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Maternal high fat diet consumption enhances offspring susceptibility to DSS-induced colitis in mice

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Abstract

Objective: Maternal high fat diet (HFD) may alter the offspring intestinal immune system thereby enhancing susceptibility towards inflammatory bowel disease. The objective of current study was to investigate the impact of maternal HFD on offspring intestinal health using a mouse model of dextran sodium sulfate (DSS)-induced colitis.

Methods: Dams were provided with either HFD (60%) or control diet. After weaning female offspring from both groups were kept on 45% HFD. At 14-weeks of age, offspring were subjected to 2.5% DSS in drinking water for 5 days, followed by 5 days of recovery.

Results: Offspring from maternal HFD had higher body weight gain before DSS-induction, and had higher liver and fat weights with increased adipocyte size at necropsy. When subjected to DSS-treatment, HFD offspring had accelerated body weight loss and exaggerated disease activity index. HFD offspring had elevated histopathological score, interleukin (IL)-1β, IL-6, and IL-17 expression with up-regulated NF-κB signaling. Maternal HFD resulted in enhanced neutrophil infiltration associated with elevated expression of monocyte chemoattractant protein-1 (MCP-1). Furthermore, maternal HFD suppressed AMP activated protein (AMPK) activity, and decreased sirtuin 1 (SIRT1) and p53 protein contents in offspring gut.

Conclusion: Maternal HFD consumption predisposes offspring to a higher susceptibility of inflammatory bowel disease development.

Keywords

Maternal high fat diet; offspring; adipocytes; colitis; AMPK

Introduction

According to the latest NHANES survey (2009–2010), 31.9% of non-pregnant women 20–39 years of age are with obesity, and another one third are overweight (1). Accompanying the rapidly increasing prevalence of obesity, the incidence of inflammatory bowel disease

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(IBD) including Crohn's disease (CD) and ulcerative colitis (UC), has rapidly increased in Europe and North America since the last decade of 20th century. More alarming, the incidence of IBD is rising quickly in young children in the USA, which was doubled from 1991 to 2002 (2). Around 1.5 million people are suffering from IBD in the USA, and is gaining commonness in the areas of the world where people are adopting a Western lifestyle that includes less physical activity, stress, and a diet rich in fat (3). IBD has resulted in huge medical cost in the USA and around the world (4). The etiological factors of IBD mainly comprise genetics, gut microbes, and environmental factors (4). Consumption of a diet rich in saturated fat increases incidence of colitis through promoting sulphite-reducing pathobiont in interleukin (IL)-10 deficient mice, which are genetically susceptible to IBD (5). Epidemiological studies further link high fat diet exposure during infancy to the incidence of IBD in adults (6).

Maternal high fat diet (HFD) intake negatively affects fetal development, which exerts lasting effects on the health of offspring, predisposing offspring to chronic diseases such as diabetes, coronary heart diseases and hypertension (7, 8). However, knowledge regarding the impact of maternal HFD or obesity on intestinal development and health of the progeny is limited (8); and the impact of maternal HFD on the incidence and susceptibility to IBD in offspring has only been sparsely tested (9). Jacobson and colleagues demonstrated that maternal high linoleic acid (18:2n-6) intake enhanced 2,4-dinitrobenzene sulfonic acid (DNBS)-induced colitis symptoms in nursing offspring (9). In our previous studies, we found that maternal obesogenic diet induced chronic gut inflammation in offspring (10, 11) and impaired gut barrier function of offspring in non obese diabetic (NOD) mice (10). Recently, Gruber and colleagues reported that maternal HFD in combination with postnatal HFD accelerated ileitis onset in the distal ileum of offspring TNF $^{\Delta ARE/WT}$ mice, a genetically susceptible model for CD like ileitis (12). In the current study, we examined the impact of maternal HFD on the IBD susceptibility of offspring using a dextran sulfate sodium (DSS)-induced colitis mouse model.

Materials and methods

Antibodies and chemicals

Antibodies against phosphor-/total AMPK, phosphor-/total-ERK1/2, IL-6, IκBα, phosphor-/total-p38, phosphor-/total-p65, p53, and SIRT1 were from Cell Signaling Technology (Beverly, MA, USA). Anti-Ly-6B.2 monoclonal and anti-β-actin antibodies were purchased from Bio-Rad Laboratories Inc. (Hercules, CA, USA) and Sigma (Saint Louis, MO, USA), respectively. IRDye 680 goat anti-mouse and IRDye 800CW goat anti-rabbit secondary antibodies were purchased from Li-Cor Biosciences (Lincoln, NE). The Vectastain Elite ABC, and DAB peroxidase (HRP) substrate kits were purchased from Vector Laboratories Inc. (Burlingame, CA, USA). Trizol® Reagent was purchased from Sigma (Saint Louis, MO, USA). DNase I and RNeasy Mini kit were purchased from Qiagen (Valencia, CA, USA), and iScript™ cDNA synthesis kit was purchased from Bio-Rad Laboratories Inc. (Hercules, CA, USA). Colitis grade DSS (MW = 36,000–50,000) was purchased from MP Biomedicals (Santa Ana, CA, USA).

Animal care and experimental design

Maternal diet and treatment—Adult (~4 months old) female C57BL/6J mice (purchased from Jackson Laboratory (Bar Harbor, ME, USA) and inbred in our facility) that had been fed regular chow diet were randomized into two groups; maternal control diet group (CON) and maternal high fat diet group (HFD). Both of the groups were fed with control diet (10% energy from fat, D12450H, Research Diets Inc., New Brunswick, NJ, USA) (Table S1&S2) up to mating with males of similar age. Mating was confirmed by the presence of vaginal plug. Then, mice were fed either CON or 60%HFD (60% energy from fat, D12492, Research Diets Inc., (Table S1&S2) diets during gestation and lactation (Fig. 1A). The 60% HFD is commonly used to induce obesity during a short duration (13). At birth, the litter sizes were balanced to 6 pups. At 3 weeks of age mice were weaned, and 9 female offspring per treatment were randomly selected for further studies. Here, we used female offspring mice because they were more vulnerable to programmed changes than males (14), and to avoid the confounding effects of sex.

Offspring diets and treatment—After weaning, female offspring of both CON and HFD fed dams were fed the 45% HFD (45% energy from fat, D12451, Research Diets Inc.) (Table S1&S2) diet *ad libitum* for ~ 13 weeks until necropsy (Fig. 1A). The 45% HFD was used to mimic the effect of typical diet of western societies during a longer period (13). The body weights of offspring mice of both the groups were recorded weekly.

DSS treatment of offspring

At 14 weeks of age, offspring mice from both CON and HFD fed dams were subjected to 2.5% (W/V) DSS water challenge for 5 days to induce colitis, followed by five days of providing plain drinking water for recovery (Fig. 1B). Mice were monitored daily during DSS induction and the recovery stage for body weight loss, fecal consistency, and blood in the stood. Then, mice were sacrificed and tissue were collected for histological and biochemical analysis. All mice were housed in a temperature controlled room with a 12 h light and 12 h dark cycle, and had free access to diet and drinking water. Experiments were conducted per the animal procedure (BAF # 04341) approved by the Washington State University Animal Care and Use Committee.

Assessment of symptoms and colitis score

The disease activity index (DAI) score was assessed according to the combined scores of weight loss compared to initial weight, stool consistency, and bleeding in the stool using criteria detailed in Table S3 (15). The scores were recorded daily during the DSS-treatment and recovery stages. The DAI score was the summation of three individual scores (body weight loss, stool consistency, and bleeding).

Tissue collection and fixation

Mice were anesthetized with CO_2 inhalation and followed by cervical dislocation. Organs including heart, spleen, liver, and cecum (containing lumen content) were collected and weighed. Subcutaneous fat (only lingual fat pad), visceral fat (Vis, gonadal fat collected around the ovaries in abdominal cavity), and brown adipose tissue (BAT, collected from the

interscapular area) were weighed. A 5 mm segment of distal colon at a constant location, and the visceral adipose tissues were fixed in freshly prepared 4% (w/v) paraformaldehyde (pH 7.0), processed and embedded in paraffin. The remaining colon tissue containing both inflamed and non-inflamed area was rinsed in PBS, frozen in liquid nitrogen, and stored at −80 °C for biochemical analyses.

Histological evaluation of colonic ulceration and adipocyte quantification

Paraffin embedded tissues were sectioned at 5 μm thickness, deparaffinized and subjected to haematoxylin and eosin (H&E) staining. Histological examination and imaging were done under a Lecia DM2000 LED light microscope (Chicago, IL, USA). At least one image was obtained per section and 9 sections per animal at constant interval were used for microscopic examination.

The pathological score of the distal colon was evaluated and recorded blindly using previously published score criteria (15), which was the sum of the scores of crypt damage (none, basal 1/3, basal 2/3, only surface epithelium intact), severity of inflammation (none, slight, moderate, and severe), and depth of injury (none, mucosal, mucosal and submucosal, and transmural). Paraffin embedded adipose tissues were sectioned and processed as previously described (16). Image J 1.30v software (National Institute of Health, Bethesda, MD, USA) was used to measure the area and diameter of adipocytes by drawing a horizontal straight edge-to-edge line in the middle of the adipocyte. Nine sections per animal at constant interval were used and all the adipocytes per image were quantified.

Immunohistochemical analyses

Immunohistochemical analyses were carried as previously described (17). Briefly, colonic tissue sections were deparaffinized, hydrated, followed by antigen retrieval, blocking and overnight incubation with anti-Ly-6B.2 antibody (BioRad Laboratories Inc.). Signals were visualized using the Vectastain ABC and DAB kits (Vector Laboratories) and haematoxylin counterstaining. Images were taken using the Lecia DM2000 LED light microscope (Chicago, IL, USA). Neutrophil infiltration scores were assessed blindly using the criteria described previously (18). Briefly, the scores for the depth of neutrophil infiltration (scored as 0–3) and staining intensity (0–4) were recorded individually. The summation of both scores resulted in the total quantified score ranging from 0 to a maximum of 7 per distal colonic section. Nine sections per animal at constant interval were used for microscopic examination and score assessment.

Immunoblotting analyses

Immunoblotting analyses were performed as previously described (19). Band density was quantified using the Odyssey Infrared Imaging System and Image Studio™ Lite software (Li-Cor Biosciences, Lincoln, NE, USA), and normalized to the β-actin content.

Quantitative Reverse Transcriptase (qRT)-PCR analyses

Total RNA was extracted from the powdered tissue with Trizol® Reagent (Sigma). RNA was treated with DNase I (Qiagen), and then purified with RNeasy Mini kit (Qiagen). cDNA was synthesized with the iScript™ cDNA synthesis kit (Bio-Rad). qRT PCR was performed per

a published method (20). 18s was used as the reference gene. Primer sequences used in the study are listed in the Table S4.

Statistical analysis

Data were analyzed as a complete randomized design using General Linear Model of Statistical Analysis System (2000). Data were expressed as mean ± standard error of mean (SEM). Student's T-test was used for calculating significance. A significant difference was considered as $P \leq 0.05$.

Results

Maternal HFD affects organ weight and visceral adipocyte size in offspring

The offspring from maternal HFD group had a significantly higher liver and lower spleen weights per percentage of body weight than those from maternal CON group (Fig. 2B), though their body weights were not different at necropsy (Fig. 2A). Similarly, the maternal HFD enhanced fat mass, including subcutaneous, BAT, and visceral fats (Fig. 2C), and visceral adipocyte diameter and area (Fig. 2D–F).

Maternal HFD affects body weight loss and disease activity index in DSS-induced colitis

Although body weight in offspring from maternal HFD group was significantly higher than that of maternal CON group before DSS induction (Fig. 3A), DSS-treatment resulted in a greater loss of body weight in maternal HFD offspring at the recovery stage (Fig. 3B). Colitis induction was further confirmed by diarrhea and blood in the stool in addition to body weight loss as shown by the DAI scores (Fig. 3C). The DAI score increased during DSS-treatment for both groups, which was significantly greater in maternal HFD offspring during the recovery stage (Fig. 3C). Further the colonic length was shorter (4.33 ± 0.14 cm) in maternal HFD fed offspring than maternal CON group (4.64 ± 0.17 cm), though it was not significant.

Maternal HFD enhances histologic distortion and inflammation in the colon of offspring mice subjected to DSS induction

Histological evaluation revealed that DSS-treatment caused injuries to the distal colonic tissues, which resulted in the loss of crypt architecture (Fig. 4A). The colon in maternal HFD offspring was more susceptible to DSS challenge with a trend of higher histopathological score ($P \leq 0.10$) than those from CON offspring (Fig. 4A&B), indicating aggravated ulceration in the distal colon.

To gain more insights on the altered histopathology, we further analyzed the expression of pro-inflammatory cytokines and associated inflammatory signaling. Maternal HFD elevated interleukin (IL)-1β, IL-6, and IL-17 gene expression (Fig. 4C) and increased IL-6 protein in offspring gut (Fig. 4F). NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling was exaggerated in the colonic tissues as indicated by enhanced phosphorylation of p65 (Fig. 4D&E) and decreased IκBα (inhibitor κB alpha, which sequesters and inactivates NF-κB Rel/p65 in cytoplasm) content (Fig. 4D&F). In addition, maternal HFD resulted in more extensive and severe neutrophil infiltration in the colonic

tissue of offspring mice (Fig. 5A&B), associated with elevated expression of monocyte chemoattractant protein-1 (MCP-1) (Fig. 5C). Accordingly, we observed decreased p38 phosphorylation (Fig. 5C&D) and enhanced ERK1/2 phosphorylation (Fig. 5C&E) in maternal HFD offspring. These findings collectively suggest that maternal HFD rendered offspring mice to be more susceptible to inflammation and colitis induced by DSS.

Maternal HFD adversely affects AMP-activated protein kinase activity in offspring mice with DSS-induced colitis

Maternal HFD reduced AMPK phosphorylation (Fig. 6A&B) in offspring colonic tissues. Consistently, both AMPK interacting proteins, SIRT1 and p53, were decreased (Fig. 6C) in offspring mice from HFD fed dams.

Discussion

The high fat diet is a part of the Western lifestyle and has been proposed to increase the risk of IBD (3). The rapid increase of IBD incidence in young children (2) suggests the potential role of maternal obesogenic diet in the development of this disease, but direct evidence remains missing. In the current study, we assessed impact of maternal HFD on the incidence of IBD in offspring using a DSS-induced colitis mouse model. We found that maternal HFD significantly aggravated the symptoms of acute colitis in the female offspring.

In this study, we initiated HFD (60%) dietary treatments after mating and maintained during gestation and lactation in order to avoid maternal obesity that could induce gestational diabetes and other physiological changes in addition to the effect of high fat diet (21). All offspring were fed obesogenic diet after weaning to mimic the typical diet of Western societies. The maternal HFD offspring were heavier at weaning, body weight was higher in offspring of maternal HFD compared to CON group from 7 weeks till DSS induction. The higher weight at weaning in the HFD fed group offspring was likely due to the maternal HFD (60%) diet consumption during gestation and lactation. Our findings are consistent with previous investigations that maternal high linoleic acid (18:2n-6) intake resulted a higher body weight in the nursing rats (9), and maternal HFD consumption enhanced body weight gain and adiposity in the offspring mice (22, 23). During the recovery period (post DSS induction), however, the body weight loss was higher in offspring of maternal HFD, suggesting severer colitis in these mice compared to offspring of maternal CON group. Consistently, during the course of recovery, a higher DAI score was detected in the maternal HFD fed group, so for the histopathological score, showing severer colitis and slower recovery of offspring of HFD fed dams. DSS, administered to mice in the drinking water, triggers intestinal inflammation by binding to medium chain length fatty acids in the mouse colon, resulting in the disruption of colonic epithelial barrier (24), and eliciting inflammation (25). Activated immune system produces pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α that further amplify the NF-κB inflammatory cascade (26). IL-17 in return mediates neutrophil infiltration and upregulation of TNF-α and IL-6, which are the key mediators in chronic inflammation of UC (26, 27). Consistent with previous reports and the observed severer histopathological damage (9), maternal HFD enhanced IL-1β, IL-6, and IL-17 production with amplified NF-κB signaling in the offspring. These findings are

aligned with earlier observations that maternal obesity predisposes offspring gut to inflammation in sheep (11) and NOD mice (10), as well as in young rats (9).

In IBD, excessive activation and infiltration of neutrophils in colonic lesions result in epithelial cell necrosis, mucosal injury and exaggerated colitis symptoms (28). High density neutrophil flux across epithelial monolayers from basolateral to apical surface disrupts epithelium (29), and weakens the epithelial barrier, which worsens inflammation and IBD symptoms (28). Maternal HFD exacerbated mucosal neutrophil infiltration in offspring subjected to DSS-treatment, which could contribute to the enhanced IL-17, and severer tissue damage and elevated histopathological score in DSS-induced colitis. Consistent with enhanced neutrophil infiltration, MCP-1, the main chemokine regulating migration and infiltration of neutrophils (30), was increased in offspring gut from HFD fed dams. These data were supported by a recent publication where maternal HFD promotes an early onset of ileitis in a genetically-driven CD mouse model, with enhanced neutrophil infiltration (12). Rapid apoptosis and removal of neutrophils are vital in the resolution of inflammation to avoid undesirable tissue damage. In human neutrophils, lipopolysaccharide or TNFα-stimulated ERK-activation contributes to the delayed apoptosis (31), while activation of p38 MAPK induced neutrophil apoptosis in *vitro* (32). Accordingly, the enhanced ERK1/2 phosphorylation and decreased p38 activation were detected in the offspring gut from HFD fed dams, indicating that maternal HFD might delay neutrophil apoptosis in the inflamed colonic tissues.

AMP-activated protein kinase (AMPK) is the central regulator of cellular energy balance (22). AMPK mediates the inflammatory responses such as IL-6 expression (33), and reduced AMPK protein level results in impaired epithelial barrier function (34). The reduced AMPK level due to maternal HFD in offspring with DSS-induced colitis suggested that AMPK signaling might be important in the pathophysiological effects of maternal HFD on inflammation and colitis in offspring gut. AMPK inhibits inflammation through inducing the expression or activation of a number of mediators such as SIRT1, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), p53, and Forkhead box O factors (35, 36). AMPK activates SIRT1 deacetylase via increasing cellular NAD+ levels (35) while SIRT1 stimulates LKB1 activity, which subsequently activates AMPK (37). SIRT1 deacetylates the RelA/p65 and inhibits NF-κB signaling (36). Thus, the reduction in AMPK and SIRT1 might contribute to the enhanced activation of NF-κB signaling in HFD offspring gut. In this sense, AICAR-induced AMPK activation down-regulates the innate and adaptive immune responses of TNBS induced colitis (38). AMPK also activates p53, a tumor suppressor that mediates growth arrest or induces apoptosis (39). Mice deficient in p53 developed tumors upon DSS-treatment even without azoxymethane (AOM) injection (40), suggesting a vital protective role of p53 in IBD pathogenesis. Consistent with decreased AMPK activation, p53 protein was decreased in offspring colon of HFD fed dams, which likely contributes to the colitis induction in the maternal HFD offspring.

In conclusion, maternal HFD exposure accelerated offspring body weight gain, but enhanced DSS-induced body weight loss, and colitis symptoms by activating NF-κB signaling and stimulating IL-1β, IL-6, and IL-17 expression, as well as neutrophil induction in colonic tissues. Furthermore, maternal HFD exposure suppressed AMPK activity and down-

regulated SIRT1 and p53 that further aggravated DSS-colitis in the offspring. Collectively, this study suggests that maternal HFD consumption predisposes offspring mice to IBD and related inflammatory gut diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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What is already known about this subject?

- High fat diet (HFD) consumption promotes inflammation
- HFD consumption can enhance susceptibility to IBD
- Maternal HFD is related to the increased risk for IBD in offspring

What does your study add?

- Maternal high fat diet HFD aggravates colitis in the offspring by activating NF-κB signaling
- Maternal HFD enhances colonic inflammation and distortion in the offspring induced by DSS
- Maternal HFD suppresses AMPK activity and SIRT1content in offspring gut

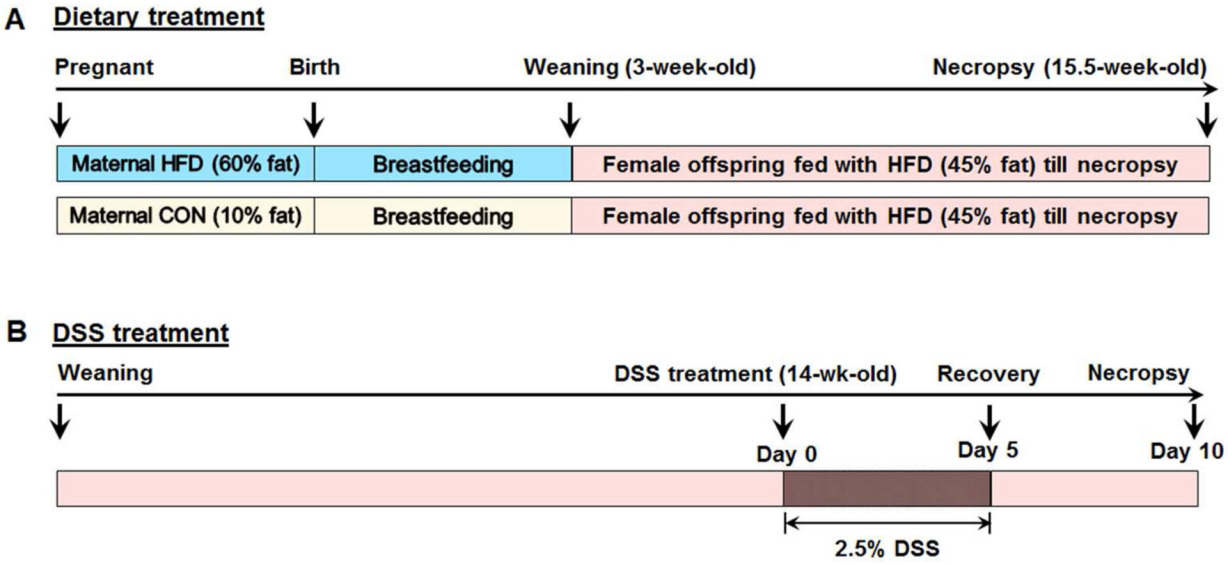

Fig. 1.

Experimental design. A. Maternal and offspring dietary treatment timeframe. B. Offspring mice at age of 14-week-old were subjected to 2.5% DSS water for 5 days followed by a 5 days recovery. Offspring of both maternal HFD and CON groups were fed with a 45% HFD (45% energy from fat) from weaning to necropsy.

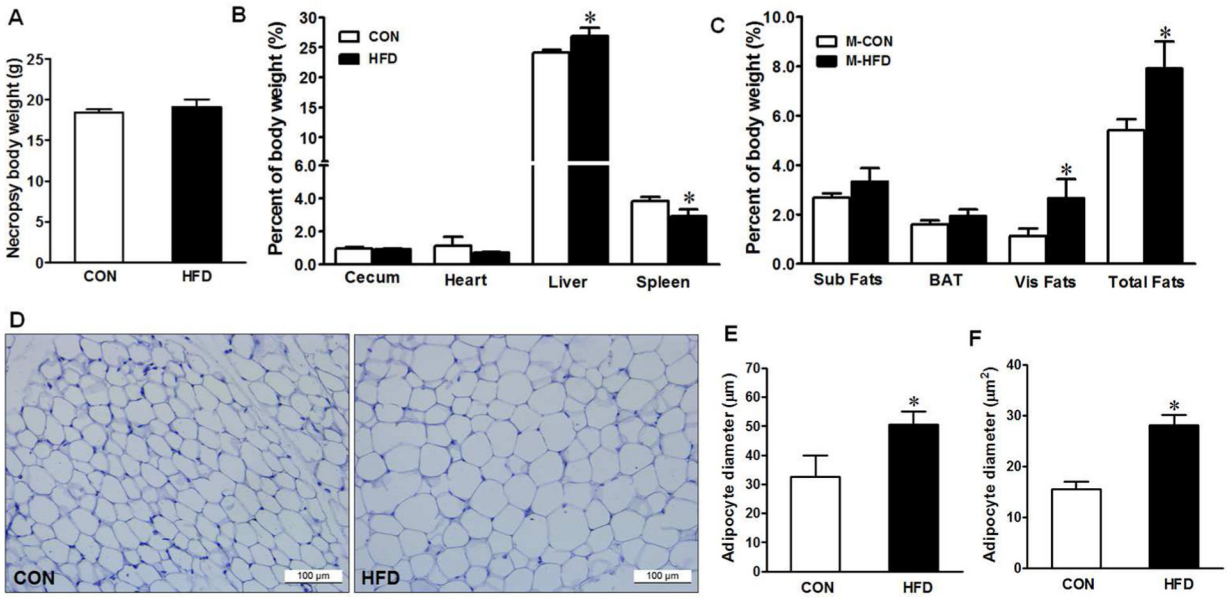

Fig. 2.

Body and organ weight in offspring of CON (□) or HFD (■) fed dams at necropsy. (A) Body weight, (B) Organ weight, (C) Fats weight, (D) Representative images of hematoxylin and eosin (H&E) staining of visceral adipose tissue section, (E) Adipocyte diameter (μm), and (F) Adipocyte area (μm^2). Sub = Subcutaneous fats, BAT = Brown adipose tissue, and Vis = Visceral fats. Means ± SEM, n = 9, *: $P \leq 0.05$.

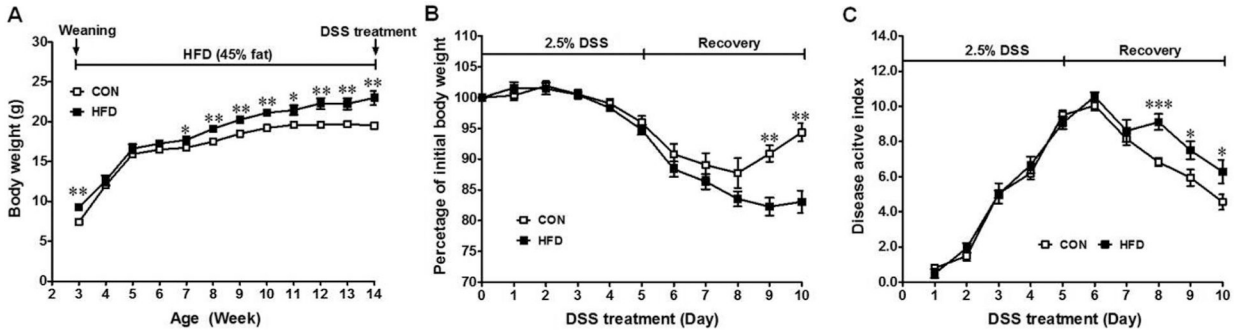

Fig. 3.

Symptoms of DSS-induced colitis in offspring of CON (□) or HFD (■) fed dams. (A) Weekly body weight of offspring after weaning and before DSS treatment, (B) Body weight loss and (C) Disease activity index during DSS-treatment and recovery process, a higher score correlates with severer symptoms. Means ± SEM, n = 9, *: $P \leq 0.05$, **: $P \leq 0.01$, and ***: $P \leq 0.001$.

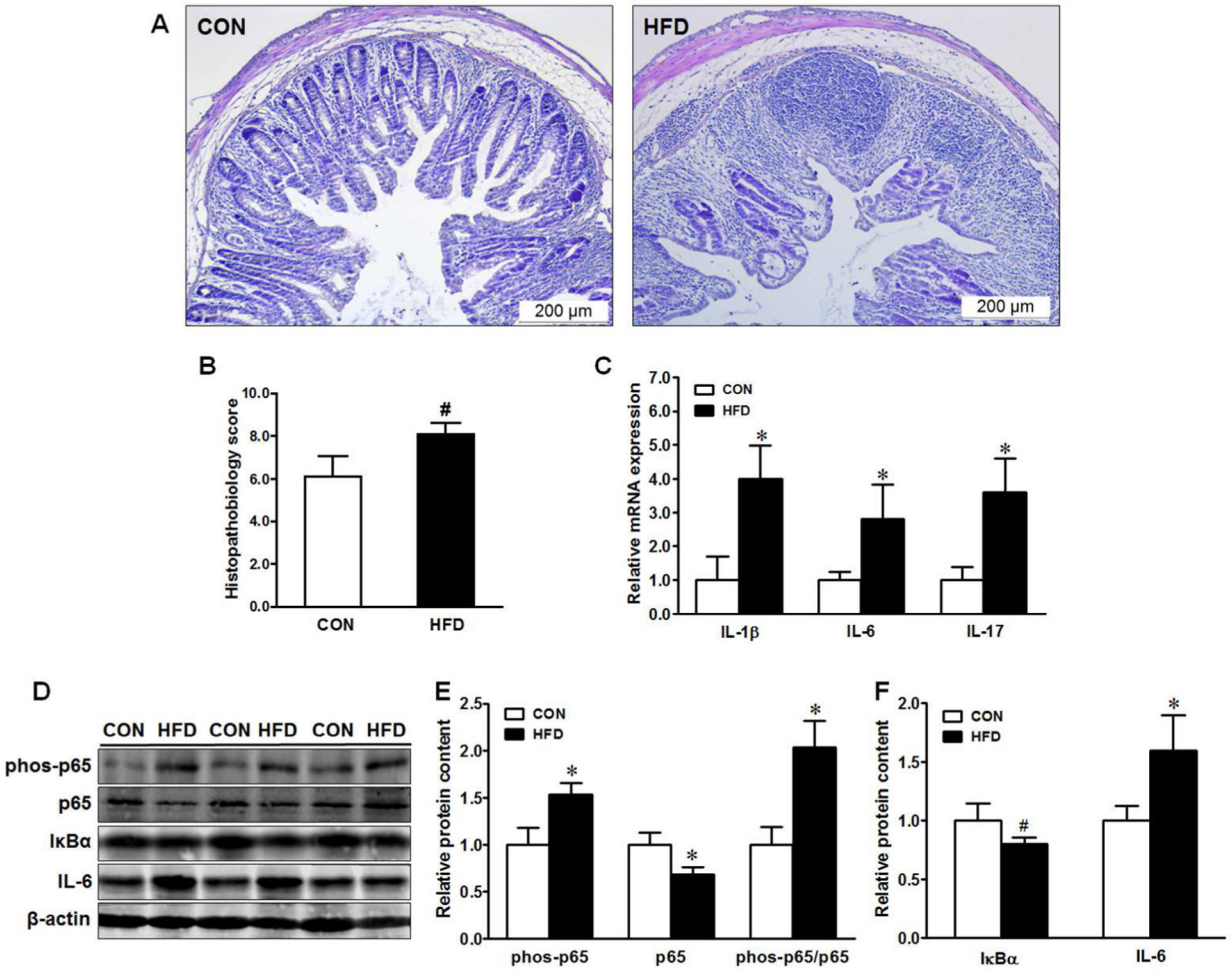

Fig. 4.

Histopathological score and inflammatory mediators in offspring of CON (□) or HFD (■) fed dams. (A) Representative images of H&E staining of distal colonic sections, (B) Histopathological score, (C) mRNA expression of pro-inflammatory cytokines, (D-F) Representative immunoblotting bands and statistical data of p65, IκB-α and IL-6. Means ± SEM, n = 9, *: $P \leq 0.05$, #: $P \leq 0.10$.

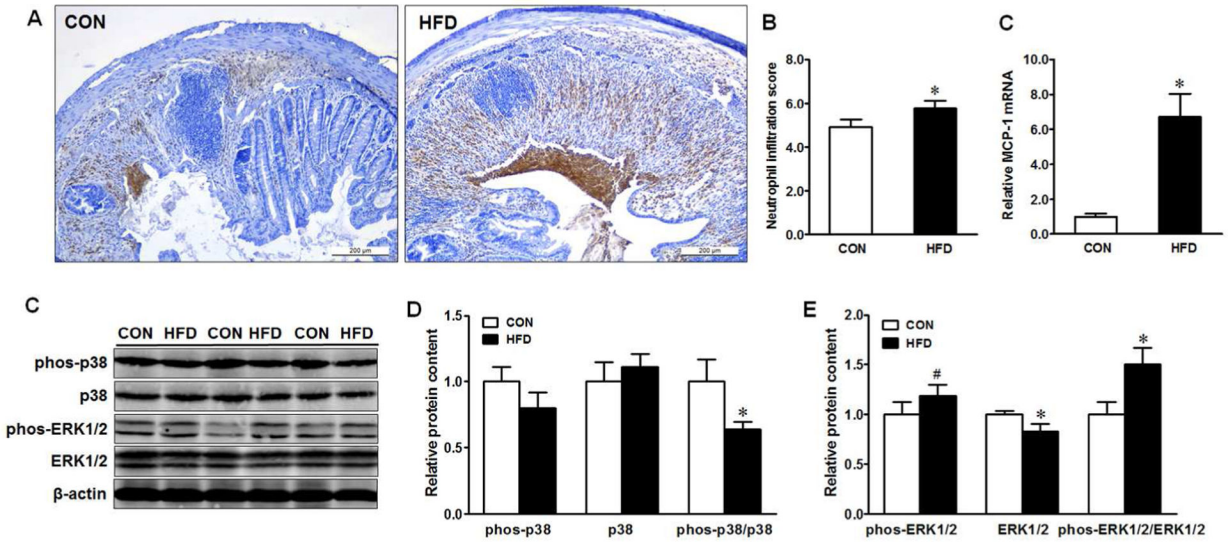

Fig. 5.

Neutrophil immunohistochemical staining in distal colonic tissues of offspring of CON (□) or HFD (■) fed dams. (A) Representative images of neutrophil staining, (B) Neutrophil infiltration score, (C) mRNA expression of MCP-1, (D-F) Representative immunoblotting bands and statistical data of p38 and ERK1/2. Means ± SEM, n = 9, *: $P \leq 0.05$, #: $P \leq 0.10$.

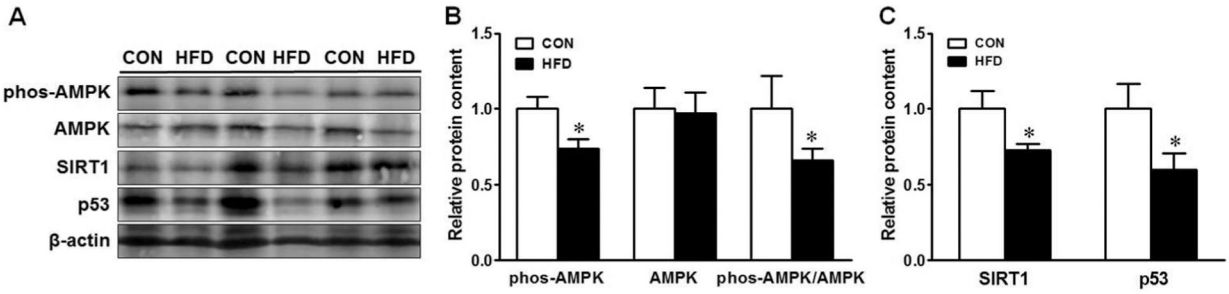

Fig. 6.

AMP-activated protein kinase (AMPK) signaling in the colon of offspring of CON (☐) or HFD (■) fed dams. (A) Representative immunoblotting bands, (B) Relative protein expression of AMPK, (C) Relative protein expression of SIRT1 and p53. Means ± SEM, n = 9, *: $P \leq 0.05$.