown chronic hyperglycemia and elevated AGE levels in 15-week-old KK-Ay mice [17].

Hence, we speculate that AGEs may increase the activation of the SREBP signaling pathway, which is involved in lipid deposition in hepatocytes of diabetic mice. Previous studies have demonstrated that carboxymethyl lysine, one of the most important components of AGEs, promotes the cleavage and activation of SREBP from precursor to mature SREBP, which in turn participates in lipid metabolism [18]. Therefore, our aim is to investigate the effect of AGEs on SREBP-1c-associated NAFLD in KK-Ay mice with diabetes and its possible mechanism.

Methods

Animal housing and treatment

Male C57BL/6j mice ($n=8$) and KK-Ay mice ($n=24$) (Beijing HFK Biotechnology Co., Ltd., Beijing, China) aged 6 weeks were purchased and housed in the animal research center of Jinzhou medical University. This present experiment was formally performed after adaptive feeding for one week. Seven weeks aged C57BL/6j mice were fed with normal diet (cat no. 1002, Beijing HFK Biotechnology Co., Ltd., Beijing, China) ($n=8$). Eight KK-Ay mice were fed with their specific chow (cat no. 1042, Beijing HFK Biotechnology Co., Ltd., Beijing, China) for 8 weeks (aged 15 weeks) to get the models of mice with diabetes and NAFLD. Eight KK-Ay mice with their specific chow (described above) and FPS-ZM1(in DMSO with a concentration of 1%) (cat no. HY-19370, MedChemExpress LLC, Shanghai, China) (3 mg/kg/day, i.p) [19] for 4 weeks after with their specific chow for 8 weeks was defined as KK-Ay+FPS-ZM1 group. Eight KK-Ay mice with their specific chow and DMSO (cat no. ST038-100 ml, Beyotime Biotechnology, Shanghai, China) (i.p) with a concentration of 1% for 4 weeks after with their specific chow for 8 weeks was defined as KK-Ay+Veh group. Upon the completion of the experimental procedures, the mice were subjected to anesthesia with a dosage of 50 mg/kg sodium pentobarbital. Cardiac puncture was employed for the collection of blood samples. All mice were sacrificed by cervical dislocation. After sacrificing, the liver tissues of mice were excised and meticulously cleansed. Subsequently, the tissues were either fixed with 4% paraformaldehyde or preserved by freezing at -80 °C. This study was approved by the Animal Studies Committee of our institute and conducted in accordance with the Guide for the Care and Use of Laboratory Animals.

Oil red O stain

All liver tissues were storage in paraformaldehyde for 3 days. Additionally, these tissues were embedded in OCT and trimmed to 15 μm sections. Oil red O stain was performed according to the protocol of the manufacturer's instructions (cat no. WLA055a, Wanlei biotechnology co. Ltd, Shenyang, China) and similar with those described previously [12]. After completing the oil red staining, we observed the results using an optical microscope (Olympus, Japan). Simultaneously, photographs were taken using the camera attached to the microscope.

Enzyme linked immunosorbent assay (ELISA)

AGEs (cat no. CEB353Ge, CLOUD-CLONE CORP., Wuhan, China) in plasma were measured by ELISA according to their manufacturer's instructions. Add 50 μL of sample or standard solution to each well of the microplate. Next, add 50 μL of detection reagent A, and incubate at 37 °C for 1 h. After washing 3 times, add detection

reagent B, and incubate at 37 °C for 30 min. After washing 5 times, add 90 μL of substrate. Incubate at 37 °C for 10 min, and then add 50 μL of stop solution. Finally, place the microplate into an ELISA reader and read the optical density (OD) value at a wavelength of 450 nm. Based on the OD values of different concentrations of standard solutions, construct a standard curve, and calculate the concentration of AGEs in the samples using their OD values.

Western blotting

After mice were sacrificed, fresh liver tissue was isolated to obtain total protein. Total protein was extracted by radioimmunoprecipitation (cat no. BL504A, Biosharp, Hefei, China) with 1% phenylmethanesulfonylfluoride supplemented. Western blotting was carried out according to our previous study [20]. Specially, primary antibody of mouse-anti-RAGE (cat no. 16346-1-AP, Proteintech Group, Inc, Wuhan, China) (dilution ratio: 1:1000), mouse-anti-SREBP-1c (cat no. WL02093, Wanlei biotechnology co. Ltd, Shenyang, China) (dilution ratio: 1:500), rabbit-anti-p65 nfκb (cat no. sc-8008, SANTA CRUZ BIOTECHNOLOGY, INC., Dallas, USA) (dilution ratio: 1:200), mouse-anti-p-p65 nfκb (cat no.WL01980, Wanlei biotechnology co. Ltd, Shenyang, China) (dilution ratio: 1:500) and rabbit-anti-GAPDH (cat no. 60004-1-Ig, Proteintech Group, Inc, Wuhan, China) (dilution ratio: 1:1000),were used. Additionally, goat-anti-mouse (cat no. SA00001-1, Proteintech Group, Inc, Wuhan, China) and goat-anti-rabbit (cat no. SA00001-2, Proteintech Group, Inc, Wuhan, China) second antibody with dilution ratio of 1:5000 and 1:2000 were used to detect the primary antibodies respectively.

Statistical analysis

Data were described as mean ± standard deviation and analyzed by SPSS 26.0 (SPSS Inc., Chicago, IL, USA). Student's t-tests were used to determine the difference between 2 groups. Additionally, one-way ANOVA followed by LSD were conducted for multiple-comparison tests. $P<0.05$ was considered as significant difference.

Results

Lipids deposition and SREBP-1c changes in KK-Ay mice with diabetes

To explore the differences in lipid metabolism in the liver of C57BL/6j mice and KK-Ay mice, oil red O staining was performed on liver tissue. Compared to C57BL/6j mice without diabetes and obesity, KK-Ay mice showed increased accumulation of lipid droplets in hepatocytes. To further clarify the mechanism of lipid deposition in the liver, the levels of SREBP-1c were measured. Although total SREBP-1c increased in the liver of diabetic mice, there was no statistically significant difference between the two groups. However, mature SREBP-1c increased in mice with diabetes (Fig. 1).

p65 nfκb and p38 MAPK changes in in KK-Ay mice with diabetes

It is suggested that chronic inflammation associated with p65 nfκb and p38 MAPK is involved in the regulation of the SREBPs signaling pathway [21]. In this study, we measured both the levels of total p65 nfκb and p38 MAPK and their phosphorylated forms (p-p65 nfκb and p- p38 MAPK) in the livers of C57BL/6j mice and KK-Ay mice to investigate the possible mechanism of SREBP-1c-associated NAFLD in diabetic mice. The levels of p65 nfκb and p38 MAPK in the liver of KK-Ay mice were not significantly different from those in C57BL/6j mice. However, there was an increase in p-p65 nfκb and p-p38 MAPK levels in the liver tissue of KK-Ay mice compared to those in C57BL/6j mice (Fig. 2).

AGEs and its receptor changes in KK-Ay mice with diabetes

In our previous study, we found that AGEs and their receptor increased in diabetic mice and rats, respectively [22, 23]. As described above, AGEs may be involved in the regulation of the SREBP signaling pathway. In this study, we detected the levels of AGEs in the plasma of mice with or without diabetes. Not surprisingly, the levels of AGEs were higher in KK-Ay mice than in C57BL/6j mice. Additionally, RAGE levels were elevated in the liver tissue of KK-Ay mice compared to those in C57BL/6j mice (Fig. 3).

FPS-ZM1 decreased the phosphorylation of p65 nfκb and p38 MAPK in KK-Ay mice

As the phosphorylation p65 nfκb and p38 MAPK are increased in KK-Ay mice with diabetes. Additionally, not only AGEs in plasma but also RAGE in liver tissue of KK-Ay mice were up-regulated. Here, FPS-ZM1 was used to block the function RAGE. Interestingly, RAGE blocking decreased the phosphorylation of p65 nfκb and p38 MAPK rather than levels of total p65 nfκb and p38 MAPK (Fig. 4).

FPS-ZM1 attenuated the deposition of lipids in liver of KK-Ay mice

To further explore the effects of FPS-ZM1 on metabolism, we performed oil red O staining to detect lipid deposition in KK-Ay mice with or without FPS-ZM1. Interestingly, we observed not only decreased accumulation of lipid droplets in hepatocytes but also downregulation of mature SREBP-1c in the liver tissue of KK-Ay mice treated with FPS-ZM1 (Fig. 5).

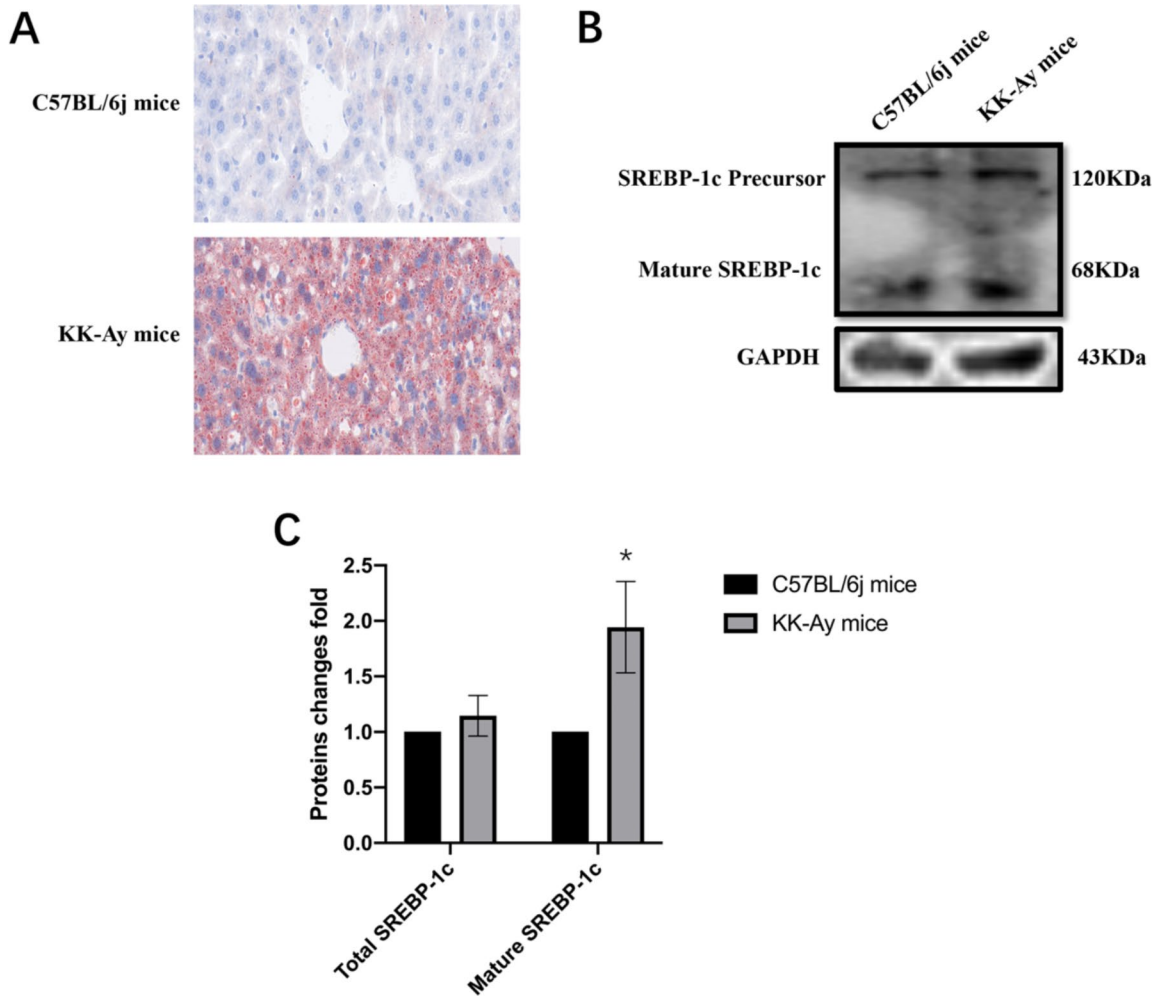

Fig. 1 KK-Ay mice showed increased lipids deposition and up-regulated mature SREBP-1c in the liver. Notes: **A** showed increased lipids deposition in the liver tissue of KK-Ay mice; **B** showed the western blotting results of SREBP-1c; **C** showed the statistical results of western blotting; "*" in **C** showed increased mature SREBP-1c in the liver of KK-Ay mice, compared with those of C57BL/6j mice

Discussion

As the prevalence of diabetes increases [1, 2], NAFLD has attracted more attention in recent years as one of the most important complications [24, 25]. To date, NAFLD may affect nearly 25–30% of adults in the general population of high-income countries, and up to 70% of those with T2DM [26]. Additionally, NAFLD is not only a risk factor for diabetes but also causes worse plasma glucose control [27]. Conversely, uncontrolled plasma glucose may be involved in the occurrence and progression of NAFLD [28]. Indeed, chronic hyperglycemia could induce a great quantity of AGEs in diabetic individuals, which are associated with many kinds of diabetes complications, including NAFLD [29–31]. This is consistent with our previous study that showed higher plasma glucose levels in HFD-induced NAFLD models [12]. Here, we used KK-Ay mice as models of diabetes with NAFLD to clarify the possible mechanisms of lipid metabolism, as our previous study showed increased body weight and increased plasma at 15 weeks old [17]. Moreover, the model of T2DM with NAFLD was also confirmed by oil red O staining.

To confirm the increased AGEs levels in KK-Ay mice, an ELISA kit was used to measure the levels of AGEs. Additionally, the receptor for AGEs (RAGE) in the liver was detected by western blotting. Indeed, increased AGEs was observed in the plasma of KK-Ay mice. Furthermore, the levels of hepatic RAGE were also found to be increased in KK-Ay mice compared to those in C57BL/6j mice. As mentioned earlier, SREBP-1c is associated with lipids, particularly fatty acid metabolism. As a transcription factor, SREBP-1c, exerts regulatory control over a multitude of genes upon nuclear translocation, thereby influencing the modulation of glucose and lipid metabolism in individuals with diabetes and NAFLD. Therefore, we also observed the levels of SREBP-1c. Despite the absence of a significant increase in total SREBP-1c expression in the diabetic KK-Ay mice,

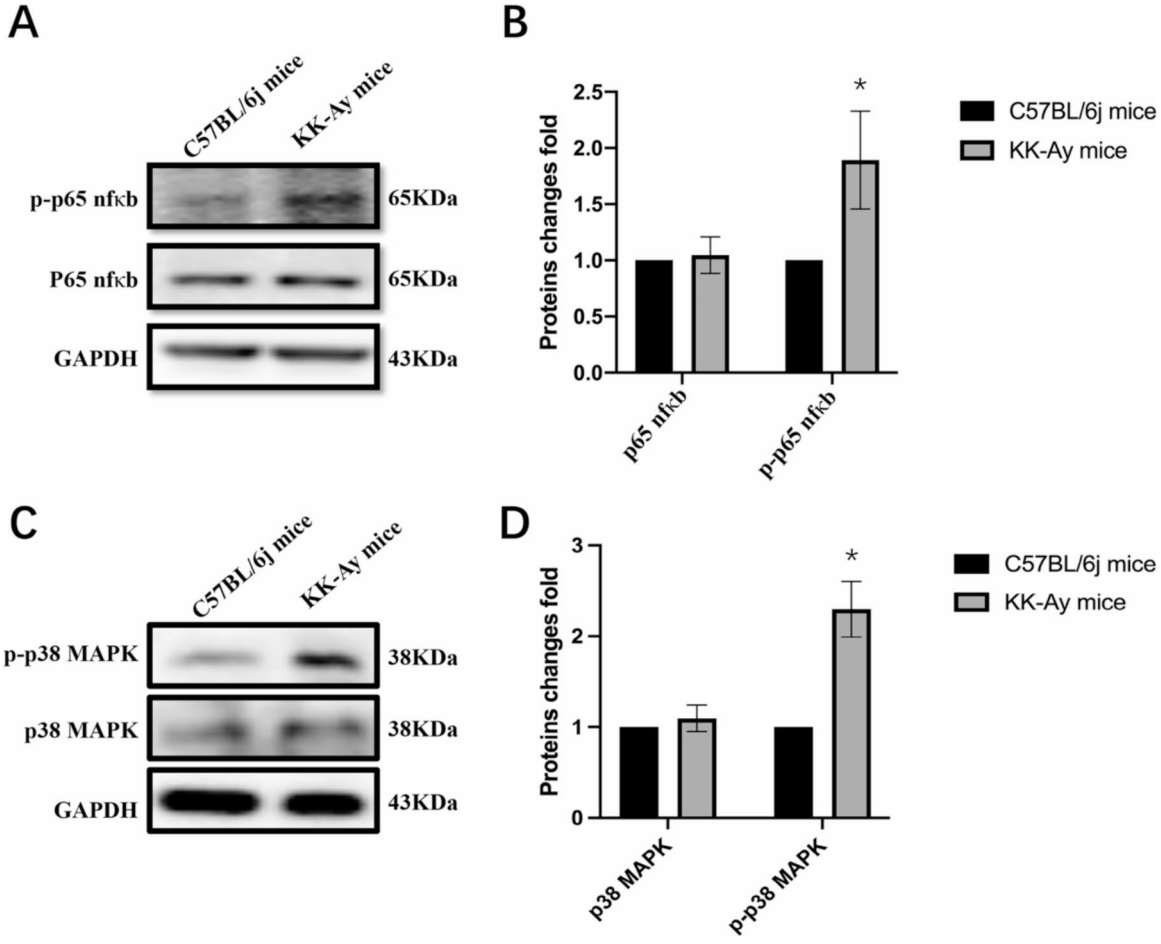

Fig. 2 KK-Ay mice showed hyperphosphorylation of p65 nfκb and p38 MAPK in the liver. Notes: **A** showed the western blotting results of p65 nfκb and p-p65 nfκb; **B** showed the statistical results of **A**; "*" in **B** showed increased mature p-p65 nfκb in the liver of KK-Ay mice, compared with those of C57BL/6j mice; **C** showed the western blotting results of p38 MAPK and p- p38 MAPK; **D** showed the statistical results of **C**; "*" in **D** showed increased mature p- p38 MAPK in the liver of KK-Ay mice, compared with those of C57BL/6j mice

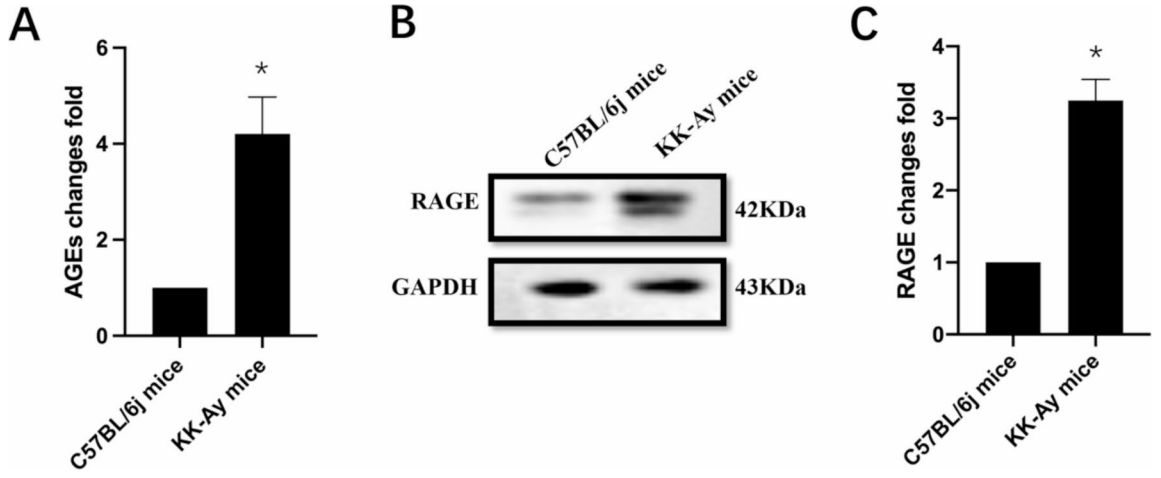

Fig. 3 KK-Ay mice showed elevated AGEs in plasma and RAGE in the liver. Notes: **A** showed the ELISA results of AGEs; "*" in **A** showed increased AGEs in plasma of KK-Ay mice, compared with those of C57BL/6j mice; **B** showed the western blotting results of RAGE; **C** showed the statistical results of western blotting; "*" in **C** showed increased RAGE in the liver of KK-Ay mice, compared with those of C57BL/6j mice

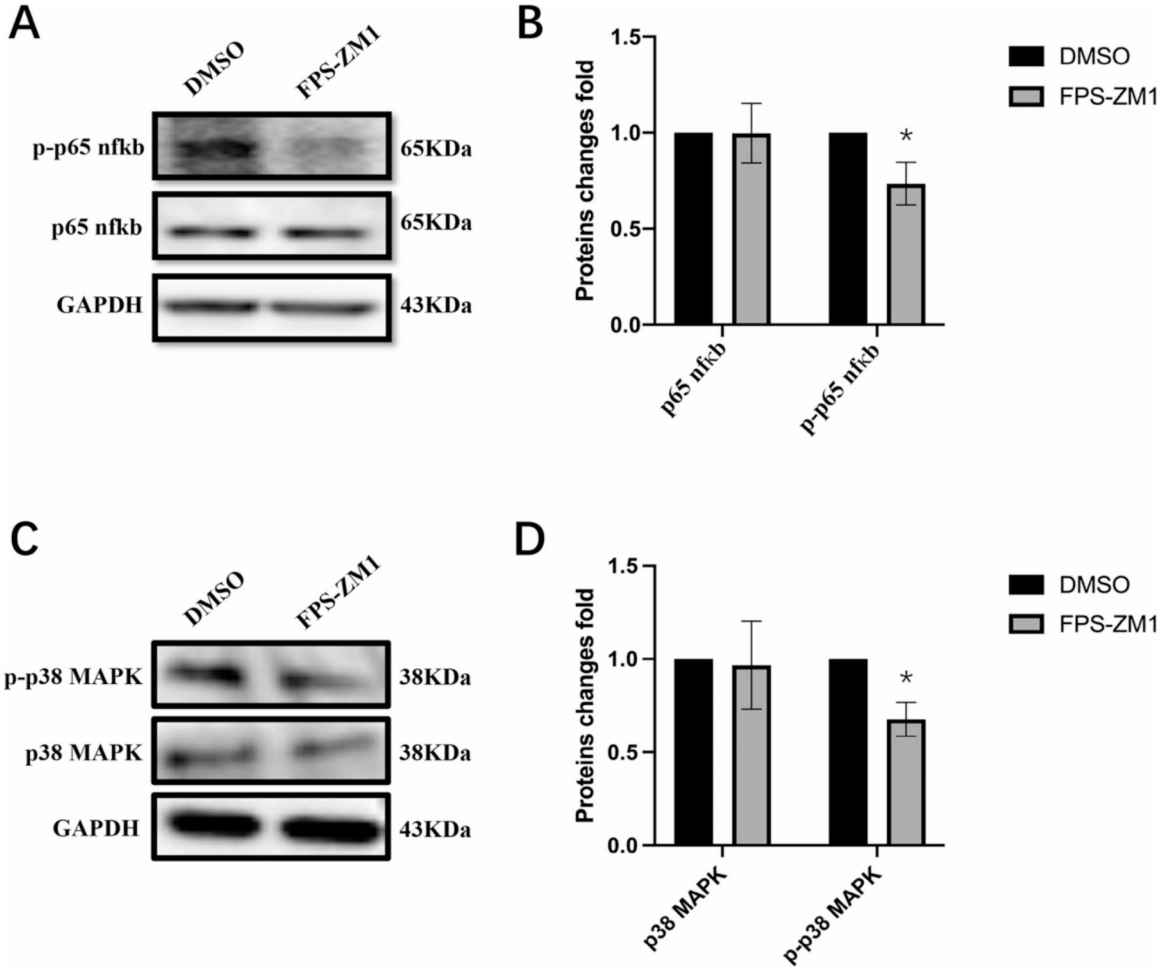

Fig. 4 FPS-ZM1 decreased the level of p-p65 nfκb and p38 MAPK in the liver tissue of KK-Ay mice. Notes: **A** showed the western blotting results of p65 nfκb and p-p65 nfκb; **B** showed the statistical results of **A**; "*" in **B** showed decreased p-p65 nfκb in the liver of KK-Ay mice with FPS-ZM1, compared with those without FPS-ZM1. **C** showed the western blotting results of p38 MAPK and p- p38 MAPK; **D** showed the statistical results of **C**; "*" in **D** showed decreased p- p38 MAPK in the liver of KK-Ay mice with FPS-ZM1, compared with those without FPS-ZM1

there was a notable elevation in the mature SREBP-1c sequence in their liver. Based on this observation, we propose the hypothesis that AGEs may contribute to the pathogenesis of NAFLD by modulating SREBP-1c activity. Additionally, prior investigations have demonstrated the involvement of AGEs in SREBP signaling pathways in both skeletal muscle [32, 33] and kidney tissues [18, 34, 35]. Research has indicated that the ingestion of fructose and glucose has been shown to have an impact on both glycemic control and liver lipid accumulation through the activation of the SREBPs cleavage activating protein pathway. Additionally, further investigations have revealed that the consumption of fructose can lead to increased generation of AGEs and the activation of the receptor for AGEs (RAGE) signaling pathway [36]. As of present, the current study has unveiled a novel association between elevated levels of AGEs and the development of SREBP-1c-related NAFLD in diabetic KK-Ay mice. Nonetheless, the precise underlying mechanism remains to be fully elucidated and warrants further investigation.

Although most NAFLD patients with obesity, NAFLD can also manifest in lean populations, particularly among individuals of Asian descent. This may due to the metabolic inflammation [37]. AGEs may take part in diabetic complications [38], including NAFLD [39], through p65 nfκb associated metabolic inflammation [40]. Indeed, p65 nfκb regulates hepatic lipogenesis by promoting nuclear entry of ChREBP in response to a high carbohydrate diet [41]. Additionally, p38 MAPK signaling pathway is also involved in the regulation of AGEs and RAGE [42]. Therefore, p65 nfκb and p38 MAPK was measured to confirm the role of p65 nfκb and p38 MAPK in AGEs-induced SREBP-1c signaling pathway activation in KK-Ay mice with NAFLD. Interestingly, we detected increased p-p65 fib and p-p38 MAPK, suggesting that AGEs induce SREBP-1c-related lipid deposition in the liver through the hyperphosphorylation of p65 nfκb and p38 MAPK.

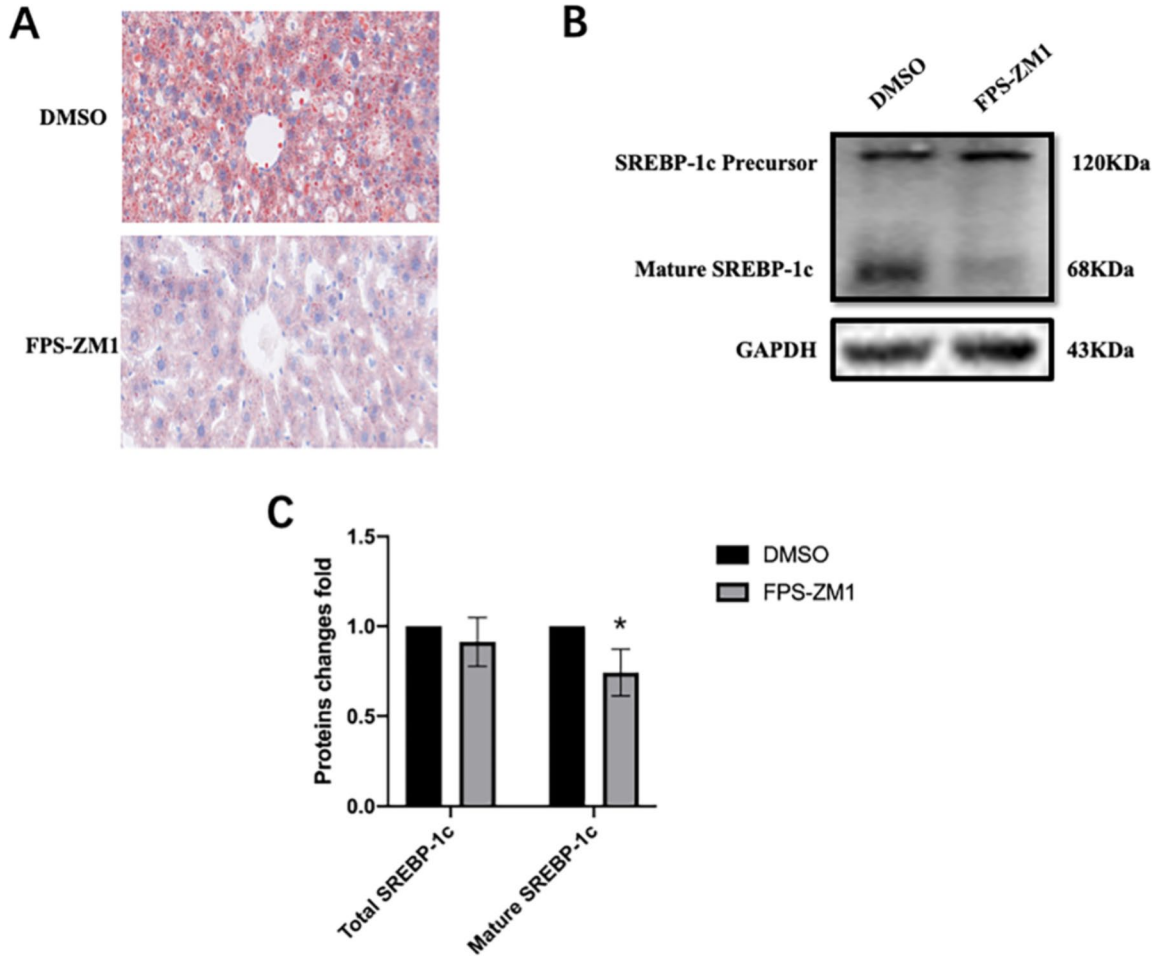

Fig. 5 FPS-ZM1 reduced the lipid deposition and down-regulated mature SREBP-1c in the liver of KK-Ay mice. Notes: **A** showed decreased lipids deposition in the liver tissue of KK-Ay mice with FPS-ZM1; **B** showed the western blotting results of SREBP-1c precursor and mature SREBP-1c; **C** showed the statistical results of western blotting; "*" in **C** showed decreased mature SREBP-1c in the liver of KK-Ay mice with FPS-ZM1, compared with those without FPS-ZM1

In general, the interaction between AGEs and its receptor, RAGE, initiates phosphorylation events involving p65 nfκb and p38 MAPK. The phosphorylation of these signaling molecules contributes to subsequent processing of the SREBP-1c precursor into its mature form, thereby culminating in dysregulation of lipid metabolism (Fig. 6). To verify our hypothesis, we used FPS-ZM1, an inhibitor of RAGE, to treat KK-Ay mice with lipid deposition in the liver. Excitingly, treatment with FPS-ZM1 not only reduced the accumulation of lipid droplets in hepatic cells but also decreased the levels of mature SREBP-1c in liver tissue. Interestingly, FPS-ZM1 further decreased the levels of p-p65 Nfκb and p-p38 MAPK in hepatic tissue. Therefore, the utilization of FPS-ZM1 has been suggested as a potential approach for mitigating lipid accumulation in the liver associated with SREBP-1c by inhibiting the phosphorylation of p65 nfκb and p38 MAPK. Concurrently, this study corroborated the involvement of AGEs in the pathogenesis of SREBP-1c-mediated NAFLD, wherein hyperphosphorylation of p65 nfkb and p38 MAPK have been identified as contributing factors.

Limitations

In this work, we explore the role of AGEs in SREBP-1c-associated NAFLD. Moreover, we used FPS-ZM1, a blocker of RAGE, to verify the aforementioned viewpoint. However, there are some limitations to our study. Firstly, we did not use different dosages of FPS-ZM1, and only performed the experiment with the previously reported dosage. Secondly, we only measured p-p65 nfκb and p-p38 MAPK and mature SREBP-1c to support their possible roles. Further inhibitor and genetically modified applications are required in the future. Last but not least, further in vitro studies and functional experiments are necessary to investigate the direct effects between AGEs, RAGE, p-p65 nfκb, p-p38 MAPK, and SREBP-1c, as well as the factors that mediate these direct effects.

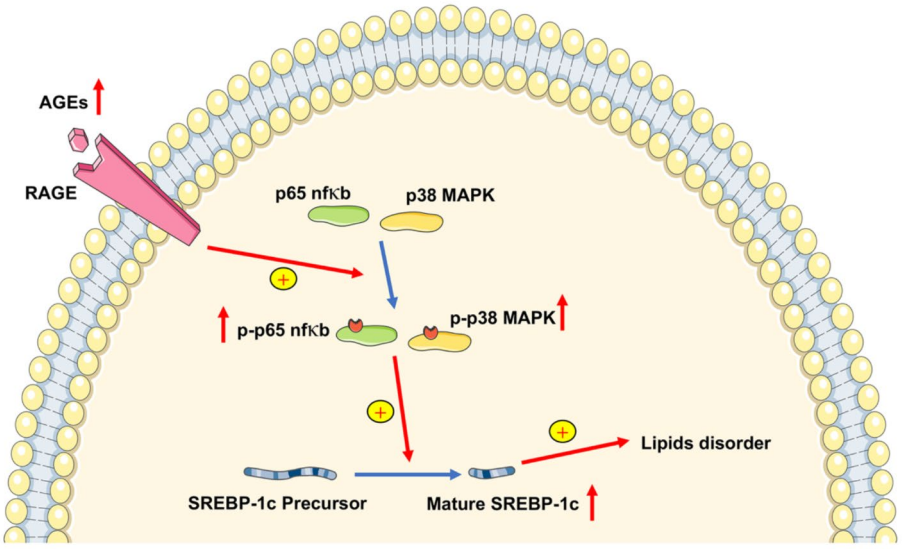

Fig. 6 The mechanism of AGEs involving in lipids disorder via SREBP-1c. Notes: The interaction between AGEs and its receptor, RAGE, initiates phosphorylation events involving p65 nfκb and p38 MAPK. The phosphorylation of these signaling molecules contributes to subsequent processing of the SREBP-1c precursor into its mature form, thereby culminating in dysregulation of lipid metabolism

Conclusions

In general, it is suggested that AGEs may be involved in the process of SREBP-1c-related lipid droplet accumulation in hepatocytes of diabetic KK-Ay mice with NAFLD. Additionally, hyperphosphorylation of p65 nfκb and p38 MAPK in liver tissue may play an important role in the development of NAFLD in diabetic mice.

Abbreviations

NAFLD	Nonalcoholic fatty liver disease
T2DM	Type 2 diabetes mellitus
AGEs	Advanced glycation end products
RAGE	Receptor for advanced glycation end products
SREBP-1c	Sterol regulatory element-binding protein-1c
p65 nfκb	Nuclear factor κB p65
p-p65 nfκb	Phosphorylated nuclear factor κB p65
p38 MAPK	Mitogen-activated protein kinase p38
p-p38 MAPK	Phosphorylated mitogen-activated protein kinase p38

Supplementary Information

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Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

Haoqiang Zhang and Jinlei Liu contributed to the idea. Mengshu Zhang and Wanwan Zhao wrote the manuscript draft. Mengshu Zhang, Wanwan Zhao, Zhen Zhang, Mengting He, Ya Zhang, and Bing Song performed the experiment. All authors revised the manuscript the version to be submitted. All authors reviewed, revised the manuscript and gave final approval of the version to be submitted.

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Data availability

The data in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All methods are reported in accordance with ARRIVE guidelines and approved by the Medical ethics committee, The First Affiliated Hospital, Jinzhou Medical University.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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