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A high-fat diet rescues muscle atrophy by restoring adiponectin and attenuating systemic inflammation in cachectic mice

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ABSTRACT

Cancer cachexia is a multifactorial syndrome characterized by progressive muscle and fat loss, driven by systemic inflammation and metabolic dysfunction. The role of adipose tissue in modulating muscle wasting through endocrine signaling remains underexplored. This study investigates the therapeutic potential of a high-fat diet (HFD) in mitigating muscle atrophy in cancer cachexia through adiponectin signaling. Lewis lung carcinoma (LLC) cells (1.5×10^6 cells per mouse) were subcutaneously implanted in C57BL/6J mice to induce cachexia. Mice were randomized to receive either a standard diet (CD) or an HFD (65% energy from fat) for 21 days post-tumor implantation. Serum and tissue samples were analyzed for inflammatory markers, muscle mass, adiponectin expression, and muscle function using enzyme-linked immunosorbent assay (ELISA), quantitative real-time PCR (qRT-PCR), hematoxylin-eosin (H&E) staining, and functional assays. The HFD did not affect tumor size or energy intake but reduced hepatosplenomegaly (liver: $P = 0.028$ 2, spleen: $P < 0.000$ 1) and circulating inflammatory factor levels (tumor necrosis factor alpha (TNF α): 22.9%, interleukin 6 (IL6): 30.4%, interleukin 1 beta (IL1 β): 33.6%, compared to LLC+CD) in cachectic mice. The HFD attenuated the loss of muscle mass ($P = 0.011$ 5), functional decline, reduction in myofiber cross-sectional area, and the expression of atrophy-related genes. It also mitigated weight loss (inguinal white adipose tissue (iWAT) mass loss: 54% in CD vs. 12% in HFD; epididymal white adipose tissue (eWAT) mass loss: 49% in CD vs. 19% in HFD) and adipocyte atrophy in both iWAT and eWAT, concurrently reducing adipose browning and inflammatory factor expression. Mechanistically, transcriptome analysis of muscle and iWAT implicated adiponectin-related pathways. The HFD enhanced adiponectin expression in iWAT, partially restored circulating adiponectin levels (9.6%, $P = 0.022$ 0, compared to LLC+CD), and upregulated *AdipoR1* expression in muscle. This increased adiponectin expression in adipose tissue appeared to be mediated by peroxisome proliferator-activated receptor gamma (PPAR γ) and CCAAT/enhancer-binding protein alpha (C/EBP α). Consequently, gene expression associated with mitochondrial biogenesis, muscle cell regeneration, and fatty acid utilization was activated in muscle tissue. An HFD mitigates fat loss and muscle atrophy in cancer cachexia. It restores adiponectin secretion in adipose tissue and attenuates systemic inflammation. These findings underscore the therapeutic potential of dietary modulation in cachexia and highlight the fat-to-muscle axis as a promising target for future interventions.

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1. Introduction

Cancer cachexia is a complex metabolic syndrome marked by involuntary loss of skeletal muscle, often with adipose tissue

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decrease^[11]. It differs from simple starvation, with a unique pathophysiology involving reduced food intake and abnormal metabolism. Cachexia contributes substantially to cancer morbidity and mortality, accounting for 20%–30% of cancer-related deaths^[12]. It diminishes quality of life, reduces treatment tolerance, increases toxicity susceptibility, and worsens prognosis. Even modest weight loss negatively impacts functional status^[13].

Adipose tissue is a metabolically dynamic endocrine organ, primarily composed of adipocytes. It's the body's main lipid storage reservoir and regulates energy and glucose homeostasis^[4]. Adipose tissue secretes bioactive factors, including adipokines like leptin, adiponectin, and inflammatory factors, which modulate food intake, insulin sensitivity, inflammation, and immune responses. This endocrine function is critical for metabolic equilibrium^[5–7]. Besides, adipose tissue is heterogeneous, including white adipose tissue (WAT), brown adipose tissue (BAT), and beige adipocytes, suggesting cancer cachexia may differentially affect these depots.

Cancer cachexia induces adipose tissue dysfunction, increasing lipolysis and altering adipokine secretion, contributing to fat mass loss. WAT shows shrunken adipocytes and increased fibrosis. Increased fat breakdown releases free fatty acids, which can promote insulin resistance and inflammation^[8]. While there is no well-established link directly connecting adipose tissue dysfunction to muscle wasting, the chronic systemic inflammation of cachexia, driven by dysfunctional adipose tissue and the tumor, may play a role. Pro-inflammatory cytokines like tumor necrosis factor alpha (TNF α), interleukin 6 (IL6), and interleukin 1 beta (IL1 β) act on skeletal muscle, inhibiting protein synthesis and accelerating protein degradation *via* catabolic pathways like the ubiquitin-proteasome system and autophagy^[9]. Adipose tissue and muscle interplay in cancer cachexia appears to be a self-perpetuating cycle, where tumor-induced factors initiate adipose tissue dysfunction, which in turn releases mediators that exacerbate muscle wasting, contributing to the progressive and debilitating nature of the syndrome^[10].

High-fat diets (HFDs) and ketogenic diets (KDs) are potential dietary interventions in cancer therapy, characterized by their low carbohydrate and moderate protein content, with a high proportion of calories derived from fat. These diets aim to reduce glucose availability, potentially inhibiting tumor growth, as many cancer cells rely on glucose for energy (Warburg effect)^[11]. KDs induce ketosis, producing ketone bodies from fat metabolism, which some cancer cells may not utilize efficiently^[12]. Preclinical studies show KDs can slow tumor growth, improve survival, and enhance treatment efficacy^[11]. Some clinical trials suggest benefits like improved physical function, reduced fat mass, and preserved lean muscle mass. Given cancer cachexia's metabolic alterations, an HFD intervention, distinct from a strictly ketogenic regimen, warrants investigation for its potential to mitigate muscle and fat atrophy. HFDs typically allow more carbohydrates than KDs, which may be more palatable for cancer patients with anorexia^[13]. Fat metabolism, even non-ketogenic, can provide an alternative energy source, potentially sparing glucose and reducing muscle protein breakdown^[12]. Exploring HFD interventions is critical to improve outcomes for cancer patients with this debilitating syndrome.

The primary objectives of this study are to investigate the effects of an HFD intervention on muscle and fat atrophy in the Lewis lung carcinoma (LLC) murine model of cancer cachexia, and to elucidate

the underlying mechanisms by which an HFD might influence muscle and fat mass in the context of cancer cachexia. We discovered that an HFD, with 65% of its energy derived from fat, not only alleviates fat loss in LLC cachexia mice but also mitigates muscle atrophy and the rise in systemic inflammation. Mechanistically, we speculated that the HFD may restore adiponectin expression in subcutaneous adipose tissue through peroxisome proliferator-activated receptor gamma (PPAR γ) and CCAAT/enhancer-binding protein alpha (C/EBP α), subsequently acting on muscles to restore muscle cell regeneration, mitochondrial turnover, and enhance fatty acid utilization. This provides new theoretical foundations for interventions in cachexia based on adipose tissue.

2. Materials and methods

2.1 LLC culture and conditioned medium preparation

LLC cells were cultured in high glucose DMEM (Gibco, USA) supplemented with 10% fetal bovine serum (FBS, Corning, USA), and 1% penicillin/streptomycin (Corning, USA). To prepare LLC-conditioned-medium, cells were seeded to achieve a 1:3 confluence. The next day, the culture medium was switched to DMEM (containing 1% penicillin/streptomycin, without FBS) and was collected 24 h later. The medium was centrifuged at $1\,000 \times g$ for 5 min. The supernatant, collected as LLC-conditioned medium, was then diluted at a ratio of 3:1 with fresh medium for use in stimulating lipolysis^[14]. High-glucose DMEM with no cells kept for 24 h in the incubator was used as control medium^[14–16].

2.2 Mouse experiments

Mice were kept in specific pathogen-free (SPF) conditions. They were subjected to a 12-h light-dark cycle (7 A.M. to 7 P.M.) at a temperature of 23 °C and provided with a standard AIN-93G diet. All animal protocols received approval from the Institutional Animal Care and Use Committee (IACUC) of Tsinghua University (China).

LLC cells are known to efficiently form tumors and lead to cachexia; therefore, LLC-tumor-bearing mice were widely used as a cancer cachexia murine model. The 8- to 10-week-old wild-type male mice with C57BL/6J background were injected with 1.5×10^6 LLC cells or 100 μ L PBS into the right flank, and then sacrificed on day 21 after tumor injection. Serum was collected *via* cardiac puncture before mice were sacrificed. Tumor weight, body weight, carcass weight without tumor, and weight of different tissues were measured. Tissues for H&E staining were fixed in 4% paraformaldehyde and others were frozen in the refrigerator at -80 °C. Non-tumor side adipose and muscle tissues were analyzed.

2.3 Diet design

To investigate the effects of an HFD in cancer cachexia, a diet was designed with fat as the primary energy source based on the standard AIN-93G mouse chow diet (CD) by adjusting the fat and carbohydrate content (Table 1). This diet uses coconut oil as the sole fat source, providing 65% of the total energy, while the carbohydrate content is reduced to 15% of the total energy. The protein content remains at 20% of the total energy, and the mineral and vitamin levels are kept constant.

Table 1

Nutritional composition and energy profile of an HFD formulation compared to AIN-93G standard diet.

Component	AIN-93G		HFD	
	Weight (g)	Energy (kcal)	Weight (g)	Energy (kcal)
Casein	200.0	800.0	200.0	800.0
L-Cystine	3.0	12.0	3.0	12.0
Corn starch	397.0	1 588.0	136.85	547.4
Sucrose	100.0	400.0	0	0
Cellulose	50.0	0	50.0	0
Maltodextrin	132.0	528.0	0	0
Hydrogenated coconut oil	0	0	288.74	2 598.66
Soybean oil	70.0	630.0	0	0
Mineral mix (S10022G)	35.0	0	35.0	0
Vitamin mix (V10037)	10.0	40.0	10.0	40.0
Choline bitartrate	2.5	0	2.5	0
TBHQ	0.014	0	0.014	0
Total	999.514	3 998.0	726.104	3 998.06

2.4 Analysis of gene expression

RNA was extracted from frozen WAT and muscle tissues and cultured cells using Eastep Super Total RNA Extraction Kit (LS1040, Promega, USA) and reverse transcribed using Prime ScriptTM RT Master Mix (RR036Q, Takara, Japan). gDNase was used to efficiently remove genomic DNA interference in total RNA. The resultant cDNA was analyzed by quantitative reverse transcription polymerase chain reaction (qRT-PCR). Primers were purchased from Invitrogen. A total of 20 ng cDNA and 100 nmol of each primer were mixed with SYBR Green QPCR Master Mix (11171ES03, Yeasen, China). Gene quantification was performed in triplicate on the CFX96TM Real-Time System (Bio-Rad, USA). Relative mRNA levels were calculated using the $2^{-\Delta\Delta Ct}$ method and normalized to β -actin. Primers used are shown in Table 2.

Table 2

Primer sequences used for qRT-PCR.

Target gene	Forward primer (5'→3')	Reverse primer (5'→3')
<i>Fbxo32</i>	CTTCTCGACTGCCATCCTGGAT	TCTTTTGGGCGATGCCACTCAG
<i>Mstn</i>	AACCTTCCCAGGACCAGGAGAA	GGCTTCAAAATCGACCGTGAGG
<i>Trim63</i>	TACCAAGCCTGTGGTTCATCCTG	ACGGAACGACCTCCAGACATG
<i>UCP1</i>	GCTTTGCCTCACTCAGGATTGG	CCAATGAACACTGCCACACCTC
<i>PGC1α</i>	GAATCAAGCCACTACAGACACCG	CATCCCTCTTGAGCCTTTCGTG
<i>Adiponectin</i>	AGATGGCACTCCTGGAGAGAAG	ACATAAGCGGCTTCTCCAGGCT
<i>TNFα</i>	TCTTCTCATTCCTGCTTGTGG	GGTCTGGGCCATAGAACTGA
<i>IL6</i>	TACCACTTCAAGTCGGAGGC	CTGCAAGTGCATCATCGTTGTTT
<i>IL1β</i>	TGGACCTTCCAGGATGAGGACA	GTTTCATCTCGGAGCCTGTAGTG
<i>AdipoR1</i>	TCTGCCTCAGTTTCTCCTGGCT	GTAATAGAGCCAGGGAACGAAGC
<i>AdipoR2</i>	TCTTCCACACGGTGTACTGCCA	GGTAGATGAAGCAAGGTTGTGGG
<i>PPARα</i>	ACCACTACGGAGTTCACGCATG	GAATCTTGCACTCCGATCACAC
<i>PPARδ</i>	GGACCAGAACACACGCTTCCCTT	CCGACATTCCATGTTGAGGCTG
<i>PPARγ</i>	GTAAGTCTCGGTTTCAGAAAGTGCC	ATCTCCGCCAACAGCTTCTCCT
<i>NRF1</i>	AGAAACGGAAACGGCCTCAT	CATCCAACGTGGCTCTGAGT
<i>TFAM</i>	TCCACAGAACAGCTACCCAA	CCACAGGGCTGCAATTTTCC
<i>MyoD1</i>	GCACTACAGTGGCGACTCAGAT	TAGTAGGCGGTGTCTAGCCAT
<i>Myog</i>	CCATCCAGTACATTGAGCGCCT	CTGTGGGAGTTCAGTTCAGTG
<i>C/EBPα</i>	GCAAAGCCAAGAAGTCGGTGGA	CCTTCTGTTGGCTCTCCACGTT
<i>β-Actin</i>	CATTGCTGACAGGATGCAGAAGG	TGCTGGAAGGTGGACAGTGAGG

2.5 Hematoxylin-eosin (H&E) staining

For H&E staining, all tissues were fixed in 4% paraformaldehyde (Servicebio, China) at 4 °C for 24 h. Samples are embedded in paraffin and then dehydrated. 4-μm sections were stained following the manufacturer's instructions (Servicebio). Images were taken using a bright-field microscope (Leica, Germany). For each section, 3 fields were randomly selected and quantified. Then cross-sectional areas of myofibers and lipid droplet areas were measured using ImageJ (Fiji). Briefly, using the "Polygon selections" tool to select and then measure the cross-sectional area of myofibers. Lipid droplets were selected by "Threshold" command and then measured.

2.6 Rotarod testing and grip strength measurement

On the same day prior to euthanizing the mice, the rotarod testing and grip strength of forelimbs were evaluated. The evaluation criterion of rotarod test was the time that mouse spends on the rotating rod before falling (Rotarod test, Unibiolab, China). The residence times at 12 r/min were recorded. Each mouse was allowed to grab a rod connected to the load cell, and at the same time pulled it horizontally away from it with its tail (Grip Strength Meter, Unibiolab, China). A 30-s rest was given between each test. The grip strength of each mouse was calculated by averaging the results from 5 repetitions.

2.7 Enzyme-linked immunosorbent assay (ELISA)

Mouse TNFα, IL6, IL1β and adiponectin concentrations were analyzed by Mouse TNFα ELISA kit (CSB-E04741m, CUSABIO, Wuhan, China), Mouse IL6 ELISA kit (CSB-E04639m, CUSABIO, Wuhan, China), Mouse IL1β ELISA kit (CSB-E08054m, CUSABIO, Wuhan, China) and Mouse adiponectin ELISA kit (CSB-E07272m, CUSABIO, China) according to the manufacturer's instructions, individually. A standard curve was generated by standard protein provided in kit.

2.8 Statistical analysis

All the results were expressed as means $\pm$ SEM. Two-group analysis was performed using Two-tailed Student's *t*-test. One-way ANOVA followed by Tukey's *post hoc* test was used for comparison of more than 2 groups. Two-way ANOVA was used for multiple comparisons. Data was analyzed in GraphPad Prism 9.0 software. $P < 0.05$ was considered statistically significant.

3. Results

3.1 HFD reduces systemic inflammation in cachectic mice

An LLC-induced cancer cachexia model was first established, and dietary interventions with HFD or CD were implemented as outlined in Fig. 1A. The HFD did not affect the weight of the tumor, ensuring the consistency of the model by not altering the source of cachexia (Fig. 1B). Tumor implantation induced a significant decrease in body weight in LLC+CD mice, and while the HFD did not lead to a statistically significant recovery in carcass weight (Fig. 1C), it did preserve muscle and fat mass as detailed below.

Additionally, there was no significant difference in average daily energy intake among the groups, ruling out malnutrition due to reduced energy intake as a confounding factor (Fig. 1D). Notably, compared to healthy PBS+CD or PBS+HFD mice, LLC+CD mice exhibited a significant increase in liver and spleen weight, indicative of hepatosplenomegaly. Intervention with an HFD significantly mitigated this hepatosplenomegaly (Fig. 1E), which is an important clinical marker in various cancers, involving mechanisms such as inflammation, congestion, infiltrative lesions, or tumor metastasis^[17]. Moreover, hepatosplenomegaly in cancer is often associated with advanced stages and lower survival rates^[18-19].

To further confirm whether hepatosplenomegaly is related to systemic inflammation, we quantitatively measured common cachexia-related inflammatory factors in the mouse circulatory system. Compared to healthy mice, the levels of inflammatory cytokines TNF α , IL6, and IL1 β in the serum of LLC+CD mice were significantly elevated (Fig. 1F). The intervention with an HFD significantly reduced the levels of these inflammatory cytokines in the serum of LLC+HFD mice, indicating that an HFD can reduce systemic inflammation in cachectic mice (Fig. 1F).

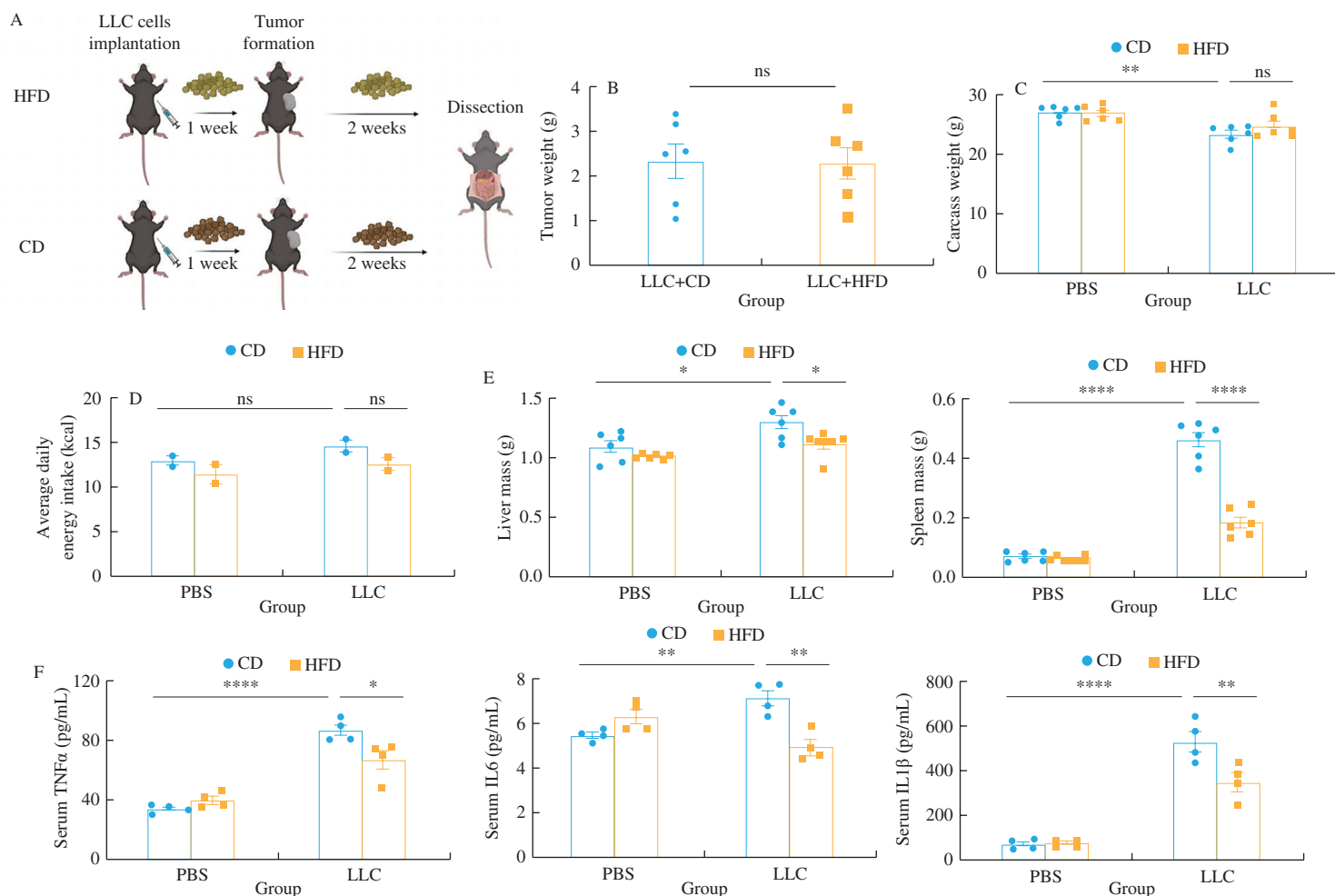


Fig. 1 Basic phenotypes of LLC-bearing mice intervened with CD or HFD. (A) Diagram of HFD intervention. (B-D) Comparison of tumor weight ($n = 6$), carcass weight (without tumor) ($n = 6$), and energy intake. Energy intake was measured per cage, with mice from each group co-housed in 2 cages ($n = 2$ cages per group). (E) Liver and spleen mass were compared ($n = 6$). (F) Serum TNF α , IL6 and IL1 β were determined by ELISA ($n = 4$). * $P < 0.05$, ** $P < 0.01$, **** $P < 0.0001$, ns, $P > 0.05$, the same below.

3.2 HFD improves muscle atrophy in cachectic mice

Muscle atrophy is one of the key phenotypes of cancer cachexia, affecting patients' basic physical abilities and quality of life. Both groups of mice exhibited a certain degree of weight loss in the gastrocnemius (GC) muscle, but not significant (Fig. S1). In contrast, the tibialis anterior (TA) muscle weight in the LLC+CD group significantly decreased, while the HFD significantly mitigated the atrophy of the TA muscle (Fig. 2A). Notably, the atrophy of the TA muscle in the LLC cachexia mouse model was more pronounced than that of the GC muscle, consistent with the findings of others^[20]. Therefore, in subsequent experiments, we focused on the structural and molecular changes in the TA muscle.

Consistent with the changes in muscle weight, muscle strength was also affected by cachexia and diet. Compared to the PBS+CD group of healthy mice, the grip strength and the duration in rotarod test in the LLC+CD group significantly decreased, while the intervention with an HFD significantly improved the forelimb grip strength and the duration, demonstrating the beneficial effects of the HFD on muscle strength in cachectic mice (Figs. 2B-C).

To observe the microscopic tissue changes in the muscles, we performed H&E staining. Muscle in the LLC+CD group showed a significant reduction in the cross-sectional area of muscle fibers and tissue damage (Fig. 2D). The distribution of muscle fiber cross-sectional areas in the LLC+CD group shifted to the left, with most muscle fibers having a cross-sectional area less than 1 000 μm^2 . In contrast, the cross-sectional area of muscle fibers in the LLC+HFD group was significantly improved and was similar to that of the PBS+CD group of healthy mice (Fig. 2D).

Muscle fiber atrophy in cachexia is primarily caused by enhanced protein degradation and reduced muscle regeneration. We measured common markers of muscle atrophy in cachexia. On the one hand, the expression of *Trim63* and *Fbxo32* genes (encoding E3 ubiquitin ligase MuRF1 and a subunit of the E3 ubiquitin protein ligase complex, Atrogin-1, respectively) in the muscles of LLC+CD mice were significantly increased (Fig. 2E). On the other hand, the expression of the *Mstn* gene, which inhibits myocyte growth and differentiation, was also significantly increased in the muscles of LLC+CD mice (Fig. 2E). In the LLC+HFD group, the expression of these genes in the muscles

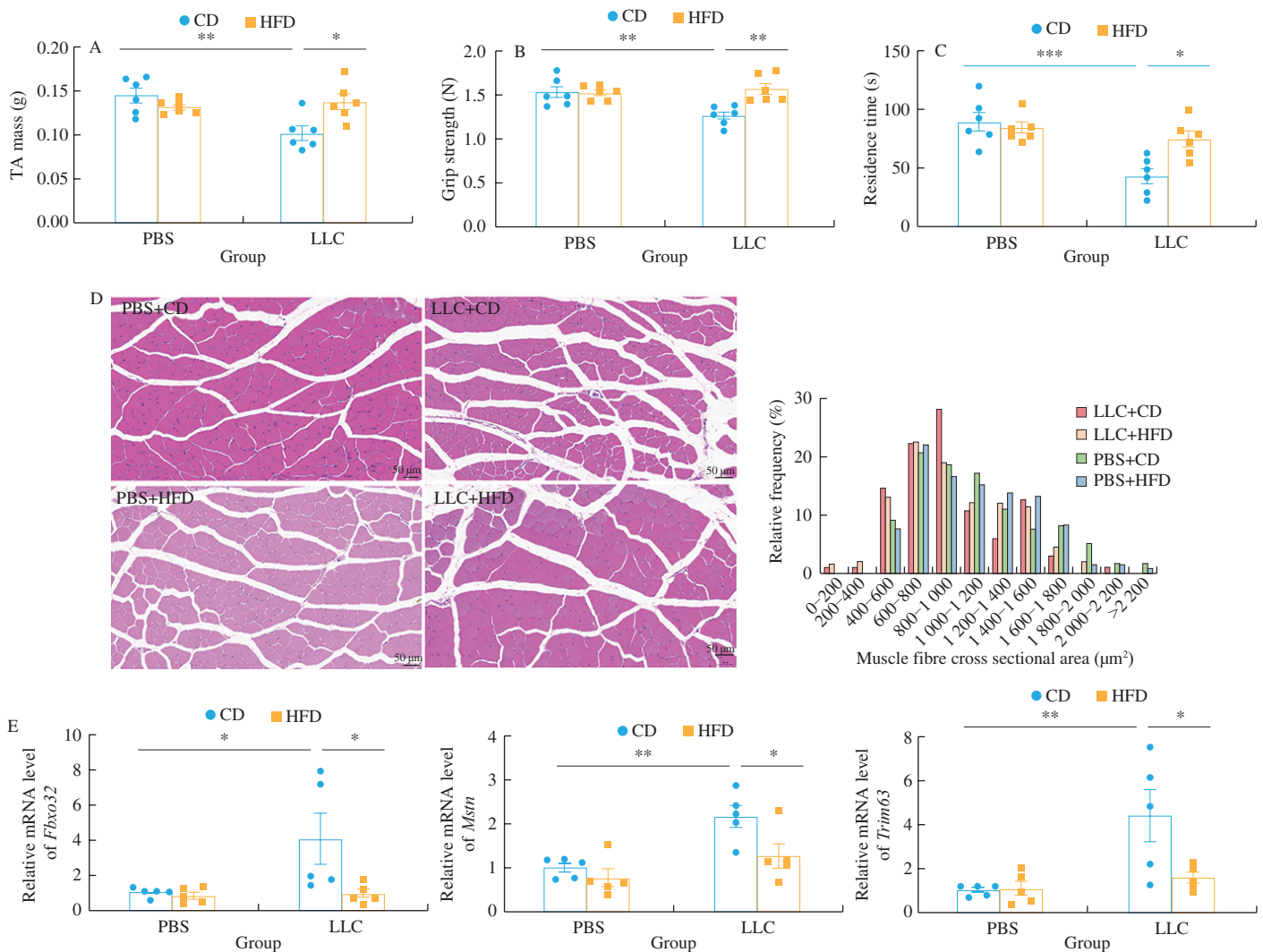


Fig. 2 HFD intervention ameliorates muscle atrophy in LLC-bearing mice. (A-C) Muscle mass, grip strength and residence time in rotarod test were measured ($n = 6$). (D) Representative H&E-stained images of TA muscle. Muscle fiber cross-sectional area was quantified. (E) The mRNA levels of *Fbxo32*, *Mstn* and *Trim63* in TA muscle were determined by qRT-PCR ($n = 5$). (F) The mRNA levels of *TNFA*, *IL6* and *IL1 β* in TA muscle were determined by qRT-PCR ($n = 5$). *** $P < 0.001$, the same below.

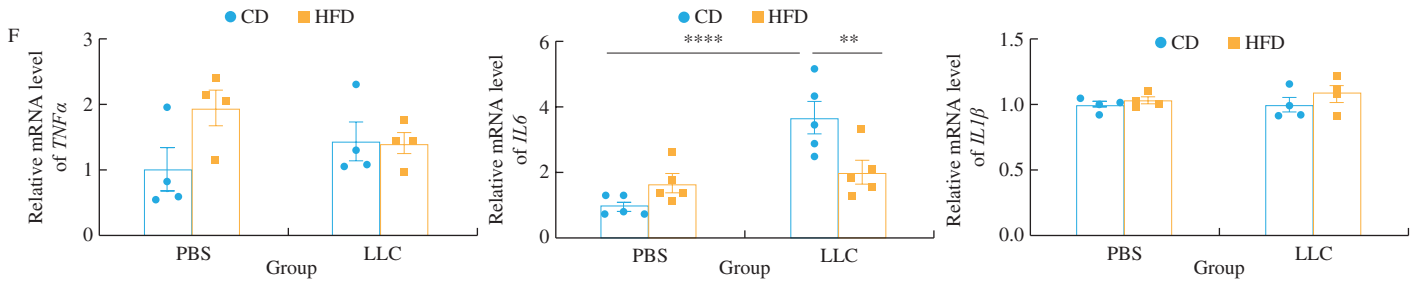


Fig. 2 (Continued)

was significantly lower compared to the LLC+CD group (Fig. 2E), indicating that the HFD may alleviate muscle atrophy in cachexia by inhibiting protein degradation and promoting muscle regeneration, thus preserving muscle strength and normal function. Besides, only the expression of *IL6* was significantly elevated in the muscles of LLC+CD group mice and was suppressed by the HFD, while *TNFα* and *IL1β* showed no significant changes (Fig. 2F). This suggests that in cancer cachexia, muscle may not be the primary source of inflammation but rather a victim of inflammatory factors.

3.3 HFD improves fat loss in cachectic mice

In cachexia, fat loss not only signifies energy depletion but also indicates metabolic and signaling disorders^[21]. Accordingly, on the one hand, the depletion of carbohydrates and fats forces the body to break down proteins for energy, affecting normal physiological functions. On the other hand, the disruption of adipose tissue leads to metabolic disorders and systemic effects through the secretion of hormones by adipose tissue.

The weights of 2 typical WATs, inguinal white adipose tissue (iWAT) and epididymal white adipose tissue (eWAT), in the LLC+CD group of mice significantly decreased, while the weights of these two adipose tissues in the LLC+HFD group were significantly improved (Fig. 3A). Notably, the 2 groups of mice without LLC tumor implantation, i.e., the PBS+CD and PBS+HFD groups, did not show a significant increase in the weight of the 2 adipose tissues, suggesting that short-term HFD does not mitigate fat loss in cachexia by increasing fat intake and synthesis but rather by slowing down fat degradation (Fig. 3A).

Furthermore, we performed sectioning and H&E staining of iWAT and eWAT. In the LLC+CD group, both subcutaneous and visceral adipose tissues exhibited structural damage and significant lipodystrophy (Figs. 3B and S2). The intervention with an HFD significantly rescued lipodystrophy and structural damage (Figs. 3B

and S2). Quantitative analysis of lipid droplet area showed that in the 2 adipose tissues of the LLC+CD group, the distribution of lipid droplet area was significantly shifted to the left, while the distribution in the LLC+HFD group was similar to that of healthy mice (Figs. 3C-D).

Subcutaneous adipose tissue and visceral adipose tissue differ significantly in their metabolic and endocrine patterns. Current research indicates that the main secretory functions of adipose tissue are carried out by subcutaneous adipose tissue, and relatively, subcutaneous adipose tissue, rather than visceral adipose tissue, plays a role in maintaining metabolic balance^[22]. Therefore, we focused on the molecular changes in iWAT. Browning of WAT is a phenomenon where WAT exhibits a BAT-like appearance due to increased mitochondria. The increase in mitochondria enhances the adipose tissue's capacity to utilize fat for energy. Browning of adipose tissue is accompanied by upregulation of uncoupling protein 1 (UCP1). UCP1 mediates uncoupling in mitochondria, directly converting the energy produced from the breakdown of carbohydrates or fats into heat rather than supporting physiological functions, thereby exacerbating energy depletion in cachexia. iWAT and eWAT in the LLC+CD group of mice exhibited significant browning, and the expression of *UCP1* in iWAT tissue was significantly increased (Fig. 3E). The intervention with an HFD inhibited browning and the high expression of *UCP1*, reducing energy expenditure in adipose tissue in cachexia (Fig. 3E).

The expression of inflammatory factors *TNFα*, *IL6*, and *IL1β* were also significantly increased in the iWAT of LLC+CD mice. The HFD suppressed the expression of these inflammatory factors to normal levels (Fig. 3F), which partly explains why the levels of serum inflammatory factors in LLC+HFD group mice were lower than those in LLC+CD group (Fig. 1F). While the tumor is a major source of serum inflammatory factors, metabolically disordered adipose tissue may also be an important contributor, further highlighting the significant role of adipose tissue in the development and progression of cancer cachexia.

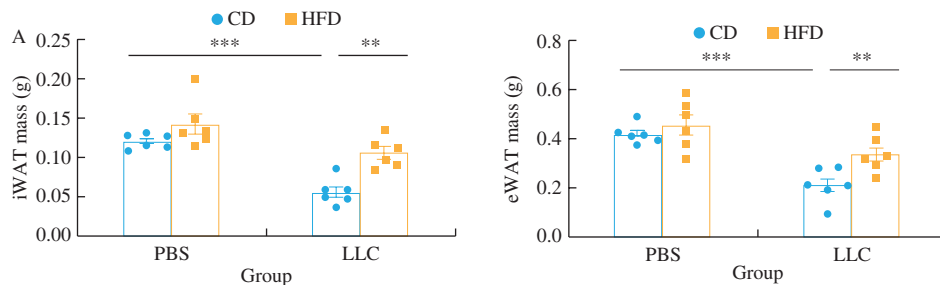


Fig. 3 HFD intervention ameliorates adipose loss in LLC-bearing mice. (A) iWAT and eWAT mass were measured ($n = 6$). (B) Representative H&E-stained images of iWAT. (C-D) Adipocytes size distribution in iWAT and eWAT were quantified. (E) The mRNA levels of *UCP1* in iWAT were determined by qRT-PCR ($n = 5$). (F) The mRNA levels of *TNFα*, *IL6* and *IL1β* in iWAT were determined by qRT-PCR ($n = 5$).

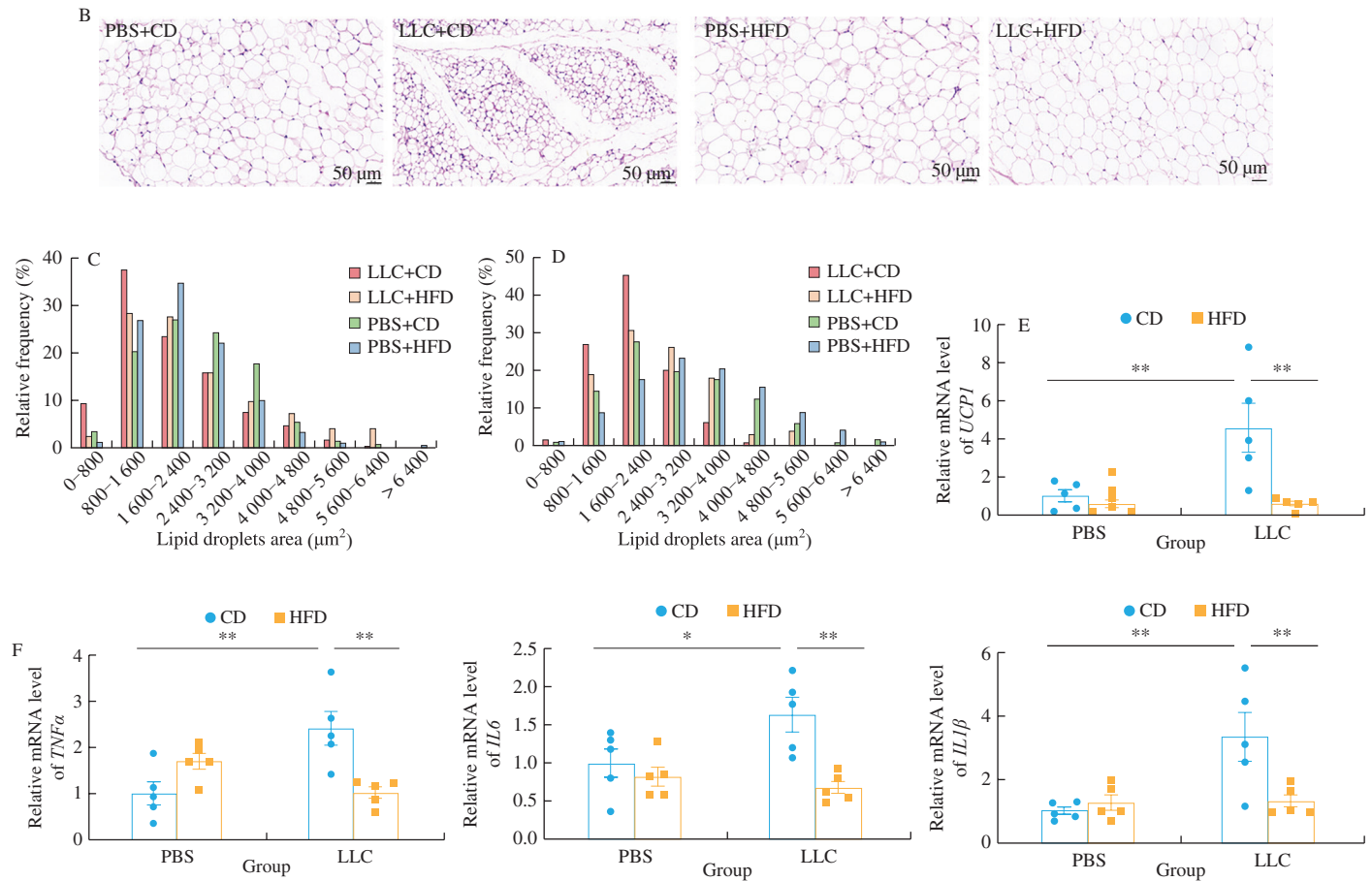


Fig. 3 (Continued)

3.4 HFD restores adiponectin secretion in adipose tissue

Intervention with an HFD altered gene expression in the muscles of cachectic mice. The differentially expressed genes between LLC+HFD and LLC+CD groups were enriched in AMPK signaling pathway, Insulin signaling pathway, and adipocytokine signaling pathway in Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis (Fig. 4A), leading us to hypothesize that the HFD affects muscle gene expression by influencing adiponectin levels. Notably, consistent with the differential gene expression in muscle tissue, the adipocytokine signaling pathway was also enriched in iWAT (Fig. 4A).

Adiponectin is primarily secreted by WAT, with subcutaneous adipose tissue contributing more. After secretion from adipose tissue, adiponectin circulates through the bloodstream to various tissues and organs, with muscle and liver being the 2 main target organs. There are 2 types of adiponectin receptors, with *AdipoR1* mainly expressed in muscle and *AdipoR2* mainly expressed in the liver.

We further investigated the generation, circulation, and function of adiponectin. We found a significantly reduced serum adiponectin level in LLC+CD cachectic mice, while the HFD intervention partially restored serum adiponectin levels (Fig. 4C). Correspondingly, in iWAT tissue, LLC tumor significantly reduced the expression of adiponectin, while the HFD intervention greatly increased the mRNA expression level of adiponectin (Fig. 4B). Finally, in the TA muscle, the HFD also significantly increased the mRNA expression of *AdipoR1* but not *AdipoR2*, ensuring that adiponectin can exert its effects in muscle

tissue (Fig. 4D). Above results indicate that an HFD indeed enhances the expression and secretion of adiponectin in adipose tissue, which then circulates to muscle tissue to exert its effects.

Existing literature indicates that the transcriptional regulation of the adiponectin gene relies on the transcription complex formed by the nuclear receptor *PPAR γ* and the transcription factor *C/EBP α* ^[23]. Further validation revealed that the HFD significantly activated the expression of *PPAR γ* and *C/EBP α* (Fig. 4E), suggesting that the HFD may upregulate the *PPAR γ -C/EBP α* signaling axis to enhance the transcriptional activity of the adiponectin gene, thereby reestablishing the metabolic dialogue mechanism between adipose and muscle tissues.

Besides, in LLC+CD cachectic mice, the gene expression patterns in cancer-related pathways, inflammatory response and cytokine production, lipolysis, and adipokine secretion pathways were significantly different compared to the PBS+CD healthy mice. In contrast, gene expression patterns in LLC+HFD group were similar to the PBS+CD group (Figs. S3 and S4). This suggests that HFD intervention enhances the resistance of adipose tissue to cachexia, enabling it to maintain normal energy storage and secretion functions.

3.5 Elevated adiponectin improves the metabolism and regeneration of muscle

It has been reported that adiponectin binds to *AdipoR1* on the cell membrane in muscle. On one hand, this interaction can activate the AMPK signaling pathway through adaptor protein, phosphotyrosine

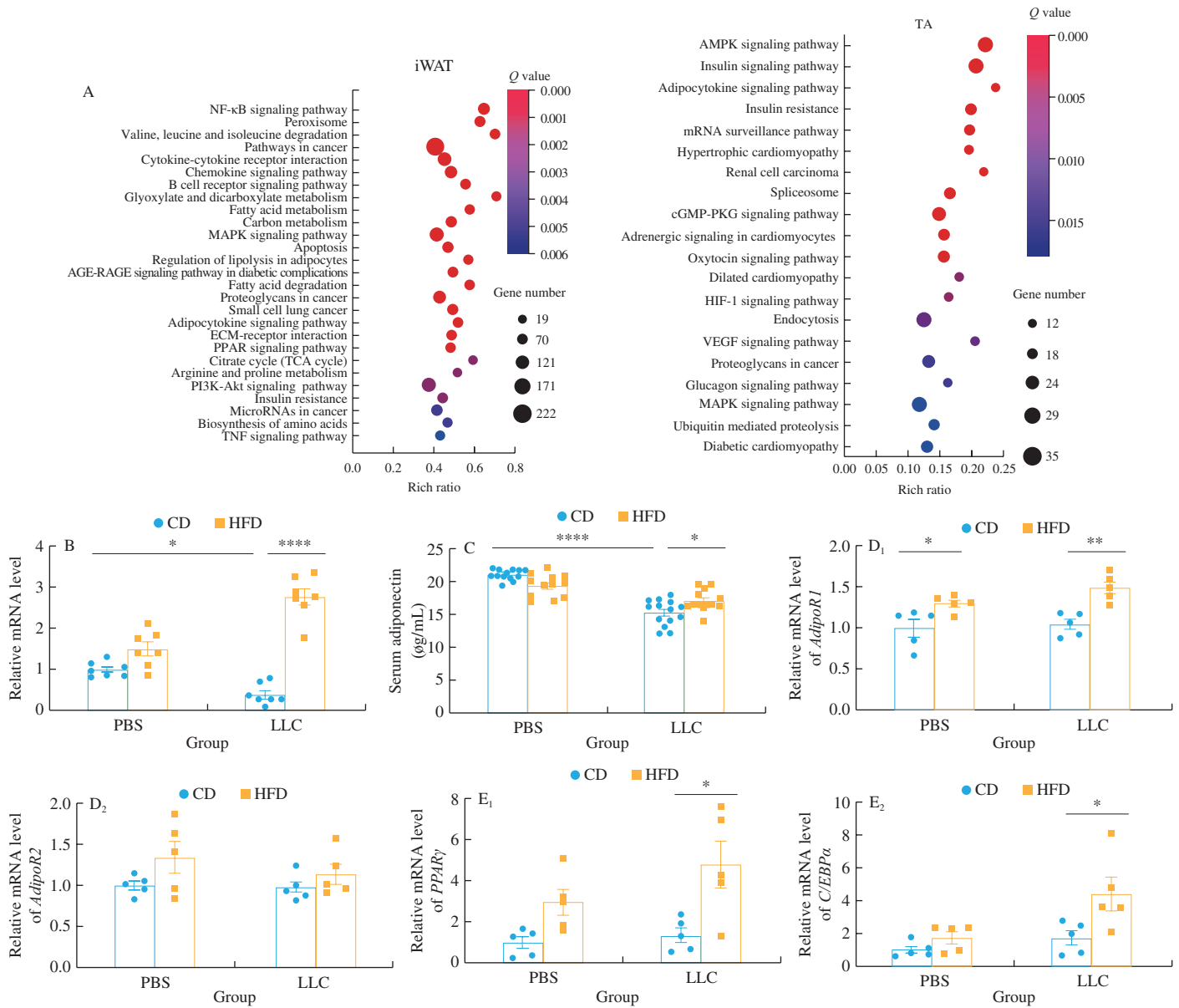


Fig. 4 Effect of an HFD on the adiponectin-PPAR γ axis in adipose tissue and muscle of LLC-bearing mice. (A) KEGG pathway enrichment map of iWAT and TA muscle between LLC+CD and LLC+HFD group. (B) The mRNA levels of adiponectin in iWAT were determined by qRT-PCR ($n = 7$). (C) Serum adiponectin were determined by ELISA ($n = 12-14$). (D) The mRNA levels of *AdipoR1* and *AdipoR2* in TA muscle were determined by qRT-PCR ($n = 5$). (E) The mRNA levels of *PPAR γ* and *C/EBP α* in iWAT were determined by qRT-PCR ($n = 5$).

interacting with PH domain and leucine zipper 1 (APPL1) and liver kinase B1 (LKB1), subsequently activating PGC1 α and downstream PPAR α , thereby enhancing mitochondrial regeneration and fatty acid oxidation capacity. On the other hand, the activation of AdipoR1 can induce calcium ion influx, activate calcium/calmodulin-dependent protein kinase kinase beta (CAMKK β), further activate AMPK, and promote sirtuin 1 (SIRT1) expression. The activation of SIRT1 may inhibit inflammation by suppressing the NF κ B pathway. Finally, the activation of AdipoR1/APPL1 or AMPK can act on the insulin receptor and glucose transporter 4 (GLUT4), improving insulin sensitivity and glucose uptake^[24].

The PPAR family, primarily composed of PPAR $\alpha/\delta/\gamma$, collectively regulates the balance between fatty acid oxidation and storage, and activates the transformation of muscle fibers into oxidative type IIa fibers, increases muscle fiber cross-sectional area, and enhances exercise endurance^[25-26]. Although cachexia did not directly affect PPAR subtypes,

the HFD significantly activated their expression (Fig. 5A), which may benefit muscle energy supply and functional maintenance.

Cachexia reduced the expression of *PGC1 α* and its downstream *NRF1*, while the HFD restored their expression to normal levels (Fig. 5B), indicating that the HFD may activate mitochondrial replication and regeneration, maintaining normal metabolism and function of muscle cells. Correspondingly, the expression of *TFAM*, a gene indicative of mitochondrial content, showed some improvement under HFD intervention (Fig. 5B). Finally, *MyoD1* and *Myog* are key synergistic genes in muscle regeneration. *MyoD1* activates satellite cells in muscle, promoting muscle cell regeneration, while *Myog* facilitates myotube fusion, increases muscle fiber cross-sectional area, and enhances muscle strength. Both *MyoD1* and *Myog* were activated by the HFD intervention (Fig. 5C), demonstrating the effect of the HFD in promoting muscle fiber recovery and regeneration.

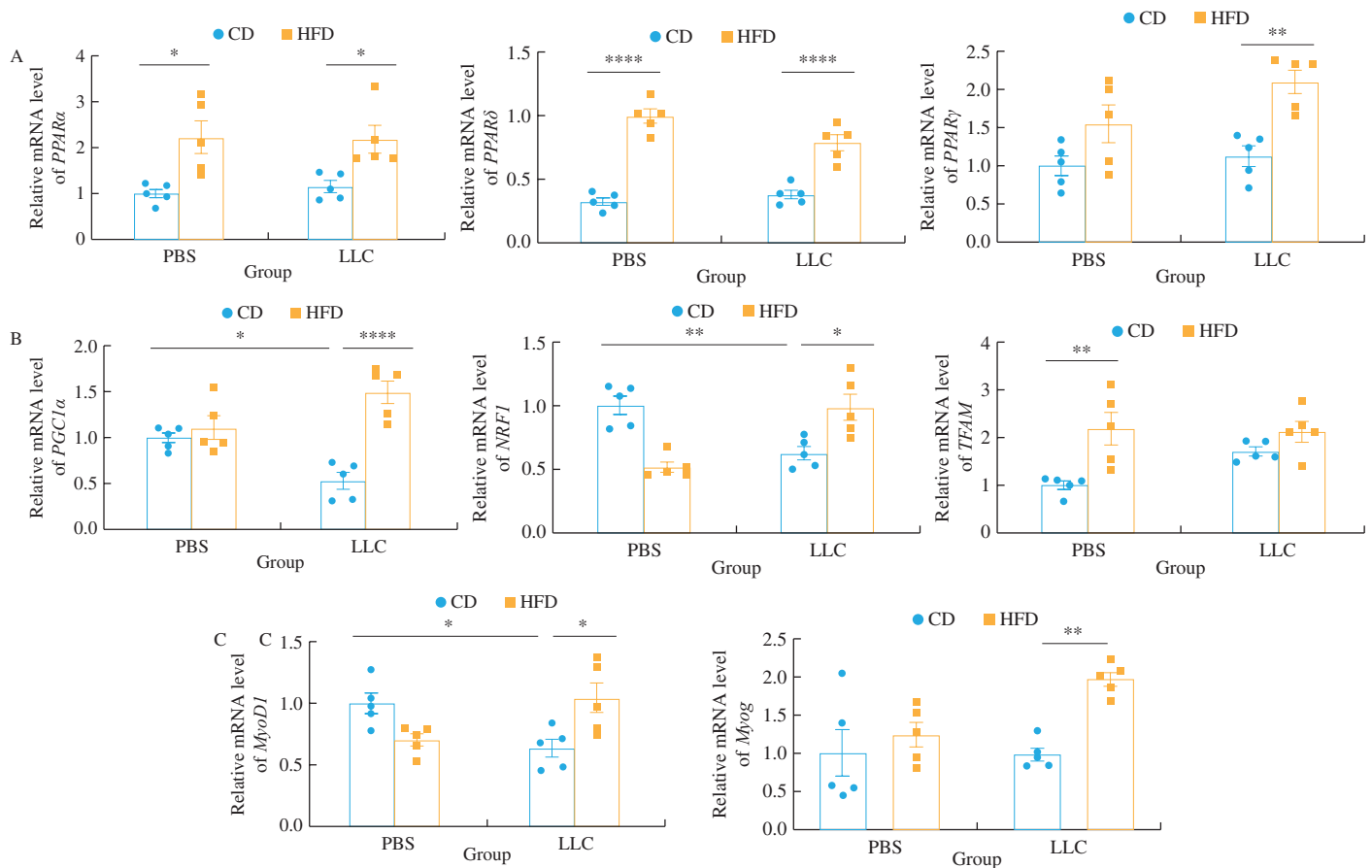


Fig. 5 HFD activates adiponectin downstream genes in muscle of LLC-bearing mice. (A) The mRNA levels of *PPARα*, *PPARδ* and *PPARγ* in TA muscle were determined by qRT-PCR ($n = 5$). (B) The mRNA levels of *PGC1α*, *NRF1* and *TFAM* in TA muscle were determined by qRT-PCR ($n = 5$). (C) The mRNA levels of *MyoD1* and *Myog* in TA muscle were determined by qRT-PCR ($n = 5$).

4. Discussion

In this study, we intervened in a cachexia mouse model using an HFD. The results showed that the HFD reduced the levels of inflammatory factors in the serum of cachectic mice and significantly alleviated hepatosplenomegaly. The HFD also mitigated the weight loss of the TA muscle and the reduction in muscle fiber cross-sectional area, correspondingly alleviating the muscle strength decline and protein degradation caused by cachexia. Finally, the HFD slowed the loss and browning of subcutaneous and visceral fat. Notably, the HFD significantly reduced the expression of inflammatory factors in adipose tissue. These results demonstrate that the HFD not only improves adipose tissue in cachectic mice but also alleviates muscle atrophy and overall inflammation levels^[27-28]. A notable finding was the differential response between muscles, where the TA muscle showed more pronounced atrophy and a stronger response to the HFD intervention than the GC muscle. This could be attributed to differences in muscle fiber type composition, as the predominantly fast-twitch TA muscle is often reported to be more susceptible to cachectic wasting than more mixed-fiber-type muscles like the GC^[20,29].

Mechanistically, through transcriptome sequencing analysis, we found that the HFD intervention led to the enrichment of adiponectin-related signaling pathways in both muscle and adipose tissues. Additionally, pathways related to inflammation and cancer were also ameliorated by the HFD. Further experimental validation confirmed the upregulation of adiponectin expression in subcutaneous

adipose tissue, increased circulating adiponectin levels in serum, and activation of the specific receptor AdipoR1 in muscle, collectively elucidating the complete pathway by which adipose tissue influences muscle tissue. Further analysis of muscle tissue revealed that adiponectin primarily activated genes related to mitochondrial biogenesis and muscle cell renewal, thereby enhancing the utilization of carbohydrates and fatty acids in muscle and maintaining muscle strength and function. Finally, preliminary results suggested that the upregulation of adiponectin expression in adipose tissue by the HFD may be mediated through the synergistic regulation of *PPARγ* and *C/EBPα*. This indicates that the HFD can maintain normal muscle function by improving the metabolism and secretion of adipose tissue.

It is important to acknowledge that the therapeutic role of HFDs in cancer cachexia remains controversial. The protective effects of the HFD observed in this study contrast with some recent reports^[30-32], such as the findings by Ferrer et al.^[30] and Cardaci et al.^[31], which suggest that extreme ketogenic or standard HFDs may exacerbate cachexia through corticosterone induction or impaired mitochondrial quality control, respectively. These discrepancies likely stem from fundamental differences in macronutrient proportions and specific fatty acid compositions. Extreme KDs restrict carbohydrates to near-zero levels, triggering intense physiological stress responses. Our formulation retained a 15% carbohydrate content, which is likely sufficient to maintain basic glycemic balance and prevent the excessive activation of stress axes associated with severe ketosis. Furthermore, standard obesogenic diets often rely on lard, containing

high levels of long-chain fatty acids that require carnitine shuttling and can exacerbate mitochondrial stress. In contrast, our study utilized hydrogenated coconut oil as the primary lipid source. This oil is rich in medium-chain triglycerides, which bypass the carnitine transport system and undergo direct, rapid oxidation in mitochondria. This alternative and highly efficient metabolic routing may circumvent the mitochondrial quality control bottlenecks highlighted in previous studies, providing an accessible energy substrate without inducing lipotoxic stress.

Another important aspect to consider is the underlying driver of weight loss in this model. The observation that LLC+CD mice lost weight despite no significant reduction in energy intake compared to controls suggests that anorexia is not the primary cause. This points towards a state of hypermetabolism, where an elevated resting energy expenditure drives the catabolic state. This phenomenon, while debated in human cachexia, has been identified as a potential prognostic marker in patients with lung cancer^[33]. The ability of the HFD to preserve tissue mass without altering caloric intake suggests it may counteract this hypermetabolic state, possibly by providing a more efficient energy substrate or by reducing the inflammatory signaling that contributes to elevated energy expenditure.

Due to the directness and importance of muscle function for survival, early cachexia research has primarily focused on muscle atrophy as the “terminal effect”, with relatively less attention paid to other tissues^[9,34-36]. In recent years, the function and changes of adipose tissue during cachexia have gradually gained attention, particularly its potential role in the early stages of the disease. However, current research on the specific mechanisms of adipose tissue in cachexia still lacks systematic elucidation, limiting our understanding of its complex physiological processes. Other studies found that significant loss of adipose tissue occurs before the onset of muscle atrophy^[14-15,34-35,37]. This phenomenon suggests that abnormal fat metabolism may be one of the initial steps in the occurrence and development of cachexia. However, most current research focuses on specific types or locations of adipose and muscle changes, lacking in-depth analysis and validation at the transcriptomic and metabolic levels. Therefore, future research needs to further explore the patterns of gene expression and metabolic changes in different tissues and organs at various stages, in order to reveal the potential mechanisms of interaction between these tissues and organs.

Based on existing research findings, it can be inferred that the dynamic changes in adipose tissue may serve as important clinical markers and intervention targets for cancer cachexia. If future research can further clarify the role of adipose tissue in the early stages of cachexia, it will facilitate early screening of cachexia in cancer patients and provide more attention to susceptible populations. Additionally, precise intervention targeting tissues and organs that undergo early changes may delay the overall progression of cachexia, reduce the involvement of other tissues and organs, thereby improving patients’ quality of life and providing adjunctive support for tumor treatment. In this study, the primary focus was on adipose tissue, which is one of the earliest affected tissues in cachexia and plays a crucial secretory role. We found that the secretory function of adipose tissue in cachexia is significantly impaired. On one hand, the expression of harmful inflammatory factors is markedly increased, while on the other hand, the secretion of beneficial adiponectin is reduced. Both of these changes can influence other tissues and organs through the circulatory system, highlighting the central role of adipose tissue in the interaction network of multiple tissues and organs.

While short-term high-fat intervention demonstrates a protective effect on the adipose-muscle axis in murine models, translating this strategy to human clinical applications requires caution. Long-term consumption of diets with extremely high fat proportions inherently carries the risk of inducing metabolic syndrome, encompassing hyperlipidemia and cardiovascular complications. Additionally, the metabolic demands and tumor microenvironments vary significantly across different cancer types and individual patients, meaning a high-fat intervention cannot be treated as a universal therapy. Instead of chronic dietary overhauls, future clinical strategies should focus on precision, phased nutritional support. Transient supplementation with medium-chain triglycerides during critical windows of intense cachectic waste could potentially restore adiponectin signaling and stabilize systemic metabolism without imposing a long-term metabolic burden on the patient.

Several limitations of the present study must be acknowledged. Although the significant downregulation of *UCP1* expression indirectly supports a reduction in energy dissipation, direct metabolic flux data are absent. Mechanistically, while high-throughput transcriptomics and gene set enrichment analyses provide systemic evidence for the involvement of the adiponectin-mediated adipose-muscle axis, direct causal validation through protein-level phosphorylation assays or *in vitro* co-culture systems was not performed. Consequently, our mechanistic findings remain primarily based on robust transcriptomic correlations. Furthermore, the subcutaneous LLC model does not fully recapitulate the complex physiological environment of advanced, multi-organ metastasis in humans. Future investigations integrating metabolic tracing and targeted molecular interventions will be essential to precisely delineate the signal transduction within the fat-to-muscle axis.

5. Conclusion

In summary, this study innovatively proposes that the HFD improves muscle atrophy in cachexia through the adipose-muscle axis *via* adiponectin signaling, providing an important theoretical basis for the clinical intervention of cachexia (Fig. 6). This study not only expands our understanding of the importance and role of adipose tissue in cachexia but also lays an experimental foundation for translational research in cachexia intervention.

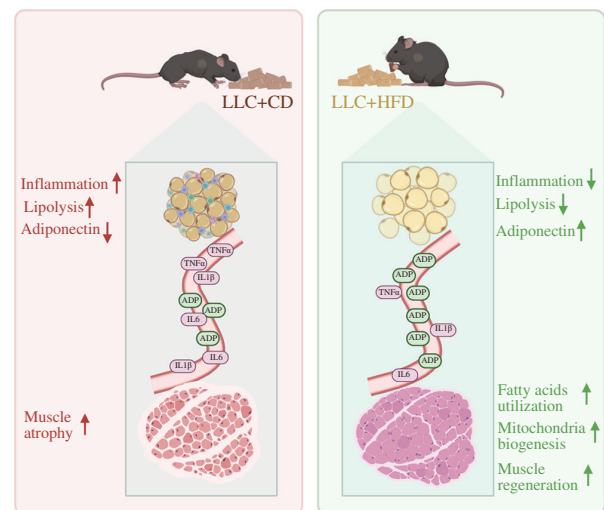


Fig. 6 HFD rescues muscle atrophy in cancer cachexia by restoring adiponectin and attenuating systemic inflammation in mice.

Compliance with ethics requirements

All experiments involving animals were carried out in strict adherence to the ethical policies and procedures approved by Institutional Animal Care and Use Committee (IACUC) of Tsinghua University (approval No. 18-WZ1, 25-WZ1).

Declaration of competing interest

Zhao Wang is an associate editor for *Food Science and Human Wellness* and was not involved in the editorial review or the decision to publish this article. 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.

Data availability statement

All data can be found in the manuscript or the supplementary materials. Requests for materials or correspondence should be directed to the corresponding author.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.26599/FSHW.2026.9251119>.

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