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Sestrin2 knockout exacerbates high-fat diet induced metabolic disorders and complications in female mice

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Abstract

Background Obesity and its associated complications raise significant public concern, revealing gender disparities in the susceptibility to metabolic disorders, with females often displaying greater resistance to obesity-related metabolic disorder than males. Sestrin2 is a crucial protein involved in metabolism and energy balance. This study seeks to explore whether *Sesn2* knockout (KO) exacerbates high-fat diet (HFD) induced obesity in female mice.

Methods Female mice with wild-type (WT) and *Sesn2* KO were subjected to a 12-week regimen of normal diet or HFD. Using a Body Composition Analyzer, body composition was gauged. Biochemical assays encompassed glucose, lipid, and liver function measurements, alongside 24-hour urine albumin excretion. Echocardiographic evaluation assessed cardiac function. Histopathological analysis of key metabolic tissues (liver, kidney, and heart tissues) were conducted. Western blotting or qRT-PCR evaluated key proteins and genes linked to inflammation, mitochondrial, and lipid metabolism in adipose tissues.

Results In comparison to mice fed a regular diet, those on a HFD exhibited significant increases in body weight and fat mass. Notably, *Sesn2* KO further aggravated obesity, showcasing the most pronounced metabolic anomalies: elevated body weight, fat mass, impaired glucose tolerance, and insulin sensitivity, alongside heightened levels of free fatty acids and triglycerides. Additionally, KO-HFD mice displayed exacerbated multi-tissue impairments, including elevated hepatic enzymes, increased urinary albumin excretion, compromised cardiac function, and accumulation of lipids in the liver, kidney, and heart. Moreover, adipose tissue showcased altered lipid dynamics and function, characterized by enhanced triglyceride breakdown and modified adipokine levels. Browning was diminished, along with decreased *Pgc1a* and *Sirt1* in KO-HFD mice.

Conclusion Sesn2 KO exacerbates HFD-induced obesity and metabolic disorders in female mice. These findings underscore Sestrin2's novel role as a regulator of obesity in female mice.

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Keywords Sestrin2, Obesity, Female, UCP-1, Adipose tissue

Introduction

Obesity has emerged as a significant global health concern, presenting a growing burden on public health worldwide [1]. This multifactorial condition is characterized by excessive adipose accumulation, leading to various metabolic disturbances and comorbidities such as cardiovascular disease, non-alcoholic fatty liver disease, and chronic kidney disease [2–4]. Unhealthy dietary habits, particularly the consumption of high-fat diets (HFD), have been identified as one of the major contributors to this epidemic [5–7].

Intriguingly, while both males and females are susceptible to the adverse effects of HFD, there may be sex-specific differences in metabolic responses and disease outcomes [8, 9]. Specifically, females generally exhibit a greater resilience to the onset of obesity and its associated metabolic comorbidities compared to males [10]. This differential response is not only relevant in understanding the full spectrum of metabolic disease mechanisms but also critical in tailoring gender-specific interventions. Hence, investigating the precise mechanism for this sex-specific differences is imperative for comprehensive comprehension of obesity-related complications.

Sestrins are stress-responsive proteins that have gained attention for their potential roles in modulating cellular metabolism and homeostasis [11]. Among the three known isoforms (Sestrin1, Sestrin2, and Sestrin3), Sestrin2 (*Sesn2*) stands out as a promising candidate in regulating metabolic pathways under various stress stimuli, including nutrient excess. Sestrin2 is associated with autophagy regulation, oxidative stress inhibition, aging, and metabolism, acting as a metabolic regulator to help cells adapt to stress [12]. It activates catabolic responses, inhibits anabolic activities, and initiates cellular repair mechanisms [13]. The functions mentioned are primarily associated with AMP-activated protein kinase (AMPK)/mechanistic target of rapamycin (mTOR), which acts downstream of Sestrin2 and serves as an energy switch controlling glucose and lipid metabolism [14, 15]. Thus, sestrin2 plays a crucial role in metabolic regulation, particularly in the context of obesity and overnutrition. Lee et al. [16] demonstrated that Sestrin2 is upregulated in response to overnutrition, helping to mitigate the effects of chronic mTOR activation in liver tissue. This adaptive response helps maintain metabolic balance by modulating lipid metabolism and preventing mitochondrial dysfunction.

Our previous evidence from *Sesn2* knockout (KO) studies in male mice show more pronounced obesity and metabolic disturbances when subjected to HFD compared to their wild-type littermates [11]. Moreover, Sestrin2 plays protective roles against diet-induced metabolic complications, including cardiac dysfunction and obesity [11, 17]. However, the specific effects of Sestrin2 and HFD on metabolic parameters and disease progression in females remain unexplored. Additionally, female subjects are often underrepresented in metabolic disorder studies. Focusing on female mice, our study aims to fill this research gap and offer crucial insights for tailoring therapeutic strategies to sex-specific needs. Thus, we delve into the sex-specific role of Sestrin2 in HFD-induced metabolic disorders and complications in female mice, providing insights into potential therapeutic interventions for prevalent health issues.

Materials and methods

Animals

Six-week-old female C57BL/6J mice (Pengyue Animal Breeding Co., Ltd.) and *Sesn2* whole-body KO mice (Cyagen Biosciences Inc.) accommodated in ventilated cages. The mice were categorized into four groups based on body weight (6–8/group), each with two subgroups: wild type (WT) and *Sesn2* KO. The WT-NC and KO-NC groups were fed a standard chow diet (10% fat, 320 kcal per 100 g), while the WT-HFD and KO-HFD groups were fed a HFD (60% fat, 524 kcal/100 g; Fanbo Biotechnology, Wuxi, China). Body fat was quantified using the Body Composition Analyzer (Bruker, Germany). The mice were housed in standard laboratory conditions for a duration of 12 weeks. All animal experiments were conducted with the approval of the Animal Ethics Committee of Weifang Medical University.

Biochemical assays

After a 12-hour fasting period, mice underwent either an oral glucose tolerance test, where they were administered 2 mg/g of glucose, or an insulin tolerance test, where they received intraperitoneal injection of 0.75 u/kg regular insulin. Blood glucose levels were measured at 0, 15, 30, 60, and 120 min after the test using tail venous blood. Plasma triglyceride (TG) and free fatty acid (FFA) concentrations were determined using commercial test kits (BC0625 and BC0596, Solarbio, China). Urine albumin excretion (UAE) was measured using an enzyme-linked immunosorbent assay (CEB028Mu, Cloud-Clone Corp, China). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured by Jiancheng (Nanjing, China).

Echocardiographic evaluation

For the evaluation of cardiac function, various parameters, including ejection fraction (EF) and the ratio of

early to late diastolic mitral inflow velocity (E/A), were assessed as previously described [18]. To conduct these assessments, mice were anesthetized with isoflurane and underwent transthoracic M-mode echocardiography (Vevo 3100, Visualsonics, Toronto) to assess cardiac function.

Histopathological analysis

Liver, kidney, and heart tissues were dissected in chilled saline, promptly fixed in 4% paraformaldehyde, and subsequently embedded in paraffin. Sections measuring five millimeters in thickness were obtained from the paraffin blocks and subjected to hematoxylin and eosin staining for histopathological analysis. To assess tissue fibrosis levels and lipid accumulation. Masson staining and Oil Red O was employed. Photographic documentation was accomplished using the Motic digital microscope.

Western blotting

The livers and fat of four groups of mice were pulverized and prepared in an equivalent system using lysis buffer and 5x loading buffer. The livers were separated using 10% and 8% sodium dodecyl sulfate–polyacrylamide gel electrophoresis. The protein is then transferred to PVFM. The proteins were incubated with antibodies to p-AMPK (CST, #4186S), AMPK (CST, #5831S), p-mTOR (CST, #5536S), mTOR (proteintech, 66888-1-Ig), UCP-1 (abcam, ab234430), β-actin (biorbyt, orb621019) and GAPDH (proteintech, 10494-1-AP) at 4 °C overnight, and then incubated with secondary antibodies for development.

Quantitative PCR analysis

RNA was extracted using Trizol and reverse transcribed into cDNA. qPCR was performed using TB Green Premix Ex Taq II, and expression was calculated using Gapdh as control. The primer sequences were shown in the Supplementary Table 1.

Statistical analysis

Results were analyzed using GraphPad Prism 9.0; all data are presented as mean ± SEM and assessed as normality. One-way ANOVA was used among the four groups of data followed by post-hoc tests. $P<0.05$ indicated statistical difference.

Results

Sesn2 knockout aggravates HFD-Induced obesity in female mice

Obese models were established in both female C57BL/6J mice with WT and *Sesn2* KO backgrounds. Following a 12-week HFD regimen, significant obesity was observed in both the WT-HFD and KO-HFD mice (Fig. 1A-B). Notably, the KO-HFD mice exhibited the most pronounced increases in body weight, body fat, and fat percentage ($P<0.05$, Fig. 1C-E). This was accompanied by elevated circulating levels of triglycerides and FFA, with KO mice exhibiting notably higher levels compared to the other groups ($P<0.05$, Fig. 1F-G). While fasting blood glucose levels were similar between NC and HFD groups, KO-HFD mice exhibited the highest glucose levels compared to the KO-NC group (KO-HFD: 10.42 ± 0.89 mmol/l vs. KO-NC: 6.92 ± 0.52 mmol/l, $P<0.05$, Fig. 1H). Moreover, glucose tolerance and insulin sensitivity were impaired in the HFD group, with the KO-HFD mice displaying the most severe impairment ($P<0.05$, Fig. 1I-J).

Sesn2 knockout aggravates HFD-Induced liver injury in female mice

Initially, an evaluation of HFD-induced liver injury was conducted. Remarkably, the HFD led to impaired liver function, particularly in KO-HFD mice. This was accompanied by elevated *Ccl2* and *Il6* mRNA levels in liver tissues (Fig. 2A-D). Subsequent analysis of histological staining revealed enlarged hepatocyte volumes, and increased accumulation of lipid droplets, notably accentuated in the KO-HFD group (Fig. 2E). Masson's staining depicted disruptions in lobular architecture, adipocyte hyperplasia, perisinusoidal fibrosis, and heightened collagen deposition within the HFD mice, with the most prominent effects observed in the KO-HFD group (Fig. 2E and F).

Given that the critical role of Sestrin2 in liver, we focused on the Sestrin2-AMPK-mTOR pathway and its response to *Sesn2* KO. The results demonstrated inhibited p-AMPK expression in the HFD group, with its expression remaining diminished in *Sesn2* KO groups (Fig. 2H-J). This decrease in p-AMPK activation alleviated p-mTOR inhibition, resulting in heightened p-mTOR expression. Notably, Western blot results showed elevated p-mTOR expression within the KO-HFD groups (Fig. 2H-J).

Sesn2 knockout aggravates HFD-Induced cardiac dysfunction in female mice

Subsequently, we undertook an assessment of HFD induced cardiac dysfunction. Interestingly, our investigation revealed that there were no discernible differences in cardiac function between the WT mice on a normal chow (WT-NC) and those on a HFD (WT-HFD). Surprisingly, however, KO-HFD mice exhibited evident cardiac dysfunction with reduced E/F ratio and increased E/A ratio ($P<0.05$, Fig. 3A-B). Histological analysis revealed significant myocardial hypertrophy, reflecting an enlargement of heart muscle cells, along with pronounced and severe cardiac fibrosis, most prominently observed in KO-HFD mice (Fig. 3C-E).

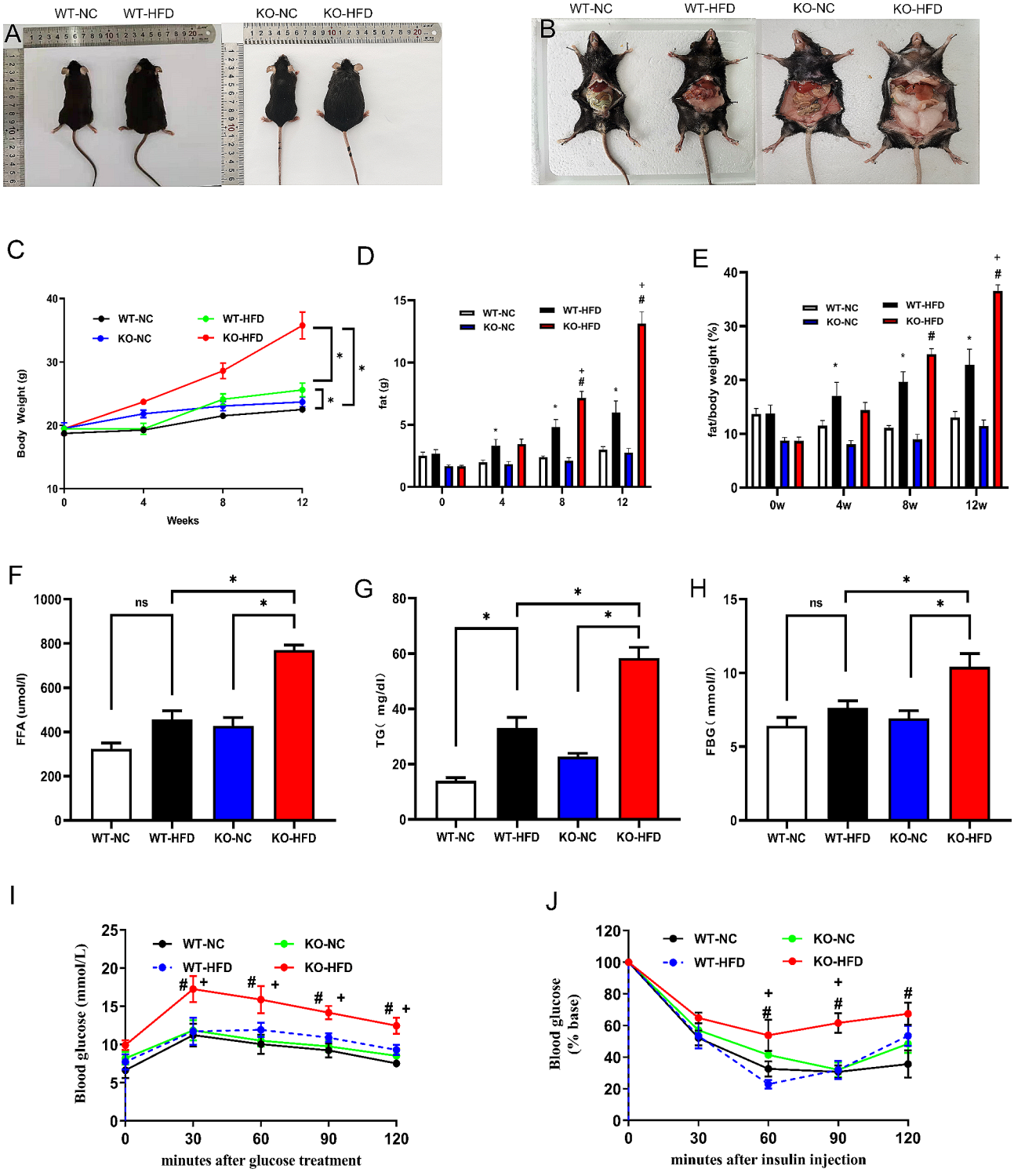

Fig. 1 *Sesn2* knockout aggravates obesity in female mice. (**A**-**B**) mice in four groups; (**C**) body weight; (**D**-**E**) fat mass; (**F**) FFA; (**G**) TG; (**H**) FBG; (**I**-**J**) OGTT and ITT; $n = 4$–6/group. $^{*}P < 0.05$; $^{\#}P < 0.05$ vs. KO-NC. $^{+}P < 0.05$ vs. WT-HFD

Sesn2 knockout aggravates HFD-Induced renal injury in female mice

Apart from its effects on the liver and heart, the absence of *Sesn2* exacerbates the kidney dysfunction caused by a HFD in female mice. Functional assessment revealed that the HFD-fed groups exhibited higher 24-hour UAE levels compared to the NC groups. Notably, the mice in KO-HFD group displayed the highest 24-hour UAE among

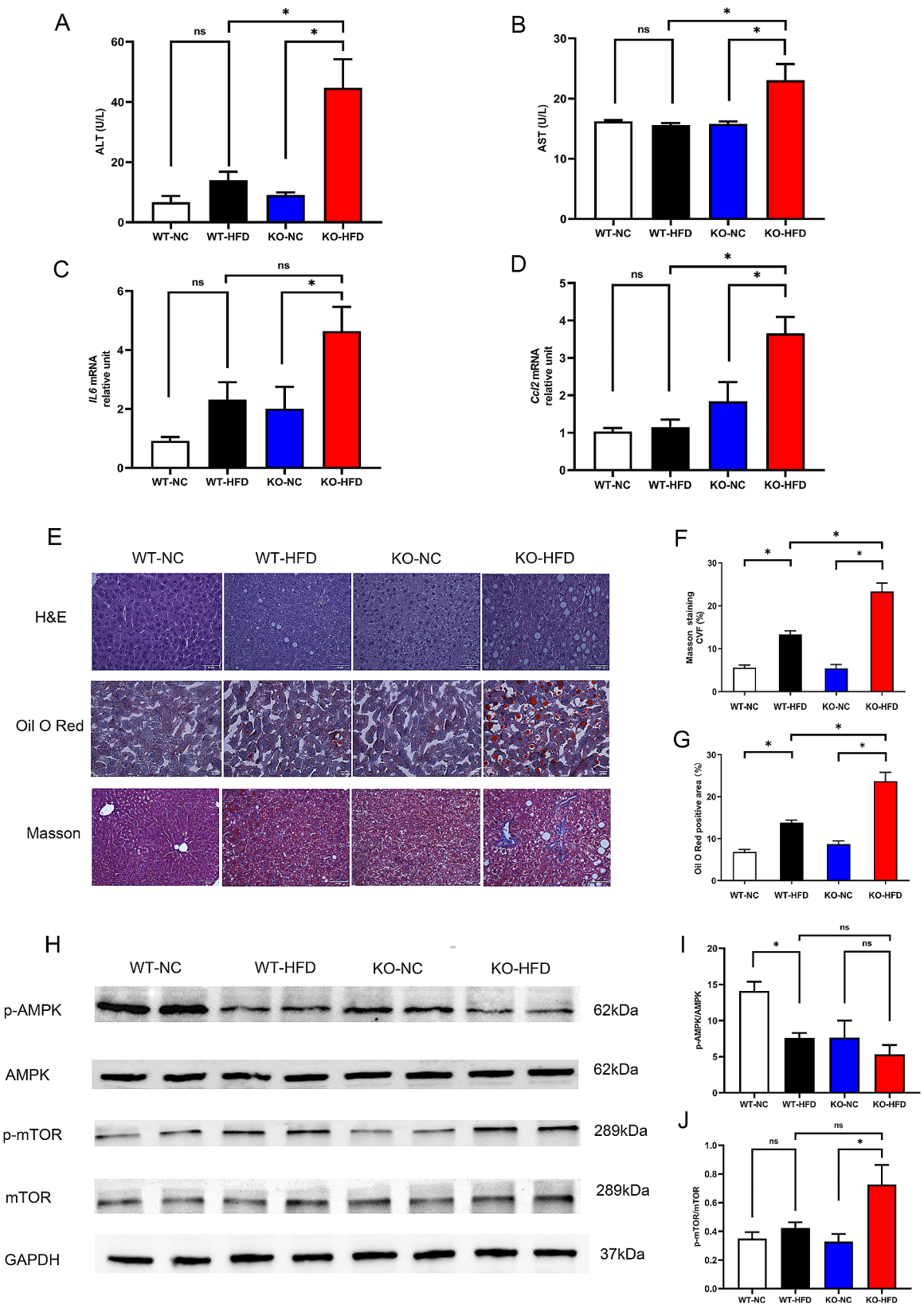

Fig. 2 *Sesn2* knockout aggravates liver injury in female mice (**A**) ALT; (**B**) AST; (**C**) *Ccl2* mRNA levels (**D**) *Il6* mRNA levels; (**E**-**G**) H&E, Masson's staining and Oil O Red; (**H**-**J**) Western blot for AMPK and mTOR; $n = 4–5$/group, $^{*}P < 0.05$

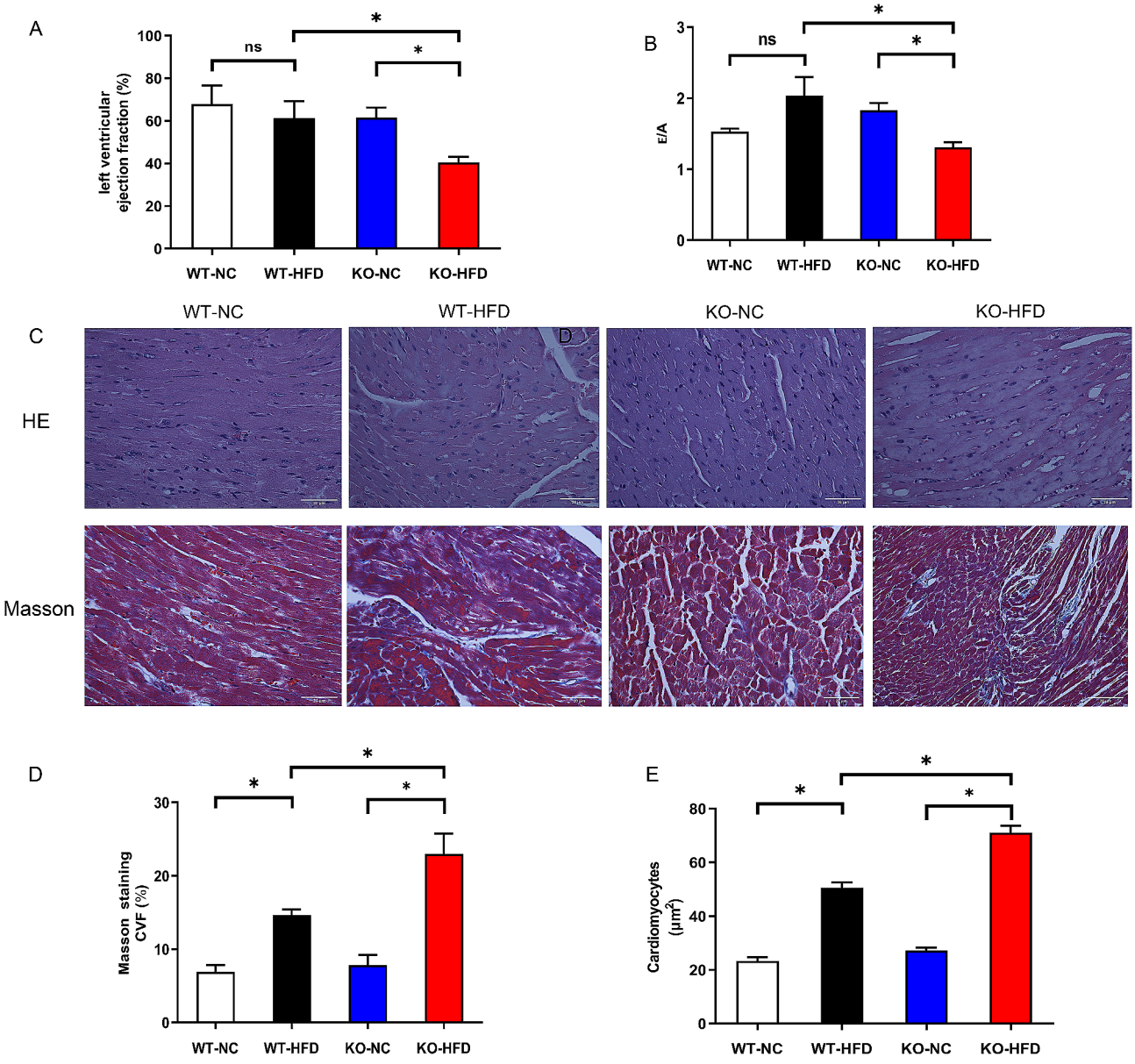

Fig. 3 *Sesn2* knockout aggravates cardiac dysfunction in female Mice. (**A**-**B**) cardiac dysfunction (E/F ratio and E/A ratio); (**C**-**E**) H&E and Masson's staining; $n = 4–5$/group, $^{*}P < 0.05$

all four groups, confirming the most pronounced kidney damage in this cohort (Fig. 4A and B). Histological analysis using HE staining demonstrated more pronounced glomerular hypertrophy in the HFD-fed groups in contrast to the NC groups. Remarkably, the KO-HFD group exhibited the most severe renal fibrosis among all groups (Fig. 4C-D).

Sesn2 knockout aggravates HFD-Induced adipose dysfunction in female mice

Being a pivotal organ for energy storage, the impact of *Sesn2* KO on adipose tissue lipid dynamics necessitates further exploration. Notably, the results demonstrated elevated expressions of *Lpl* and *Agtl* in inguinal WAT within the HFD group, with their peak expressions observed in the KO-HFD group, suggestive of augmented triglyceride breakdown ($P < 0.05$, Fig. 5A-B).

Additionally, *Sesn2* KO in the context of a HFD initiates a cascade of alterations within white and brown adipose tissue (WAT/BAT). Strikingly, *Cidea* expression in BAT decreased the most in the KO-HFD group (Fig. 5C). Conversely, *Ucp1* expression in BAT exhibited an ascending trend under HFD conditions, reaching its peak in the KO-HFD group, indicative of enhanced thermogenic activity (Fig. 5D and L). Next, we investigated the potential transition of WAT to BAT, observing a reduction in

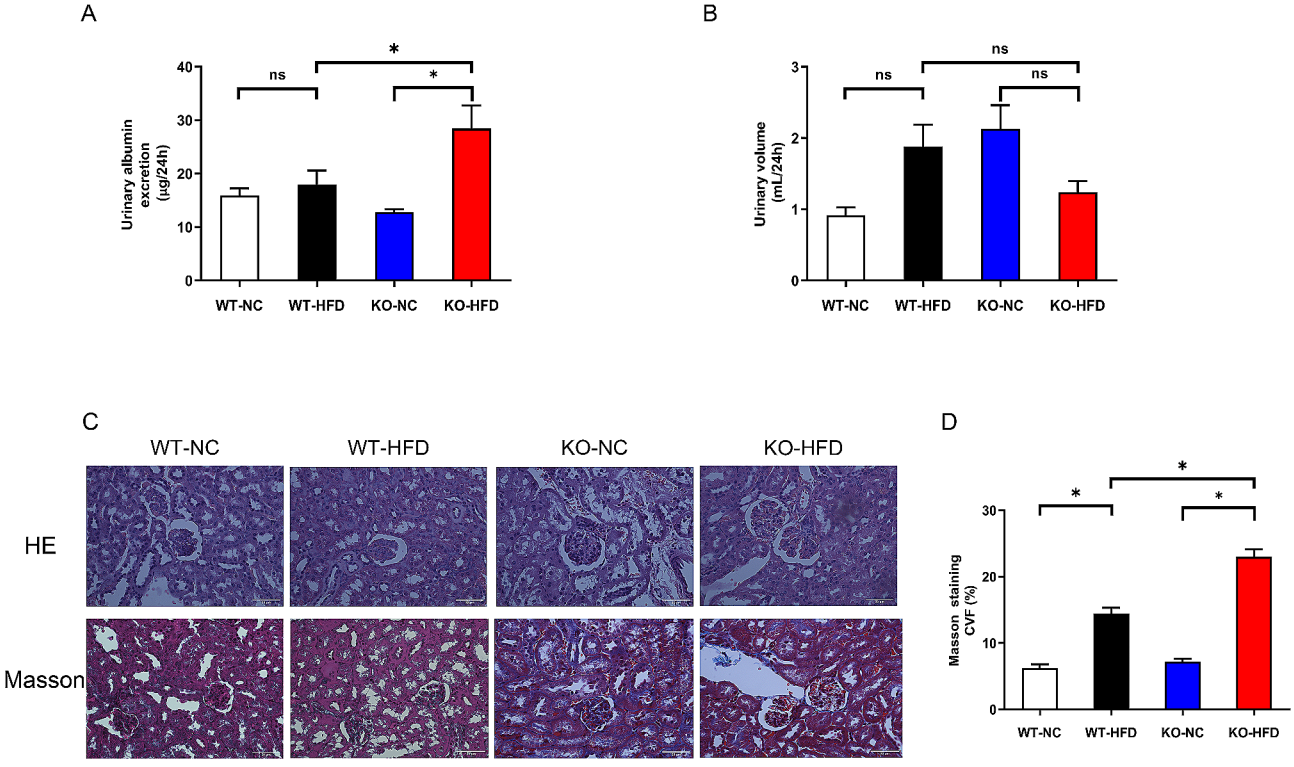

Fig. 4 *Sesn2* knockout aggravates renal injury in female mice (**A**) 24-hour UAE; (**B**) 24-hour urinary volume; (**C**, **D**) H&E and Masson's staining; $n = 5$/group
$^{*}P < 0.05$

mRNA levels of both *Adrb3* and *Ucp1* in inguinal WAT occurring in the KO-HFD mice (Fig. 5E, F, I). To assess mitochondrial biogenesis in WAT, we evaluated the expressions of *Pgc1α* and *Sirt1*. Both *Sirt1* and *Pgc1α* in inguinal WAT demonstrated reduced expressions within the HFD groups, reaching their lowest levels in the KO-HFD group, suggesting compromised mitochondrial biogenesis (Fig. 4G-H).

Considering the profound connection between obesity and inflammation, we also studied *Adipoq*, *Il6*, and *Tnf* levels in inguinal WAT across the four experimental cohorts. PCR results revealed a decrement in *Adipoq* levels within the HFD mice, with the most substantial reduction observed in the KO-HFD mice ($P<0.05$; Fig. 5I). Conversely, the levels of *Il6*, and *Tnf* exhibited an increase in response to a HFD, attaining their peak in the *Sesn2*-KO mice ($P<0.05$, Fig. 4J-K).

Discussion

The results presented in this investigation offer a comprehensive insight into the role of *Sesn2* KO in aggravating the adverse impacts of HFD on various physiological aspects in female mice. These findings highlight the importance of Sestrin2 in maintaining metabolic homeostasis and protecting against the detrimental effects of HFD-induced obesity and its associated complications.

Obesity presents a growing global health concern, imposing a significant burden on public health. Notably, metabolic responses exhibit sex-specific differences, suggesting potential greater resilience in females. In this study, we delve into this phenomenon, uncovering intriguing insights. Specifically, a 12-week HFD yielded only a modest increase in body weight in female mice. Strikingly, this HFD had minimal impact on circulating triglyceride and FFA levels, as well as glucose regulation, implying a degree of resistance to HFD-induced metabolic alterations in female mice.

Sestrin2, a stress-responsive protein, intricately links with metabolic pathways, regulating energy balance and cellular stress responses. Its central role designates Sesn2 as a potential key in addressing obesity, insulin resistance, and related complications. Its impact on pathways like AMPK-mTOR underscores its significance in coordinating cellular metabolism, holding promise for metabolic disorder treatments [19]. To elucidate Sestrin2's contribution to the resistance of female mice against an HFD, we established obesity models in both WT and *Sesn2* KO female mice using a 12-week HFD regimen. Remarkably, KO-HFD mice displayed the most pronounced increases in body weight, body fat, and fat percentage. Furthermore, elevated circulating triglycerides and FFA were evident in the KO-HFD groups. While fasting glucose levels remained comparable between WT-NC and WT-HFD

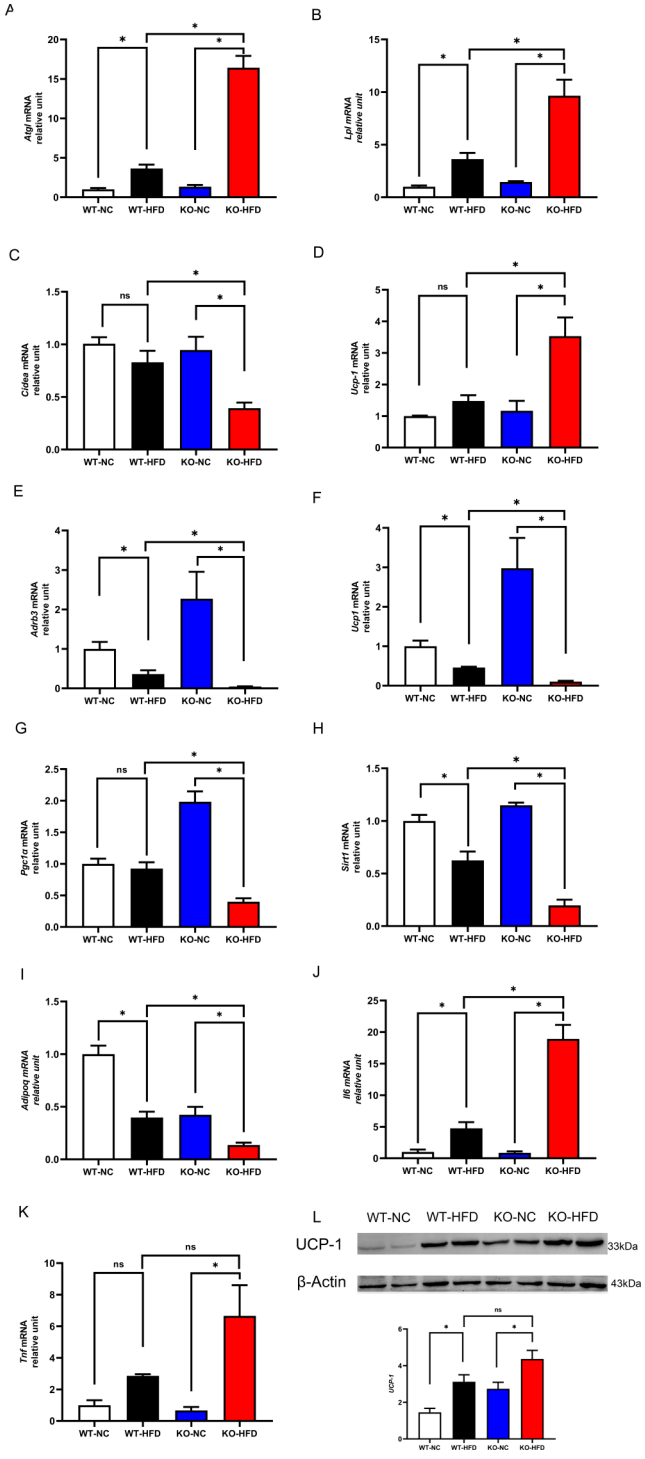

Fig. 5 *Sesn2* knockout aggravates adipose dysfunction in female mice (**A**-**B**) *Atgl* and *Lpl* in inguinal WAT; (**C**-**D**) *Cidea* and *Ucp1* in BAT; (**E**-**F**) *Adrb3* and *Ucp1* in inguinal WAT; (**G**-**K**) *Pgc1a*, *Sirt1*, *Adipoq*, *Il6* and *Tnf* in inguinal WAT; (**L**) UCP-1 protein in BAT. $n = 4–6$, $^{*}P < 0.05$

groups, KO-HFD mice exhibited the highest glucose levels. Impairments in glucose homeostasis were conspicuous among the KO-HFD mice. These results emphasize Sestrin2's crucial role in HFD-induced metabolic abnormalities in female mice.

The escalating global obesity crisis leads to excessive adipose tissue, contributing to metabolic complications like injuries for liver, heart and kidney. Intriguingly, emerging research suggests females might display heightened resilience to metabolic consequences linked

with obesity. Our study aims to clarify Sestrin2's role by probing its impact on HFD-triggered metabolic disruptions. Specifically, we assessed *Sesn2* KO effects on HFD-induced hepatic injury. The absence of *Sesn2* accentuated hepatic injury, evident through impaired liver function, heightened expression of inflammatory markers *Ccl2* and *Il6*. Sestrin2 activates AMPK, leading to mTOR inhibition, effectively addressing metabolic disorders, such as insulin resistance and mitochondrial dysfunction [11, 20, 21]. Notably, *Sesn2* KO hindered AMPK activation, reducing mTOR inhibition, accentuating lipid accumulation. This effect was amplified in KO-HFD mice, aligning with disrupted liver structure and inflammation, particularly in KO-HFD. These findings align with prior research indicating activating Sestrin2 mitigates obesity-related hepatic injury [17, 22].

Shifting focus to cardiac function, although HFD alone minimally affected cardiac function in female mice, *Sesn2* KO coupled with an HFD regimen resulted in compromised cardiac function. This was evident from alterations in E/F and E/A ratios. Histological examination unveiled myocardial hypertrophy and significant cardiac fibrosis within the KO-HFD group. Our prior investigation highlighted Sestrin2's significance in the cardiovascular safeguarding conferred by SGLT2 inhibitors in cases of obesity-related cardiac dysfunction [11]. These observations underscore the notion that *Sesn2* deficiency exacerbates the cardiac consequences of an HFD in mice. Similarly, the impact of *Sesn2* KO extended to kidney function. Within the context of HFD, *Sesn2* deficiency amplified kidney dysfunction, as indicated by elevated 24-hour UAE and glomerular hypertrophy within the KO-HFD group. These outcomes strongly imply a protective role of Sestrin2 in maintaining renal health and mitigating HFD-induced kidney impairment.

Our study underscores Sestrin2's pivotal role in regulating multi-organ responses to an HFD in female mice. Adipose tissue, traditionally deemed an energy reservoir, is now acknowledged as a dynamic endocrine organ crucial for metabolic equilibrium. However, dysfunction in adipose tissue leads to ectopic lipid accumulation in vital organs, fostering organ-specific pathologies. Central to lipid metabolism are the key enzymes LPL and ATGL, which govern triglyceride hydrolysis. While ATGL and LPL are essential for mobilizing fatty acids for energy production, increased activity of these enzymes can lead to elevated levels of FFA, which may overwhelm the capacity for beta-oxidation and contribute to insulin resistance. In obesity, elevated levels of *lpl* and *Atgl* contribute to ectopic lipid deposition [23]. Our research unveils elevated levels of these enzymes in HFD-fed mice, particularly in *Sesn2* KO mice, reflecting increased lipolysis and reduced beta-oxidation, exacerbating lipotoxicity and insulin resistance. This is corroborated by elevated circulating FFA, impaired insulin sensitivity, and lower *Pgc1α* levels in the KO-HFD groups.

Adipose tissue, however, serves a dual purpose beyond energy storage, as it secretes adipokines [24]. A notable player among these is adiponectin, which offers protection against lipotoxicity and metabolic inflexibility [25]. Its reduction under HFD conditions, exacerbated by *Sesn2* KO, aligns with aggravated inflammation. Our results indicate elevated levels of *Il6* and *Tnf*, reflecting aggravated inflammation and weakened anti-inflammatory effects, corroborating lipid deposition and enhanced lipotoxicity in KO-HFD mice. Sestrin2 deficiency on an HFD triggers intricate shifts in energy metabolism within BAT and WAT. Notably, altered mitochondrial gene expression in BAT suggests enhanced thermogenic activity potential. In contrast, WAT displays compromised mitochondrial biogenesis, heightened inflammatory marker expression, and increased triglyceride synthesis. These collectively contribute to adipose tissue dysfunction and systemic metabolic perturbations.

UCP-1 is a pivotal protein involved in thermogenesis, particularly in BAT [26]. Lower levels of UCP-1 imply reduced thermogenesis, while higher levels of UCP-1 correlate with increased thermogenic capacity and energy expenditure. Conversely, Cidea, also primarily expressed in BAT, is associated with enhanced thermogenesis and energy expenditure [27]. Mice deficient in *Cidea* display heightened metabolism and elevated lipolysis, indicating an enhanced thermogenic potential [28]. Higher levels of *Cidea* could suggest an increased capacity for lipid storage within adipocytes. Notably, Cidea can negatively regulate UCP-1 activity [28]. Interestingly, KO-HFD mice exhibit reduced *Cidea* expression and increased *Ucp1* levels, suggesting that the loss of UCP-1 inhibition by Cidea enhances thermogenesis and counters excessive energy accumulation. ADRB3, prevalent in adipose tissue, is implicated in energy regulation [29]. ADRB3 shields adipocytes from excessive fatty acid exposure and consequent triglyceride buildup [30]. Reduced *Adrb3* and *Ucp*1 levels in WAT impede the transition from white to brown fat, fostering obesity. Our study shows diminished *Adrb3* and *Ucp1* expression in WAT in the KO-HFD group, hindering the browning process and contributing to obesity development.

PGC1α, a transcriptional coactivator, is vital for adaptive thermogenesis and energy metabolism. It promotes the expression of thermogenic genes like *Ucp1* in brown adipose tissue, enhancing energy expenditure and countering obesity [31]. Additionally, PGC1α interacts with various transcription factors to regulate genes involved in energy metabolism and fatty acid oxidation, contributing to metabolic homeostasis by utilizing stored energy sources [32]. SIRT1, a deacetylase, regulates PGC1α post-translationally. Together, they form a vital regulatory

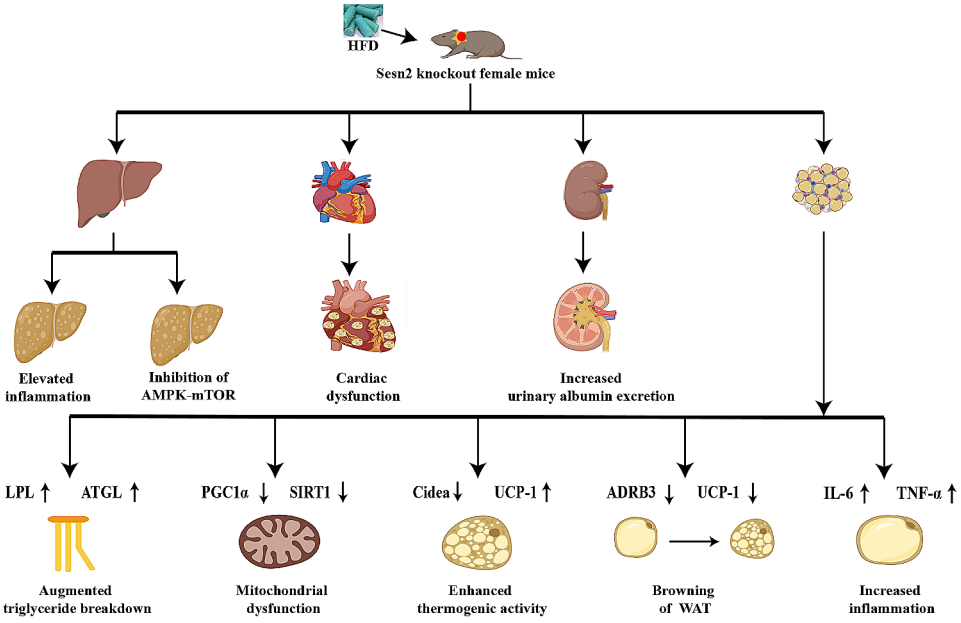

Fig. 6 *Sesn2* knockout exacerbates high-fat diet induced metabolic disorders and complications in female mice

pathway influencing cellular metabolism and mitochondrial biogenesis [33]. Dysregulation of this pathway is linked to insulin resistance, abnormal lipid profiles, and various pathological conditions. In HFD-fed mice, our findings demonstrate reduced expression of *Sirt1* and *Pgc1α*, reaching their lowest levels in KO-HFD mice. This highlights the severity of glucose and lipid metabolism dysfunction following *Sesn2* KO.

Our findings highlight the intricate consequences of HFD-induced dysfunction across multiple organs, further aggravated by *Sesn2* deficiency (Fig. 6). This study supports targeting Sestrin2 to mitigate obesity-related metabolic disruptions. Moreover, it unravels the complex interplay among adipose tissue, inflammation, and lipid metabolism. The observed inflammation, elevated lipid synthesis, and reduced WAT browning in HFD-fed KO mice shed light on altered adipose tissue function, impacting metabolic outcomes. While our study provides valuable insights, it has limitations. Exclusive use of female mice restricts direct generalization, urging gender-diverse investigations. While our study did not directly compare male and female KO mice, both showed susceptibility to HFD and metabolic disorders. In males, HFD exacerbated body fat percentage but not body weight compared to wild-type mice, while in females, both increased [11]. Variations in phenotype between male and female *Sesn2* KO mice underscore sex-specific responses, warranting further exploration of underlying mechanisms. Additionally, despite extensive molecular exploration, deeper mechanistic insights require future research. The study's 12-week duration may not capture long-term effects, prompting consideration for extended studies. In summary, our study highlights Sestrin2's role, but its limitations stress the need for comprehensive, diverse, and clinically relevant investigations to validate and expand upon our findings.

Conclusion

In conclusion, this study emphasizes the role of Sestrin2 in maintaining metabolic balance and protecting against diet-induced obesity and related complications in female mice. The findings indicate that *Sesn2* deficiency exacerbates obesity, impairs glucose metabolism, and intensifies liver, cardiac, renal, and adipose tissue dysfunction in response to a HFD. Targeting Sestrin2 could hold promise for addressing diet-induced metabolic disorders. The study underscores the need to consider sex-specific responses in obesity research and paves the way for further exploration into the intricate interplay of sex, genetics, and metabolic health. More investigation is required to uncover how Sestrin2 precisely influences these processes and to develop potential interventions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-024-00834-8.

Supplementary Material 1

Author contributions

LZ and CK were responsible for conceptualization, methodology, data curation, and writing-original draft preparation; FH and XS were responsible

for conceptualization, supervision, writing-reviewing and editing; others were responsible for data curation and investigation.

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Data availability
Data will be made available on request from correspondence author.

Declarations

Ethics approval and consent to participate
The study was conducted with the approval of the Animal Ethics Committee of Weifang Medical University.

Competing interests
The authors declare no competing interests.

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