Journal of Advanced Research 75 (2025) 291–309

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

Exercise-regulated lipolysis: Its role and mechanism in health and diseases

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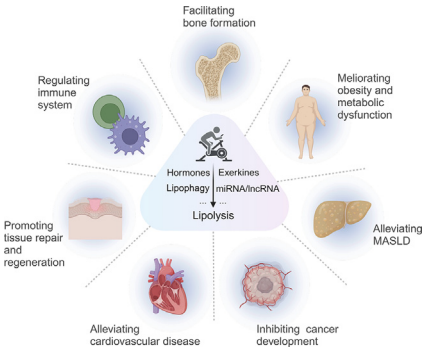
HIGHLIGHTS

- Exercise mediates lipolytic profile through various pathways such as exerkines, miRNA and lncRNA, hormones, and lipophagy.
- Exercise regulates multiple physiological processes by activating the hydrolysis of lipids.
- Exercise-induced lipolysis plays a significant role in various pathological processes to restrain the disease progression.

GRAPHICAL ABSTRACT

The graph was created with biorender.com (agreement number: BJ27LQOB7N).



ARTICLE INFO

Article history:
Received 4 October 2024
Revised 24 November 2024
Accepted 26 November 2024
Available online 28 November 2024

Keywords:
Exercise
Lipolysis
FFAs
Metabolic diseases
Tissue repair

ABSTRACT

Exercise has received considerable attention because of its importance not just in regulating physiological function, but also in ameliorating multiple pathological processes. Among these processes, lipolysis may play an important role in exercise-induced benefits. It is generally accepted that active lipolysis contributes to breakdown of fats, leading to the release of free fatty acids (FFAs) that serve as an energy source for muscles and other tissues during exercise. However, the significance of lipolysis in the context of exercise has not been fully understood. This review comprehensively outlines the potential regulatory mechanisms by which exercise stimulates lipolysis. The potential roles of exercise-mediated lipolysis in various physiological and pathological processes are also summarized. Additionally, we also discussed the potential non-classical effects of key lipolytic effectors induced by exercise. This will enhance our understanding of how exercise improves lipolytic function to bring about beneficial effects, offering new insights into potential therapeutic avenues for promoting health and alleviating diseases.

Contents

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https://doi.org/10.1016/j.jare.2024.11.031
2090-1232/

Overview of lipolysis

Fatty acids (FAs) are important for biological metabolism as they contribute to ATP production or heat generation through oxidation [1]. FAs can be stored in the form of triacylglycerols (TGs) within lipid droplet (LD) organelles in various types of cells. The majority of TGs are deposited in adipocytes of mammals and other vertebrates [2]. Under a variety of stimulation, such as exercise and cold exposure, lipolysis is activated primarily in adipocyte in order to meet the energy demands of other tissues. [3]. On the plasma membrane of adipocytes, β-adrenergic receptors (β-ARs) sense stimulation of catecholamine norepinephrine. Upon stimulation, these receptors induce a conformational change of the heterotrimeric G protein (Gα), leading to the activation of adenylyl cyclase (AC) and subsequent production of cyclic adenosine monophosphate (cAMP). Elevated intracellular cAMP levels phosphorylate and activate protein kinase A (PKA) to induce phosphorylation of lipase, thereby triggering lipolysis through the sequential hydrolysis of TGs [4,5]. Intracellular lipases are categorized into two subclasses: "neutral lipases" which function best at a pH of around 7 and are involved in breaking down cytosolic lipid droplets, and "acid lipases" which operate optimally at a pH of about 5 and are found in lysosomes. Consequently, the two primary intracellular pathways for triglyceride degradation are referred to neutral and acid lipolysis, respectively.

In the canonical enzymology of lipolysis, three consecutive steps involving at least three different enzymes are responsible for the neutral hydrolysis of TGs. Adipocyte triglyceride lipase (ATGL), encoded by *Pnpla2*, initiates the first step of lipolysis by catalyzing TGs into diacylglycerols (DGs), which are further hydrolyzed into monoacylglycerols (MGs) by hormone-sensitive lipase (HSL). Finally, MGs are hydrolyzed by monoacylglycerol lipase (MGL). Under basal conditions, ATGL and HSL are located in the cellular cytosol and remain inactive. Comparative gene identification-58 (CGI-58), also known as α/β-hydrolase domain-containing 5 (ABHD5), is a critical regulator of lipolysis. CGI-58 acts as an activator of the ATGL, which is essential for the breakdown of stored triglycerides in adipose tissue and other organs. The function of CGI-58 is to enhance the activity of ATGL by binding to it and promoting its interaction with lipid droplets, where triglycerides are stored. Under basal conditions, CGI-58 binds to perilipin, a protein that abundantly resides on lipid droplets in adipocytes, which restricts the interaction between CGI-58 and ATGL. Under lipolytic stimulation, the phosphorylation of perilipin releases phosphorylated CGI-58, which then phosphorylated CGI-58 interacts with phosphorylated ATGL to co-activate TG hydrolysis. Meanwhile, PKA activation facilitates the phosphorylation of HSL at multiple phosphorylation sites (Ser563, Ser659, Ser660). Phosphorylated HSL undergoes the movement from the cytoplasm to the surface of lipid droplets. This translocation is one of the key events in lipolytic activation because it allows the interaction between phosphorylated HSL and phosphorylated perilipin to drive the hydrolysis of DG [6–8]. What is more, a new mechanism has been revealed recently by which glucose directly senses and regulates the lipolysis process through Golgi phosphatidylinositol 4-phosphate (PtdIns4P). In a low-glucose environment, the consumption of intracellular glucose led to a decrease in Golgi PtdIns4P levels, which in turn reduced the assembly of the E3 ubiquitin ligase complex $CUL7^{FBXW8}$ in the Golgi apparatus. This reduction suppressed ubiquitination of ATGL in the Golgi to enhance lipolysis, providing a new insight into the spatial regulation of ATGL protein expression levels [9].

In addition to the well-characterized enzymes such as ATGL, HSL, and MGL, noncanonical enzymes have been reported to participate in TG mobilization. Although these enzymes may contribute to less than 10 % of TG lipolysis in adipose tissue, they play an important role in TG catabolism in other tissues, as evidenced by the existence of TG hydrolase activity even in the absence of ATGL or HSL. Over the past decades, several alternative neutral lipases in different protein families have been identified as mediators of the lipolytic cascade. Members of the PNPLA family, including PNPLA1, PNPLA3, PNPLA4, and PNPLA5, are closely related to ATGL and are likely to contribute to lipolysis because of their structural similarity. Members of the α/β-hydrolase fold superfamily, mammalian carboxylesterase (CES) and lipid droplet-associated hydrolase (LDAH), also participate in lipid catabolism. DDH domain-containing protein 2 (DDHD2) and arylacetamide deacetylase (AADAC) exert their hydrolase activity by harboring a conserved GXSXG lipase motif [10]. Additionally, lipophagy-induced hydrolysis in lysosomes serves as an alternative way of lipolysis under nutrient deprivation. Lysosomes are small organelles within the cell that contain various acidic hydrolytic enzymes. They are most active in an acidic environment and can degrade various biological macromolecules, including lipids.

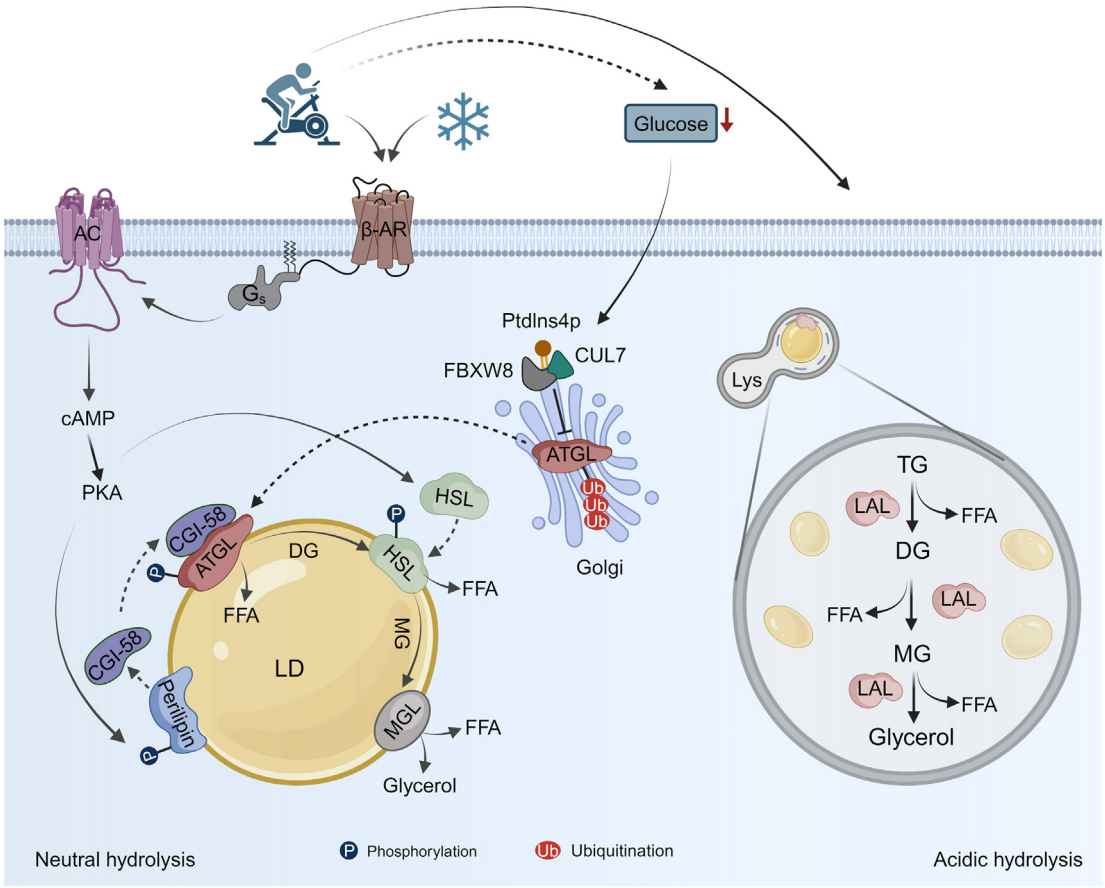

Fig. 1. Exercise triggers both neutral and acidic hydrolysis of lipid. Exercise can induce neutral lipolysis via activating β-AR signaling pathway. Upon exercise stimulation, β-AR facilitates a conformational change in the G protein, which leads to activation of adenylyl cyclase (AC) and subsequent production of cyclic adenosine monophosphate (cAMP). Elevation of intracellular cAMP phosphorylates and activates protein kinase A (PKA) to induce phosphorylation of HSL, ATGL, Perilipin and GCI-58, thereby promoting neutral hydrolysis of lipid. In a low-glucose environment, the consumption of intracellular glucose led to a decrease in Golgi PtdIns4P levels, which in turn reduced the assembly of the E3 ubiquitin ligase complex $CUL7^{FBXW8}$ in the Golgi apparatus. This reduction suppressed ubiquitination of ATGL in the Golgi to enhance lipolysis. Meanwhile, exercise could also trigger acidic hydrolysis of TG by mediating lipophagy in lysosomes (Lys). Within the lysosome, lipids are hydrolyzed by acidic lipases, such as lysosomal acid lipase (LAL), that can exert effect on degrading triacylglycerol (TG) and diacylglycerol (DG). The dashed lines indicate the potential effects await further investigation. The graph was created with biorender.com (agreement number: RT27LPY0NL).

Within the lysosome, lipids are hydrolyzed by acidic lipases, such as lysosomal acid lipase (LAL) that can exert an effect on degrading TG and DG. The activity of LAL is mainly regulated by transcriptional mechanism. It has been known that transcription factors that activate the expression of LAL include PPAR, FOXO1, and transcription factors TFEB and TFE3 [11]. Collectively, lipolysis is a complicated process in which multiple enzymes and effectors are involved (Fig. 1).

Regulation of lipolysis by exercise

Exercise training has been considered as one of the optimal strategies to maintain overall health, in which lipolysis plays an important role [12–14]. In order to deeply understand the role and mechanism of exercise-induced lipolysis in the beneficial effects brought about by exercise, responding factors regulated by exercise in the stimulation of lipolysis are worthy to be investigated.

Exerkines

Exerkines are a group of molecules including soluble proteins released in response to acute and/or chronic exercise. They function by transducing signals among adjacent cells and transferring signals to distant organs through binding to specific receptors on target cells, thereby mediating various signaling pathways. In these ways, exerkines play important roles in regulating multiple biological processes, including metabolism [15,16].

Interleukin-6 (IL-6) is a 26-kDa secreted protein identified in 1989. It is now recognized as both a myokine and an adipokine, as it can be secreted by both skeletal muscle and adipose tissue [17,18]. During exercise, plasma IL-6, which is secreted from skeletal muscle, can increase by more than 100-fold. Some evidence indicates that type I muscle fibers are the predominant source of plasma IL-6. Given that type I muscle fibers are intensively recruited at low percentages of maximal force production, it is suggested that the IL-6 response may be more pronounced in long-duration moderate-intensity exercise compared to resistance training [19]. Mechanistically, IL-6 production during exercise is mainly regulated at the transcriptional level. Various stress-related molecular mechanisms are thought to regulate IL-6 mRNA transcription during exercise. Among them, Ca^{2+} signaling takes large portion in mediating contraction-induced IL-6 mRNA transcription. Repeated membrane depolarizations lead to an increase in intracellular and nuclear Ca^{2+} via the activation of the PI3K cascade. Eventually, enhanced Ca^{2+} signaling promotes IL-6 transcription by activating transcription factors such as activator protein 1 (AP-1). Moreover, membrane depolarization can also boost the phosphorylation of c-Jun N-terminal kinase (JNK), which in turn

activates AP-1 [20]. Several studies have demonstrated the role of IL-6 in regulating the lipolytic process. In murine studies, the deficiency of IL-6 in mice resulted in a significant increase in weight gain in all dissected fat pads, which was partially rescued by IL-6 replacement, indicating the potential lipolytic effect of IL-6 [21]. This effect was further supported by the findings showing reduced FFA release in adipocyte-specific gp130 (the receptor of IL-6) knockout mice [22]. Human studies have also shown that, after acute treatment with recombinant human IL-6 infusion for 3 h, the levels of plasma FFAs and glycerol in healthy subjects were much higher than those in subjects treated with saline [23]. Notably, the administered amount of IL-6 was at a rate of 7 μg/h, which would result in circulating concentrations of IL-6 being approximately at 140 pg/ml. This dose is similar to circulating IL-6 levels in subjects after exercise training, therefore implying the significant effect of exercise-induced IL-6 production on lipolysis. Similar results were observed in another study in which the subjects were administered with a high dose or a low dose of recombinant human IL-6 [24]. Furthermore, in vitro experiments revealed that IL-6 enhanced glycerol release from 3 T3-L1 adipocytes into culture medium [25,26]. These findings support the role of IL-6 in promoting lipolysis, which can be upregulated, primarily in skeletal muscle, to exert autocrine, paracrine, or endocrine effects during exercise. The elevated level of IL-6 in the circulation correlates with the intensity and duration of exercise [27,28]. Therefore, it is likely that exercise could accelerate TG hydrolysis by increasing the serum concentration of IL-6. Indeed, a randomized placebo-controlled trial demonstrated that the use of an IL-6 receptor antibody (tocilizumab) to block the action of IL-6 in abdominally obese adults offset the exercise-mediated breakdown of visceral adipose tissue [29]. Furthermore, lipolysis can occur not only in the visceral adipose tissue but also in fast-twitch fibers of skeletal muscle, as evidenced by increased glycerol release observed in extensor digitorum longus muscles isolated from male WT mice treated with recombinant IL-6 for 60 min [30]. In summary, exercise training facilitates lipolytic processes in different types of tissues, partly by increasing the concentration of IL-6 majorly secreted from skeletal muscle during exercise.

Growth differentiation factor 15 (GDF15) acts as an emerging stress-induced cytokine that can be modulated by exercise to affect lipolysis. GDF15, a member of the transforming growth factor-β (TGF-β) superfamily, circulates as a 25-kDa homodimer [31,32]. The concentration of GDF15 in plasma is negatively related to body mass index (BMI) [33]. Vigorous submaximal exercise has been shown to elevate serum GDF15 concentration in humans and mice, establishing the relationship between exercise training and circulating level of GDF15 [34–36]. Further research has demonstrated higher levels of circulating GDF15 in mice with skeletal muscle-specific deficiency of Crif1 (a mitochondrial protein containing a long α-helix), leading to upregulation of lipolytic genes in adipose tissue, liver, and skeletal muscle, along with increased FFAs and glycerol release [37]. Consistent with the in vivo data, experiments on the human adipocytes cultured with conditioned media from both acute and chronic exercise-stimulated myotubes have shown that exercise-induced GDF15 stimulates lipolysis of those adipocytes. Electrical pulse stimulation (EPS) of human myotubes was administrated to induce forced contraction and to model two exercise paradigms: an acute high-intensity exercise model (EPS3h) and a chronic moderate exercise training model (EPS24h). Unbiased proteomic screening and ELISA analysis indicated a significant increase of GDF15 protein in the culture media of exercise-stimulated myotubes, which was further applied to human adipocytes. After conditioned media culture, it was found that the culture media of exercise-stimulated myotubes led to higher levels of FFAs and glycerol released from human adipocytes while blocking GDF15 with a neutralizing antibody blunted this effect [38].

In addition to the well-investigated thermogenic effects, irisin has been found to participate in adipose tissue lipolysis. Irisin, a myokine cleaved and secreted from fibronectin type III domain-containing 5 (FNDC5), is primarily expressed in muscle in both mice and humans. A lot of studies have reported a significant increase in irisin levels in subjects undergoing resistance training or acute exercise [39–44] and increased irisin led to increased HSL expression and phosphorylation in adipose tissues of obese mice. Circulating irisin levels were significantly upregulated in male human volunteers subjected to an 8-week long training program involving 3 training sessions per week and were correlated to lipolysis-related metabolites in muscle, hinting the potential role of irisin in facilitating lipid hydrolysis. Moreover, irisin has been shown to increase PKA activity, cAMP levels, and the level of the mRNA encoding ATGL (*Pnpla2*) in 3 T3-L1 adipocytes [45–47]. These findings indicate that irisin contributes to exercise-induced lipolysis.

Furthermore, it has been evidenced that, after acute treadmill exercise, the levels of IL-15 in skeletal muscle and plasma rapidly increased in mice [48]. Some human studies consistently showed that acute exercise increased the levels of IL-15 in skeletal muscle and plasma, regardless of whether the subjects are healthy or obese [49–53]. IL-15 exists in two forms in plasma: free IL-15 and the complex formed by IL-15 and sIL-15Rα. The combination of IL-15 and sIL-15Rα prevents IL-15 from binding to IL-15Rα on the membrane therefore restricting the biological activity of IL-15. Further research showed that serum IL-15 levels were significantly increased, while the levels of sIL-15Rα were decreased in young human subjects, after performing leg lifts and knee extensions at 75 % 1RM intensity [54]. Also, individuals who regularly engage in exercise training have significantly lower levels of sIL-15Rα in circulation compared to sedentary individuals [55]. In animal experiments, mice subjected to treadmill exercise with incremental loads until exhaustion also showed a significant decrease in plasma sIL-15Rα levels [56]. These results suggest that acute exercise increases plasma IL-15 levels while decreasing blood sIL-15Rα levels to allow more free IL-15 to bind to its membrane receptor and promote the biological effects of IL-15, which is closely associated with lipolysis in adipose tissue. Exogenous supplementation of IL-15 to differentiated 3 T3-L1 adipocytes significantly reduced lipid accumulation [57]. When porcine adipose tissue was cultured with IL-15, the rate of lipolysis was rapidly increased in a dose-dependent manner [58]. Continuous subcutaneous injection of IL-15 at a dose of 100 μg/kg for seven days in rats was found to reduce white adipose tissue mass [59]. Mice overexpressing IL-15 had significantly lower body weights compared to wild-type mice, while IL-15 gene knockout mice exhibited increased adipose tissue mass and such phenotype can be reversed by supplemental IL-15 [60]. These findings indicate that IL-15 enhances lipolysis in the body, thereby reducing the accumulation of fat in tissues. Thus, it is likely that IL-15 derived from skeletal muscle can respond to exercise intervention to promote adipose lipolysis, which awaits further study.

Apart from the aforementioned exerkines, other exerkines may also participate in the lipolytic process during exercise, such as fibroblast growth factor 21 (FGF21). It serves as a key mediator of lipid metabolism and also facilitates adipose lipolysis. Mice overexpressing FGF21 or with higher FGF21 sensitivity due to elevated β-klotho levels (a cofactor for FGF21 action) have exhibited upregulated expression and phosphorylation of lipolytic genes in white adipose tissue [61–63]. FGF21 expression level in the liver can also be increased by FFAs from adipose lipolysis under hypoxic conditions, potentially modulating the lipolytic process in adipose tissue in a positive feedback regulation manner because FGF21 can be secreted from liver and acts on adipose tissue [64–66]. Human studies indicated that acute endurance exercise led to an increase

in FGF21 levels in the body [67,68] and the levels of FGF21 in mouse serum, skeletal muscle, and liver significantly were increased in mice subjected to acute endurance exercise as well [69,70]. Besides, 8 weeks of long-term aerobic exercise significantly increased serum FGF21 levels in high-fat diet (HFD)-fed rats [71]. Thus, exercise may exert its pro-lipolysis effect through enhancing FGF21 release.

Lipases and the cofactors

Numerous studies have demonstrated the significant impact of exercise on lipases, emphasizing the importance of physical training in TG hydrolyzation [72–75].

Apart from the widely-recognized pro-phosphorylation effect on lipases, exercise might also stimulate the lipolysis through the transcriptional regulation of lipolysis-related genes expression. Resistance exercise has been reported to enhance the bioactivity and secretion of growth hormone (GH) [76–78], which promoted lipolysis as indicated by increased FFAs availability [79,80]. GH participates in the activation of lipolysis through two distinct mechanisms. The binding of GH to its receptor triggered the phosphorylation of Janus kinase-2 (JAK2) and subsequently activated the transcription factor signal transducer and activator of transcription-5 (STAT5) to directly activate *Pnpla2* transcription in both white and brown adipocytes [81,82]. Also, GH-mediated activation of JAK2 facilitated transcriptional activation of HSL therefore strengthening TG breakdown [83–85]. The second pathway includes inhibiting the expression of G0/G1 switch gene 2 (G0S2), an inhibitor of ATGL activity [86]. Moreover, Forkhead box-O1 (FOXO1) is another important transcription factor binding to the promoter of *Pnpla2* gene to impel its transcriptional activation [87–89]. Recently, Bedada et al. reported that FOXO1 can be positively regulated by exercise based on the evidence that the expression level of FOXO1 in peripheral blood increased in male subjects during exercise [90]. Besides, AMP-activated protein kinase (AMPK), an important regulator of cellular energy homeostasis and is well-known to be activated under exercise intervention [91], is a pivotal kinase in facilitating the activation of FOXO1. AKT phosphorylates Thr24 and Ser256 residues of FOXO1, leading to the inactivation of FOXO1 and its translocation from the nucleus to the cytoplasm. AMPK enhances the transcriptional activity of FOXO1 by phosphorylating it at Ser22, Ser383, and Thr649 residues [92]. In addition to the regulation of phosphorylation, AMPK can also increase activation of Sirtuin 1 (SIRT1), a deacetylase, thereby boosting the deacetylation of FOXO1, which strengthens its transcriptional activity to increase the expression of key lipolysis-associated genes, such as the gene encoding ATGL [93]. Another cofactor of lipase CGI-58 is regulated by exercise as well. It has been evidenced that exercise facilitated the expression and activation of CGI-58 in adipocytes and mammals to trigger catabolic cascade of TG because phosphorylated CGI-58 is a key cofactor of ATGL for its lipolytic activity [72,94–97].

In conclusion, the studies discussed above indicate that exercise potentially induces lipolytic procedure by enhancing the transcriptional activation of lipolysis-related genes and the activity of key lipases, in which GH, G0S2, ERK-1/2, AMPK and FOXO1 may be involved, or by regulating the expression and activation of lipase cofactors (such as CGI-58).

MicroRNA (miRNA) and long noncoding RNA (lncRNA)

MicroRNAs (miRNAs) are short noncoding RNA molecules with approximately 22 nucleotides in length, which regulate gene expression by targeting mRNAs for translational inhibition or degradation [98–102]. Physical activity has been found to take part in miRNA biogenesis and regulation, which plays an important role in lipid metabolism [103,104]. Vechetti and coworkers discovered that mice epididymal white adipose tissues (eWAT) tended to absorb muscle-specific miR-1 from skeletal muscle-originated extracellular vesicles, which were delivered during muscular mechanical overload training. Increased miR-1 in eWAT facilitated adrenergic signaling to activate lipolysis by targeting Tfap2α, an inhibitor of Adrβ3 expression. Consistently, in human study, higher circular miR-1 level was evidenced in individuals subjected to resistance training [105]. Besides resistance exercise, emerging forms of physical activity, such as hypoxic exercise, may modulate miRNA expression to promote lipid catabolism as well. In the obese rats with 4 weeks of hypoxic exercise, adeno-associated virus-mediated overexpression of miR-27b in skeletal muscle led to a higher level of FFAs in circulation, implying a potential role of miR-27b in promoting lipolysis under hypoxic exercise condition [106]. Clinical trials have identified that various other miRNAs, including miR-378 and miR-145, have been implicated in lipid catabolism or shown quantitative changes following aerobic or resistance exercise. MiR-378 has been reported to maintain energy homeostasis by enhancing lipolysis as the expression of lipolytic genes was increased in WAT, BAT, and skeletal muscle of miR-378 transgenic mice. Further exploration revealed that miR-378 facilitated lipolysis via targeting stearoyl-Coenzyme A desaturase 1 (SCD1) in fat tissues [107]. Meanwhile, swimming exercise has been shown to reduce the mRNA levels of SCD1 in the liver of HFD-fed mice to alleviate fatty liver disease [108]. Thus, it is possible that miR-378 participates in the exercise-downregulated SCD1, suggesting a potential involvement of miR-378 in the enhanced lipolysis brought about by exercise. Conversely, miR-145 takes part in adipose metabolism by suppressing lipolysis. Lin et al. showed that mature miR-145 level was reduced when KH-type splicing regulatory protein (KSRP), an RNA-binding protein that regulates gene expression at multiple levels, was ablated in mice and adipocytes because maturation process of primary microRNA 145 (pri-miR-145) was impaired by KSRP deficiency. This led to increased expression of lipolysis-associated genes by reason that miR-145 exerts its influence by directly binding to and negatively regulating the expression of FOXO1 and CGI58, both of which are key activators of lipolysis [109]. Interestingly, studies uncovered that exercise enhanced the activities of FOXO1 and CGI58 [93,95], while the underlying mechanism has not been fully understood. Whether the downregulation of miR-145 contributes to exercise-mediated lipolysis by enhancing FOXO1 and CGI58 activities merits further investigation. Unlike miRNAs, long noncoding RNAs (lncRNAs) are RNA transcripts of more than 200 nucleotides that also do not encode proteins. They are now recognized as novel regulators involved in a variety of biological processes [110–112]. SRA is a long non-coding RNA and functions in lipid metabolism. In a mice study, a significant decrease of SRA expression was observed in diet induced obese (DIO) mice treated with treadmill exercise, leading to increased ATGL expression and enhanced lipolysis [113].

MiRNAs and lncRNAs play important roles in maintaining metabolic homeostasis and have implications in fat catabolism, but their regulatory effects on exercise-mediated lipolysis are less reported, which is worthy of further exploration.

Other exercise-regulated hormones

Besides GH described above, the regulatory effects of hormones on exercise-induced lipolysis have been extensively studied. It is well-established that moderate physical exercise activates the sympathetic nervous system (SNS), leading to the release of catecholamines that stimulate the utilization of triglycerides (TG) by initiating their catabolism [114–116]. Additionally, in a human

study, exercise interventions can induce non-adrenergically-mediated lipolysis in abdominal subcutaneous adipose tissue of male individuals by atrial natriuretic peptide (ANP) [117]. ANP, a natriuretic hormone synthesized in cardiac tissue, can promote lipolysis in adipocytes through the natriuretic peptide receptor-A (NPR-A) and the downstream cyclic GMP (cGMP)/Protein kinase G (PKG) pathway to enhance the phosphorylation of HSL and perilipin 1 (PLIN1) [118,119].

Insulin is regarded as a dominant inhibitory hormone of lipolysis since it diminishes activity and gene expression of lipolytic enzymes. Insulin can activate phosphoinositide-dependent kinase-1 (PDK1) and AKT/PKB by classical phosphatidylinositol-3 (PI3)-kinase-dependent signaling pathway to activate phosphodiesterase 3B (PDE3B). This results in the hydrolysis of cAMP, the inactivation of PKA, and a decrease in the phosphorylation of HSL and perilipin [120,121]. Moderate physical activity has been shown to decrease plasma insulin levels [122]. Moreover, lots of research confirmed the beneficial effects of exercise on improving insulin sensitivity, which helps to meliorate excessive insulin production and secretion due to insulin resistance, thus attenuating the inhibitory effect of insulin on lipolysis [123–126]. These, altogether, suggest that the positive regulation of exercise on lipolysis can partly rely on repressing the antilipolytic impact of insulin.

The hunger hormone ghrelin, serves as another regulator of fatty acid mobilization. It is a 28-amino acid peptide hormone secreted by gastric X/A-like cells, known for its function in stimulating appetite [127]. Ghrelin suppressed epinephrine-stimulated lipolysis in white adipose tissue (WAT) and muscle, which is similar to insulin, through PDE3B activation, thereby inhibiting lipolysis [128,129]. As a latest systematic review and *meta*-analysis involving 24 studies that consisted of 52 trials indicated, ghrelin levels are effectively downregulated by exercise. Also, exercise intensity exhibited an inverse relationship with ghrelin levels [130], suggesting that downregulation of ghrelin is involved in exercise-mediated pro-lipolytic effect.

β-adrenergic receptor

Catecholamine is the primary stimulus for the conventional lipid catabolic process. Recent evidence elucidated that physical activity positively regulates lipolysis by increasing circulating levels of α-ketoglutaric acid (αKG), which in turn stimulates the release of adrenaline from the adrenal glands through the activation of the 2-oxoglutarate receptor 1 (OXGR1), thereby supporting lipolysis in WAT [131]. Furthermore, acute exercise training has been shown to reduce the expression of Gi proteins [132], which in turn promoted adenylate cyclase (AC) activity, thereby facilitating the restoration of the lipolytic cascade [4]. The adipose tissue microenvironment encompasses a complex cellular milieu that significantly influences the equilibrium of lipid metabolism. Apart from adipocytes, the adipose tissue harbors a considerable vascular stroma fraction (SVF) with multiple biological roles, among which adipose tissue angiogenesis is integral to the tissue regenerative and metabolic functions [133]. Endothelial cells (ECs), predominantly governing angiogenesis, also contribute to adipocyte lipolysis through activating β-ARs. It has been reported that local production of polyamines in ECs can be released to activate β-ARs thereby stimulating adipocyte lipolysis. Further study revealed that mTOR signaling pathway induces the angiocrine effect of polyamines in ECs [134]. It is reported that 9-week exercise training (TR) in Wistar male rats led to the upregulation of the gene encoding vascular endothelial growth factor A (VEGFA), an important regulator of angiogenesis and capillary growth, in SVF of white adipose tissues [135]. Notably, exercise can positively regulate angiogenesis in white adipose tissue. It has been found that 11 days of running exercise significantly increased vascularization in the iWAT of mice, as evidenced by an increase in blood vessel density and the ratio of vessels using immunofluorescence staining of the griffonia simplicifolia lectin (GSA-I), which specifically binds to the blood vessel endothelial cells. Further experiments revealed that exercise training induced the expression of factors that promote angiogenesis, such as VEGFA and its receptor (KDR/VEGFR2), the Notch ligand Jagged1 (JAG1), angiopoietin-1 (ANGPT1), angiopoietin-2 (ANGPT2). [136,137]. During the process of vascularization mediated by exercise, ECs would go through a proliferation, and increased number of ECs contribute to more production of polyamines that may enhance adipose lipolysis. Thus, the potential involvement of adipose ECs-induced β-ARs activation in exercise-mediated lipolysis awaits further examination.

Lipophagy

In addition to the classical neutral lipolysis, lysosomal acidic lipolysis can also be induced by exercise. Autophagy is a process of cellular self-digestion, degrading damaged cellular components, proteins, and organelles through lysosomes to maintain cellular homeostasis. Lipophagy, a form of autophagy, specifically targets lipid droplets for degradation, thereby releasing FFAs to meet cellular energy demands. Exercise regulates lipophagy levels in the cells through various signaling pathways. Gao et al. proposed that exercise stimulates the production of FGF21 in skeletal muscle, which is subsequently secreted into circulation. This circulating FGF21 then facilitates lipophagy in the liver through AMPK activation, which inhibits the mTOR pathway and promotes the autophagic process mediated by ULK1 [138]. The above mechanism ensures that cells can effectively utilize endogenous fat reserves under catabolic conditions, such as exercise.

Overall, exercise training contributes to the lipolytic process through the regulation of exerkines, lipolysis-associated enzymes and cofactors, miRNA and lncRNA, hormones, essential components of cell signaling and lipophagy (Fig. 2), which deepens our understanding of the factors facilitating lipolysis induced by exercise. These findings may provide valuable insights for future metabolic studies on exercise. In addition, all the described pathways contribute to exercise-induced activation of lipolysis. It is hypothesized that these pathways may come into effect synergistically, and blockage of one or more of these pathways may compromise the activation of lipolysis in response to exercise to some certain extent. Another possibility is that some pathways may act in a compensatory way to keep the level of exercise-triggered lipolysis when some other pathways were impaired.

Potential implication of exercise-mediated lipolysis in health and disease

Physical exercise mediates multiple physiological processes by activating the breakdown of lipids, which also plays a significant role in various pathological processes to restrain the progression of diseases (Fig. 3).

Regulation in immune system

Immune cells are in charge of sensing stimulatory signals in the microenvironment followed by turning on specific immune functions in response to the stimulus. In the process of immune response, tissue-resident macrophages are activated to clear damaged cells, thereby facilitating cellular renewal [139,140]. Emerging evidence indicates that lipolytic procedure in exercise may take part in adjusting immune function. Apart from WAT, bone marrow adipose tissue (BMAT) contains a rich source of LD, and

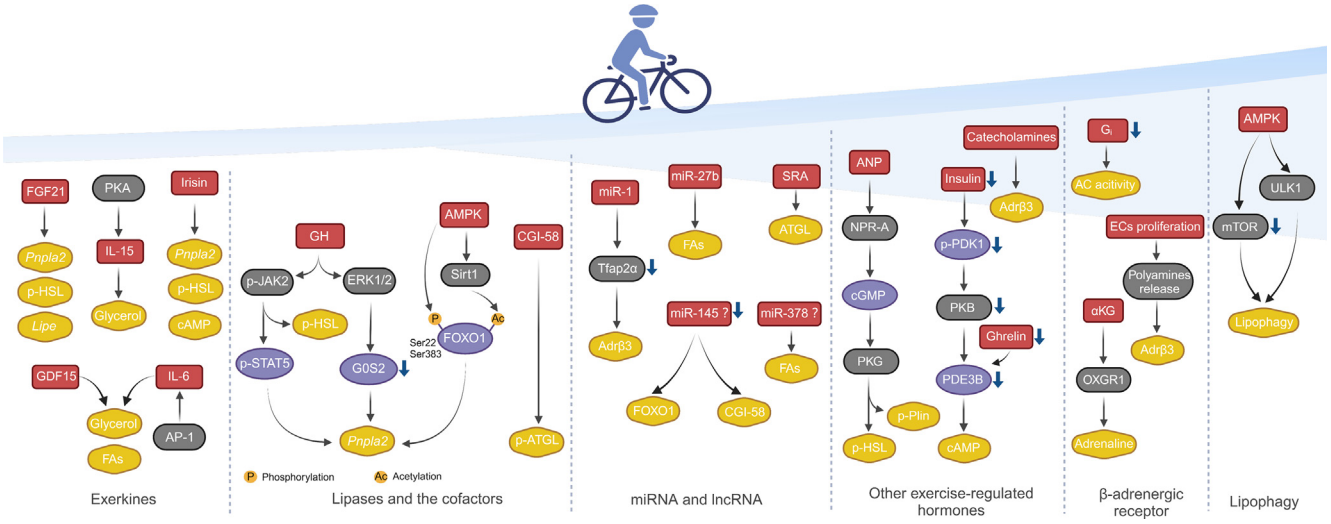

Fig. 2. Exercise promotes lipolysis via multiple pathways. Physical activity exerts lipolytic effects by modulating a complex interplay of molecular factors and biological mechanisms including exerkines, lipolytic enzymes and their cofactors, miRNA and lncRNA, hormonal signaling, the β-adrenergic receptor (β-AR) pathway, and lipophagy. During exercise, a suite of exerkines, including interleukin-6 (IL-6), growth differentiation factor 15 (GDF15), irisin, fibroblast growth factor 21 (FGF21), and interleukin-15 (IL-15), are upregulated, thereby augmenting lipid catabolism. Exercise induces IL-15 expression though activating PKA pathway and enhances transcriptional activation of IL-6 via activating activator protein 1 (AP-1). Exercise stimulates lipolysis by modulating the expression and activity of key lipolytic enzymes, such as adipose triglyceride lipase (ATGL), encoded by the *Pnpla2* gene. The expression of *Pnpla2* is enhanced through several signaling pathways: the growth hormone (GH)/phospho-JAK2 (p-JAK2)/phospho-STAT5 (p-STAT5) axis, the GH/ERK/G0S2 pathway, and the AMPK/Sirt1/FOXO1 cascade. Exercise-induced GH also triggers the phosphorylation of Janus kinase 2 (JAK2), subsequently elevating the levels of phosphorylated hormone-sensitive lipase (HSL). Additionally, the phosphorylation of ATGL is facilitated by GCI-58, which is upregulated in response to exercise. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs), also play roles in exercise-induced lipolysis. Exercise facilitates lipolysis through miR-1, miR-27b, and SRA. MiR-378 and miR-145 may also participate in exercise-mediated hydrolysis of lipid as well. Hormonal regulation is another layer of control in exercise-induced lipolysis. Exercise activates the atrial natriuretic peptide (ANP)/natriuretic peptide receptor-A (NPR-A)/cGMP/protein kinase G (PKG) pathway, leading to the phosphorylation of HSL and perilipin (Plin). The downregulation of insulin and ghrelin by exercise enhances cAMP activity by inhibiting phosphodiesterase 3B (PDE3B). The β-AR signaling pathway is pivotal in mediating fat catabolism during exercise. Exercise activates this pathway by inhibiting the inhibitory G protein (Gi) and elevating the levels of α-ketoglutaric acid (αKG) in circulation. Exercise-induced endothelial cell (EC) proliferation may also activate β-AR signaling in adipocytes by producing polyamines. Lipophagy, a process of autophagic degradation of lipid droplets, is another mechanism by which exercise promotes lipid hydrolysis. This process may involve the AMPK/mTOR and AMPK/ULK1 pathways, which are activated in response to exercise. The graph was created with biorender.com (agreement number: LU27LPYLQ4).

mainly scatters in the bone marrow cavity, surrounding skeletal and hematopoietic lineage cells. BMAT is responsible for producing energy substrates to fuel neighbor cells. A recent study proved that treadmill intervention stimulates bone marrow fat lipolysis. This is important for lymphopoiesis as a higher frequency of hematopoietic stem cells (HSCs) and common lymphoid progenitors (CLPs) was observed in exercised male rats, implying the importance of lipolysis in preserving immune homeostasis of skeletal microenvironment after exercise [141]. In addition, it has been evidenced that exercise results in an anti-inflammation effect to reduce the injury of many tissues. One underlying mechanism could be that the strengthened lipolysis drives metabolic reprogramming to facilitate the polarization of M2 macrophage [142,143]. Macrophages are crucial for regulating immune responses during inflammation and they adopt alternative activation states depending on different situations. M2 macrophage is generally accepted as the immune cell producing anti-inflammatory cytokines to maintain tissue homeostasis, which prefers fatty acid oxidation to fuel mitochondrial oxidative phosphorylation. Ching and co-workers revealed that macrophage lysosomal lipolysis participates in increased expression of M2-associated genes to support M2 activation by enhancing cellular oxidative phosphorylation [144]. Together, exercise-boosted lipolysis might participate in the regulation of immune systematic homeostasis (Fig. 4).

Facilitating bone formation

Bone is a dynamic active tissue maintaining skeletal homeostasis via bone remodeling. One of its pivotal procedures is differentiation of mesenchymal stem-cell derived osteoblasts, which is followed by collagen synthesis playing an essential role in structural support and bone mechanical stability to improve bone matrix quality. Afterwards, mineralized process is initiated to foster bone formation and maintain the bone mass [145,146]. BMSCs possess the potential for both osteogenic and adipogenic differentiation, which is significant for maintaining the balance in skeletal system [147]. Excessive marrow adipose tissue (MAT) expansion may exaggerate the detrimental bone microenvironment and worsen disease progression such as osteoporosis [148]. During the state with high bone formation, bone-resident cells predominantly use FFAs to meet the energy demand [149]. Actually, those FFAs can derive from lipolysis of bone marrow fat after exercise. Physical exercise enhances secretion of reticulocalbin-2 (RCN2), a 55-kDa Ca^{2+}-binding protein containing six EF-hands [150], from the bone marrow macrophages to bind to a receptor complex composed of neuronilin-2 (NRP2) and integrin beta-1 (ITGB1) on bone marrow mesenchymal stem cells (BMSC)-derived adipocytes. This was confirmed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) to analyze membrane proteins isolated from bone marrow stromal cells (BMSC)-derived adipocytes incubated with His-labeled RCN2 and co-immunoprecipitation (co-IP) experiments in human embryonic kidney (HEK) 293 T cells. In addition, cAMP and phospho-PKA substrate expression was remarkably increased in BMSC-derived adipocytes overexpressing RCN2 while eliminating the combination of RCN2 with its receptor complex blunted such effect and subsequently undermined the activation of HSL. Then, micro-CT analysis and osteocalcin staining, a marker for bone formation, in rat femurs confirmed that exercise-induced RCN2 expression enhanced lipolysis to increase the level of FFAs, which promotes the osteogenic differentiation of mesenchymal

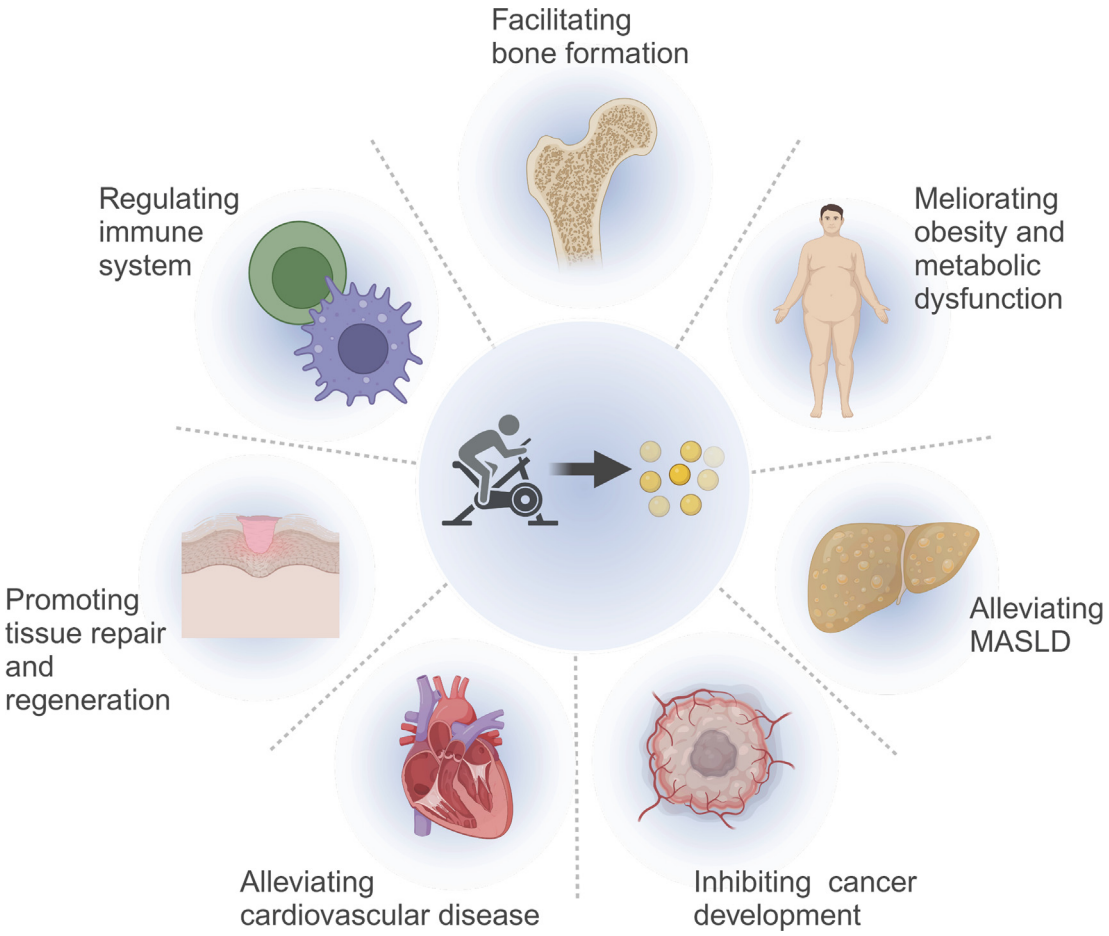

Fig. 3. Exercise-induced lipolysis plays important roles in various physiological and pathophysiological processes. Exercise-elicited lipolysis is involved in multiple physiological processes, such as facilitating bone formation, regulating immune system and promoting tissue repair and regeneration. In pathophysiological processes, exercise-induced lipolysis exhibits diverse roles in meliorating obesity and metabolic disorder, alleviating MASLD, inhibiting cancer development, alleviating cardiovascular disease. The graph was created with biorender.com (agreement number: YF27LPYVKW).

and stem cells, thereby promoting bone formation [141]. These results demonstrate that exercise can accelerate lipolysis in BMAT, which is beneficial for osteogenesis (Fig. 4).

Alleviation of fatty liver disease

Metabolic dysfunction-associated steatotic liver disease (MASLD) has received increasing attention because it is one of the most common chronic metabolic diseases ranging from hepatic steatosis to further stage of severe inflammation and fibrosis defined as metabolic dysfunction-associated steatohepatitis (MASH) [151–152]. Excessive accumulation of intrahepatic lipid is regarded as a detrimental metabolic and hepatic pathology related to the ongoing obesity epidemic [154–155].

In the liver, there is a delicate balance between FFAs uptake to storage into TG and consumption of TG through fatty acid oxidation (FAO) [157–158]. Growing clinical and epidemiological evidence has declared a remarkable alleviation of MASLD induced by physical activity. [160–161]. Although blocking adipose tissue lipolysis seems to limit the hepatic FFAs intake to reduce hepatic TG accumulation to some degree, it has been reported that when the level of adipose lipolysis was enhanced by inhibiting dephosphorylation or overexpression of lipase, less lipid accumulation was found in the liver of HFD-fed mice [163,164]. More importantly, several studies uncovered that exercise-induced lipolytic process led to a direct increase of FAO-associated genes (such as CPT-1a and PPARα) in liver [165,166]. Hepatic FFAs perform as PPARα ligands to strengthen transcriptional program [167]. ATGL-catalyzed lipolysis was found to trigger the hepatic FAO in a SIRT1-dependent manner. The deacetylase activity of SIRT1 was enhanced by β-adrenergic signaling-induced ATGL. This led to the upregulation of PGC-1α and PPAR-α, independently of alterations in NAD + levels, to strengthen hepatic lipid expenditure [156,169,169]. In addition to promoting lipolytic procedure, exercise has been showed to activate hepatic SIRT1 to meliorate steatosis in mice livers [170]. So, it is quite likely that exercise exerts its protective effect on MASLD at least partially via lipolysis-induced SIRT1 activation. In short, lipolysis, which can be activated by exercise, supports melioration of fatty liver disease, in which enhanced FAO is involved.

Apart from the pro-FAO effect, exercise-induced lipolysis may indirectly alleviate fatty liver through promoting adipose browning. As mentioned above, lipolysis activates PPARα and SIRT1 signaling pathways, both of which can act as activators of adipose browning [171–173]. Many studies have demonstrated that adipose browning not only enhances energy expenditure, but also reduces hepatic lipid accumulation, thereby exerting beneficial effects on alleviating MASLD [175]. Thus, lipolysis-induced thermogenesis in WAT may contribute to exercise-mediated amelioration of MASLD. Another cause of MASLD is impaired hepatic TG secretion.

The hepatic secretion of TG is mediated by very-low density lipoproteins (VLDLs). Disruption in the secretion of VLDLs results in the accumulation of TGs and promotes the storage of lipotoxic

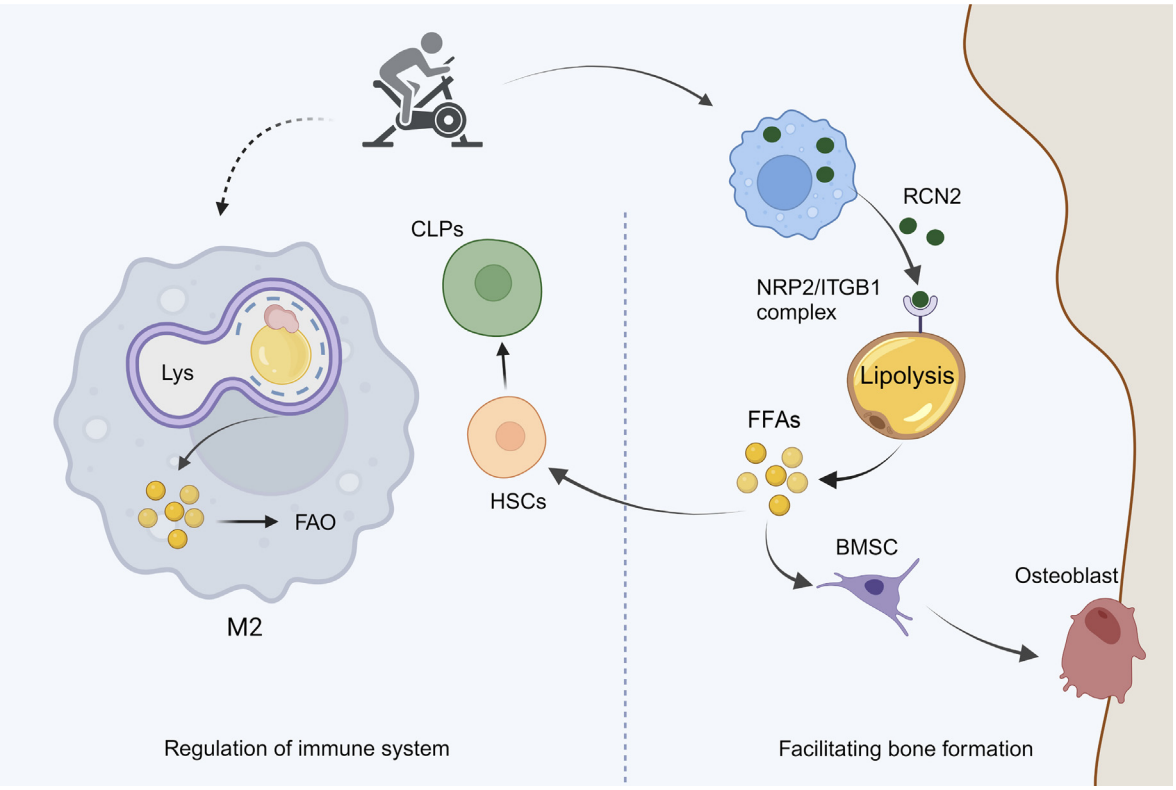

Fig. 4. The roles of exercise-induced lipolysis in promoting bone formation and modulating immune system. Physical exercise stimulates the secretion of reticulocalbin-2 (RCN2) from bone marrow macrophages, which subsequently engages a receptor complex consisting of neuronilin-2 (NRP2) and integrin beta-1 (ITGB1) on adipocytes derived from bone marrow mesenchymal stem cells (BMSCs). This interaction leads to an elevated level of free fatty acids (FFA) in circulation, promoting the osteogenic differentiation of mesenchymal and stem cells, thus facilitating bone formation. Concurrently, lipolysis induced by exercise in BMSC-derived adipocytes enhances the frequency of hematopoietic stem cells (HSCs) and common lymphoid progenitors (CLPs), which can sense mechanical stimuli and foster lymphopoiesis. Furthermore, exercise may augment lysosomal lipolysis in macrophages, promoting the polarization towards M2 macrophages, which exert anti-inflammatory effects. This is achieved by boosting fatty acid oxidation to fuel mitochondrial oxidative phosphorylation, potentially involving the AMPK/mTOR and AMPK/ULK1 pathways. The dashed lines indicate the potential effects await further investigation. The graph was created with biorender.com (agreement number: YF27LQMK91).

lipids. This contributes to the development of fatty liver disease. PNPLA3 has been demonstrated to have the lipolytic activity against TG and is characterized as a TG lipase with a preference for substrates rich in polyunsaturated fatty acids (PUFAs). Liver specific knockout of PNPLA3 aggravated hepatic steatosis in mice subjected to a PUFA-enriched lipogenic diet. Further experiments showed that PNPLA3 facilitates the hydrolysis of TG, releasing PUFAs that are subsequently utilized for the synthesis of phospholipids, which is crucial for assembly of VLDL to propel secretion of triglyceride-rich VLDL [176]. Whether exercise can facilitate the removal of TG by inducing hepatic PNPLA3 to mitigate lipid accumulation in liver requires more investigation.

Together, exercise-mediated lipolysis holds great potential in preventing fatty liver disease, in which multiple biological processes including FAO and adipose browning may be involved, and the underlying mechanisms await to be elucidated further (Fig. 5).

Melioration of obesity and its related metabolic dysfunction

Obesity constitutes a global health priority due to its rising prevalence and its association with numerous complications, including type 2 diabetes, cardiovascular disease, osteoarthritis, obstructive sleep apnoea, and cancers. The continuing rise in the prevalence of obesity requires a multifaceted, effective strategy for its prevention and treatment [177–183]. Because of the outstanding weight loss effect, lifestyle intervention such as regular exercise has been recognized to be effective for prevention and treatment of obesity and its associated metabolic disorder [185–188]. However, it is not easy for individuals with severe obesity and high risk of metabolic syndrome to benefit from exercise due to their poor initiative and compliance. The underlying mechanisms of metabolic improvement induced by exercise need to be investigated further. Lipolysis is one of the most prominent pathways that is modulated by exercise to facilitate fat loss and metabolic homeostasis maintenance [190]. A variety of factors that participate in the above processes have been identified in recent years. Yuan et al. found that acute resistance exercise promotes the generation of α-ketoglutaric acid (αKG), which is a tricarboxylic acid (TCA) cycle intermediate, thereby stimulating the adrenal release of adrenaline through binding to 2-oxoglutarate receptor 1 (OXGR1) to increase the expression of key lipolytic proteins in WAT of HFD-fed mice. The enhanced lipolytic profile drives reduction of adiposity and leads to the activation of adipose thermogenesis, thereby augmenting the cold tolerance and anti-obesity capacity of diet-induced obesity (DIO) mice [191]. Additionally, hepatic cysteine dioxygenase 1 (Cdo1) was identified as an exercise-responsive factor very lately. It is a key enzyme in taurine synthesis via catalyzing the addition of oxygen to L-cysteine and transforming L-cysteine into L-cysteine sulfinic acid (CSA). In endurance exercised-mice model, PKA-CREB signaling pathway was activated during treadmill training to induce hepatic Cdo1 expression [192]. Another study revealed the potential role of adipocyte Cdo1 in combating against obesity and its associated metabolic disorder. Adipose Cdo1 depletion greatly impaired

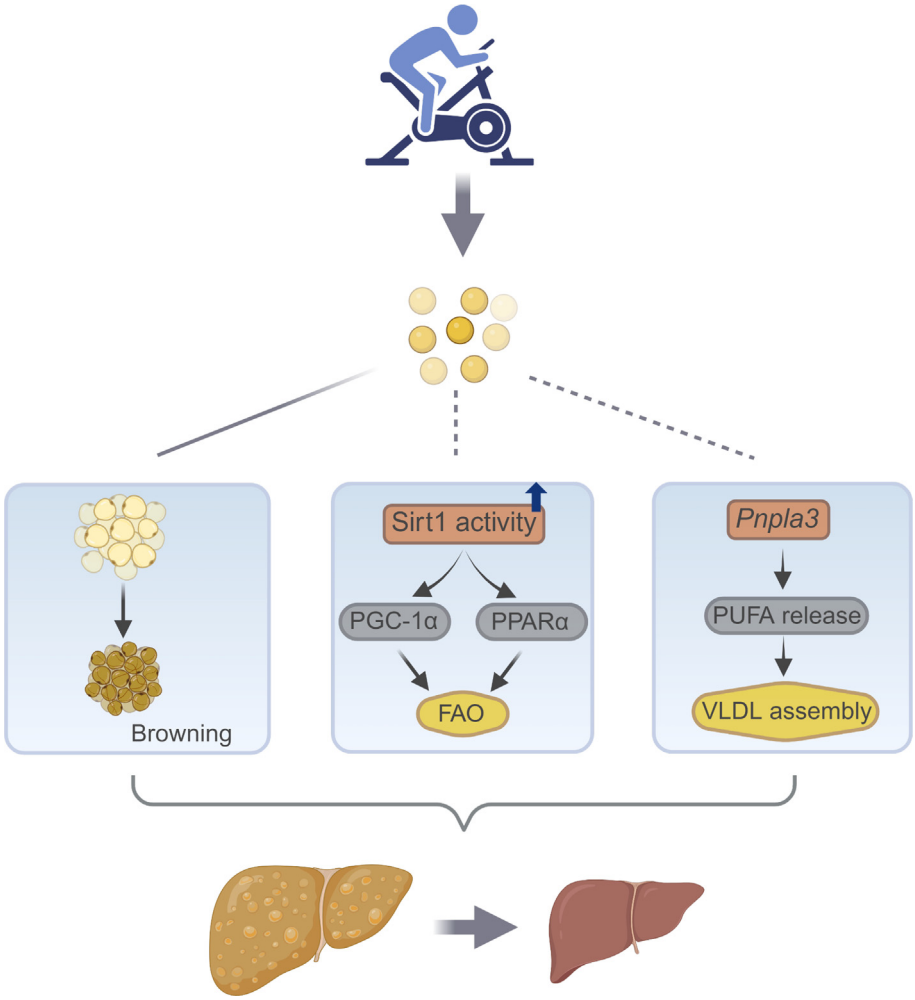

Fig. 5. The roles of exercise-induced lipolysis in alleviation of non-alcoholic fatty liver disease. Exercise-triggered lipolysis could enhance hepatic Sirt1 activity to upregulate expression of receptor-gamma coactivator 1-alpha (PGC-1α) and peroxisome proliferator-activated receptor-alpha (PPAR-α), which strengthen fatty acid oxidation to alleviate fatty liver disease. Exercise-induced lipolysis facilitates the browning of white adipose tissue, which helps to reduce hepatic steatosis. Additionally, exercise may facilitate release of polyunsaturated fatty acids (PUFAs) through regulating expression of patatin-like phospholipase domain-containing protein 3 (*Pnpla3*), a TG lipase with a preference for substrates rich in polyunsaturated fatty acids (PUFAs), thereby boosting very-low density lipoproteins (VLDLs) assembly to increase secretion of TG from fatty liver to relieve the hepatic lipid overload. The dashed lines indicate the potential effects await further investigation. The graph was created with biorender.com (agreement number: SH27LQMUED).

FFAs and glycerol release through inhibiting the transcription of *Pnpla2* and *Lipe*, the genes encoding ATGL and HSL, respectively. Meanwhile, Cdo1 deficiency in adipose tissue led to the reduction of energy expenditure, glucose intolerance and blunted thermogenesis. In contrast, mice with adipose-specific overexpression of Cdo1 exhibited lower TG storage by boosting adipose lipolysis. Then, rescue experiment by AAV-mediated re-expression of ATGL and HSL in adipose tissues was applied to confirm that decreased lipolysis was the main driver of the compromised metabolic phenotype caused by adipocyte-Cdo1 knockout. Mechanistically, Cdo1 can interact with PPARγ and promotes the recruitment of core subunit of mediator complex, Med24, to the promoters of *Pnpla2* and *Lipe* genes, therefore bringing about their transcriptional activation. It is possible that adipocyte Cdo1 may also be upregulated by exercise to improve obesity-associated metabolic disorder by boosting lipolysis, which deserves to be further explored. Moreover, inositol-requiring enzyme 1α (IRE1α), a key ER stress sensor involved in the initial process of unfolded protein response, is another enzyme that could be regulated by exercise [193]. Voluntary physical activity significantly decreased the phosphorylated level of IRE1α and the expression level of it was retrained by irisin, a well-known exercise-induced myokine [194,195]. Inhibition of IRE1α activity and expression contribute to combating obesity because IRE1α blunts lipolysis and beiging of subcutaneous white adipose tissue to promote obesity in HFD-fed mice [196]. Furthermore, p21-activated kinase 4 (PAK4) has been reported to exacerbate DIO and metabolic disorder in mice. PAK4 is upregulated in the adipose tissue of obese mice and goes through a PKA-mediated proteasomal degradation in response to cold exposure, fasting, or adrenergic stimulation. Knockout of PAK4 in adipose tissue or treatment with a PAK4 inhibitor significantly strengthened adipose lipolysis, ameliorated DIO and insulin resistance, increased energy expenditure and enhanced adipose tissue browning. Mechanistically, PAK4 phosphorylates fatty acid-binding protein 4 (FABP4) at T126 and HSL at its non-activating site (S565), which disrupts their interaction to inhibit lipolysis. In visceral fat of obese individuals, levels of PAK4 and the phosphorylation of FABP4-T126 and HSL-S565 are elevated compared to their lean counterparts, which may exacerbate obesity [197]. PKA is well-recognized as a downstream factor of exercise and triggers the lipolytic process [5,199,199], which suggests that exercise may lead to PAK4 downregulation via PKA signaling. In conclusion, lipolysis may

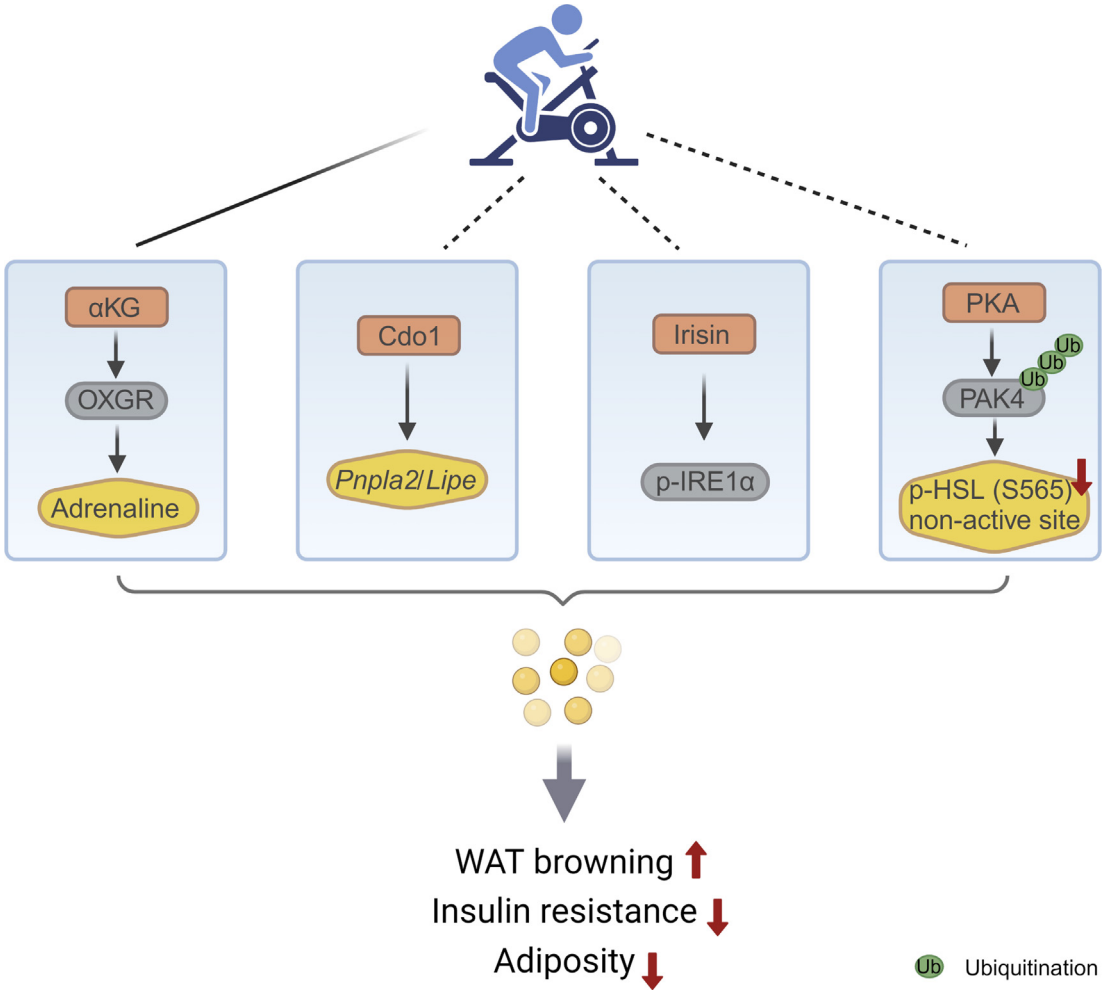

Fig. 6. The roles of exercise-induced lipolysis in melioration of obesity and its related metabolic dysfunction. Exercise activates αKG/OXGR/Adrenaline pathway and potentially induces Cdo1/Lipases, Irisin/p-IRE1α, as well as PKA/PAK4/HSL axes. These pathways collectively enhance lipolysis, a process that is crucial for the browning of white adipose tissue, the improvement of insulin sensitivity, and the reduction of adiposity. Consequently, these adaptations induced by exercise ameliorate obesity and its associated metabolic dysfunctions. The dashed lines indicate the potential effects await further investigation. The graph was created with biorender.com (agreement number: JB27LQN22A).

mediate exercise-mediated mitigation of obesity and its related metabolic disorders through diverse pathways (Fig. 6).

Inhibition of cancer development

Lipid metabolism is now receiving increasing attention in the regulation of oncogenesis. Lipolysis in cancer cells can play an inhibitory role in tumor growth in a hypoxia-dependent manner. Hypoxia brings about metabolic alterations in tumor, facilitating aggressive malignancy and metastasis [200]. Emerging evidence shows lipid droplet (LD) accumulation as a hallmark of hypoxic cancer cells. Under hypoxic conditions, the expression of Hypoxia-Inducible Gene 2 (HIG2) is activated due to the stabilization of Hypoxia-Inducible Factor-1α (HIF-1α), which functions as a transcription factor to enhance the expression of genes related to cell adaptation to hypoxia, with HIG2 being one of them. HIG2 suppresses TG hydrolase activity of ATGL by directly binding to it, thereby reducing breakdown of TG to facilitate LD accumulation. Usually, the FFAs from lipolysis undergo FAO to fuel the energy demand for cancer cells. However, during hypoxia, FAO process consumes a significant amount of oxygen, which intensifies the shortage of oxygen, and can result in the production of reactive oxygen species (ROS), which induces the cellular apoptosis. Thus, increased lipolysis under hypoxia condition could result in oxidative stress through the subsequent FAO procedure to threaten the survival of cancer cells [201,202]. Furthermore, another potential mechanism of lipolysis-mediated tumor inhibition is that increased lipolysis causes repression of mTORC1 activity and arrest of cellular growth by activating AMP-activated protein kinase (AMPK). It has been indicated that lipolysis is involved in energy-consuming futile cycle of FA generation and esterification in the tumor cells, which is responsible for AMPK activation. A significant fraction of mobilized FA is re-esterified to TG by DGAT enzymes during active lipolysis and this futile cycle causes consumption of ATP to increase cellular AMP level, therefore activating AMPK [203]. In conclusion, lipolysis may play an important role in exercise-mediated anti-cancer effects (Fig. 7).

Alleviation of heart diseases

Heart is the powerhouse of the circulatory system. It drives blood flow, provides sufficient blood flow to organs and tissues to supply oxygen and various nutrients (such as water, inorganic salts, glucose, proteins, various water-soluble vitamins, etc.) and carries away the end products of metabolism (such as carbon dioxide, urea and uric acid, etc.), maintaining normal cellular metabo-

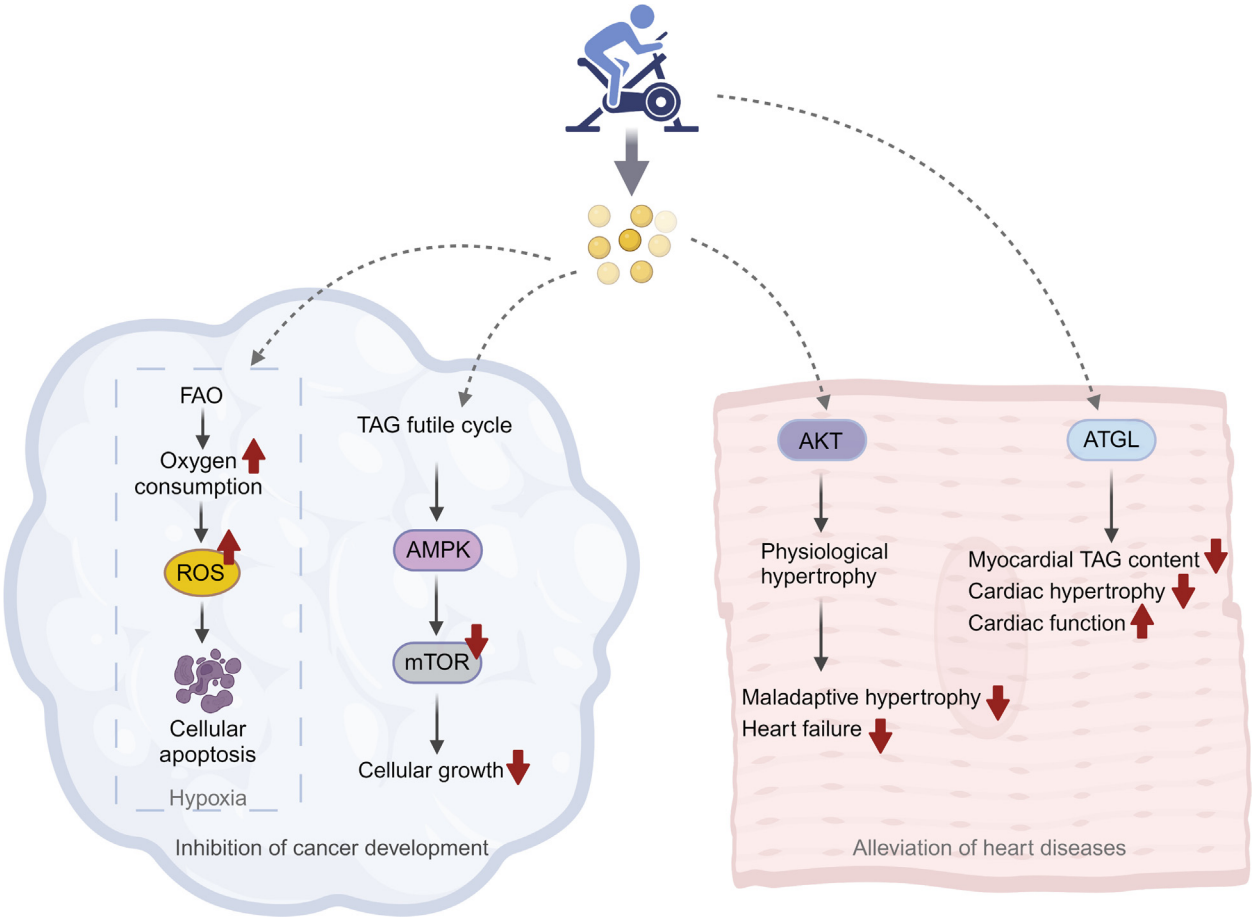

Fig. 7. The roles of exercise-induced lipolysis in inhibiting cancer development and alleviating heart diseases. Exercise-induced Lipolysis fuels the TG futile cycle to activate AMPK, which suppresses tumor cell growth by inhibiting mTOR signaling pathway. Under hypoxic condition, FFA triggers the process of fatty acid oxidation (FAO). This process consumes a significant amount of oxygen, which intensifies the shortage of oxygen and can result in the production of reactive oxygen species (ROS), which induces the cellular apoptosis to deter tumor development. In addition, exercise might meliorate maladaptive hypertrophy of heart and heart failure via AKT-mediated physiological hypertrophy. Also, the upregulation of ATGL expression during lipolytic procedure induced by exercise could contribute to reducing myocardial TG content, restricting pathological cardiac hypertrophy, and improving cardiac function. The dashed lines indicate the potential effects await further investigation. The graph was created with biorender.com (agreement number: RL27LQNBF4).

lism and function. Heart disease has become one of the most lethal health problems worldwide [204–207]. Regular aerobic exercise can significantly reduce the risk of cardiac diseases and have a protective effect on the heart [209]. Some evidence hinted that exercise may protect against heart diseases via promoting lipolysis in cardiomyocytes. Researchers identified that deficiency of cardiomyocytes ATGL would result in a pathological phenotype in the heart of mouse model, including increased myocardial TG content, cardiac hypertrophy, and impaired cardiac function. In contrast, the regaining of cardiac lipolysis in those mice by overexpression ATGL led to a decrease in cardiac TG deposition, recovery of cardiac mitochondrial function, and pro-longed lifespan [210]. Moreover, lipolysis elicited by exercise stimulation is shown to improve cardiac function as well. Rigorous and sustained physical exercise triggers substantial adaptive responses in heart, which enhance cardiac output to meet the heightened peripheral demand for oxygen and energy. These exercise-induced cardiac modifications encompass physiological cardiac hypertrophy characterized by an increase in the internal dimensions of the left ventricle (LV) and a thickening of the LV wall. Exercise-induced cardiac hypertrophy is of clinical significance as molecular effectors such as insulin-like growth factor 1 (Igf1) that mediate beneficial cardiac growth are potential therapeutic targets for the treatment of maladaptive hypertrophy and heart failure [211,212]. Foryst-Ludwig et al. found that mice with adipocyte-specific ablation of ATGL exhibited attenuated exercise-induced cardiac hypertrophy, which is probably mediated by the lack of C16:1n7-palmitoleate actions in the heart. C16:1n7-palmitoleate can directly act on cardiomyocytes, promoting myocardial cell growth by inducing the phosphorylation of Akt kinase, a sign of an adaptive physiological hypertrophic response. The serum level of C16:1n7-palmitoleate was positively correlated with echocardiographic parameters of left ventricular hypertrophy in endurance athletes, indicating that C16:1n7-palmitoleate may play a similar role in the hearts of humans [213]. Based on the evidence above, exercise-induced lipolysis is important for physiological cardiac hypertrophy, which holds potential to improve heart function and to alleviate heart diseases (Fig. 7).

Promoting tissue repair and regeneration

Different types of injuries such as traumatic wounds, acute post-surgical wounds, and burns significantly impact both patients and society [147,215,215]. Successful wound healing entails a series of stages starting from inflammation and progressing through proliferation and reconstruction following initial haemostasis [216,217]. This process requires intricate coordination between resident and recruited cells [218]. Disorders in these stages can dis-

turb the precise equilibrium of cell types and molecules essential for proper wound healing thereby resulting in chronic wounds and fibrotic scarring [219]. Tissue repair involves coordinated communication among various cell types to restore damaged tissue. Adipocytes are now recognized as crucial niche cells within multiple tissues such as skin, bone marrow, and mammary glands [220,221]. Using high-resolution magnetic resonance imaging, Querleux et al. have delineated the three-dimensional structure of the tissues at the interface between the dermis and subcutaneous fat, as well as the fibrous septa within the subcutaneous layer. A distinct type of fat in the dermis has been identified and termed dermal white adipose tissue (dWAT), establishing it as a unique form of white adipose tissue [222,223]. Subsequently, mature adipocytes in dWAT were found to play a key role in skin repair. Valerie Horsley and colleagues demonstrated that dermal adipocytes are important in facilitating the efficient repair of both epithelial and dermal cells. Through genetic strategies that selectively ablated resident adipocytes in the skin, they observed compromised macrophage-mediated inflammation following injury. Furthermore, they found that lipolytic procedure was initiated in mature adipocytes of dWAT, which led to release of fatty acids into skin wounds before macrophage infiltration [224]. However, the repair progression would be delayed due to reduced fatty acid levels in wound sites and decreased numbers of inflammatory macrophages in mice with genetic depletion of *Pnpla2*. Additionally, using genetic lineage tracing of mature adipocytes in mouse wounds and employing single-cell RNA sequencing (scRNA-seq) combined with transcriptional profiling, they discovered that lipolysis also induces dermal adipocytes to dedifferentiate and generate diverse myofibroblasts that produce extracellular matrix (ECM) in the wound bed [225]. These findings underscore the critical role of adipocyte lipolysis in tissue repair, enabling mature adipocytes to influence skin inflammation and alter their fate to produce ECM for wound healing. In the early stage of tissue repairing, M1 macrophages in the wound site produce and release proinflammatory cytokines to clear damaged tissue from the wound through phagocytosis, while M2 macrophages are involved later in promoting migration and proliferation of fibroblasts, keratinocytes, and vascular endothelial cells by producing and releasing anti-inflammatory cytokines and growth factors. Exercise is found to be conducive to wound healing. In rodents, moderate-intensity exercise induced recruitment of M2 macrophages and increased TGF-β1 derived from M2 macrophages, which may be associated with enhanced angiogenesis and wound healing [226]. A systematic review summarized the therapeutic approach of whole-body vibration (WBV) exercise on wound healing, which suggests the beneficial effects of WBV exercise on wound healing [227]. Additionally, Goh et al. discussed that exercise training can improve the regulation of macrophage polarization, normalize the inflammatory process, and potentially improve wound healing in older individuals [228]. As mentioned before, lysosomal lipolysis facilitates polarization of M2 macrophages, so lipolysis may be the link between exercise and recruitment of M2 macrophages. Together, exercise-induced lipolysis may promote ECM formation and exert distinct effects on macrophages at different stages of tissue repair to facilitate wound healing (Fig. 8).

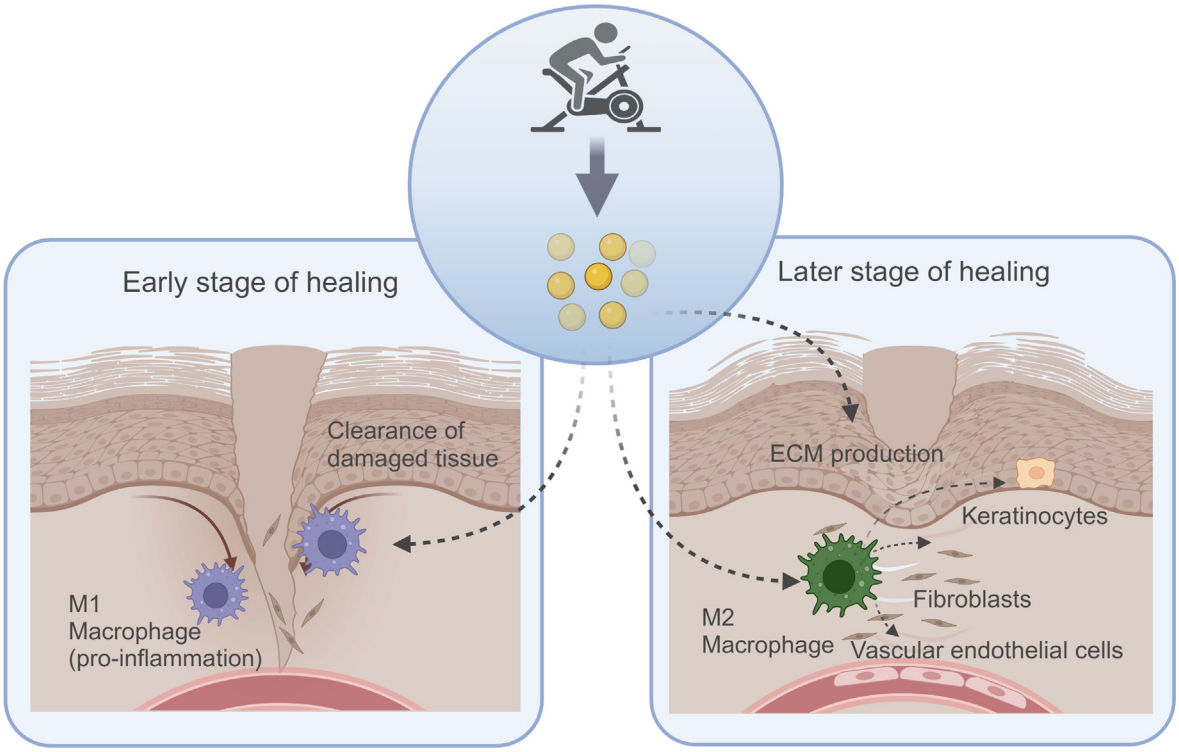

Fig. 8. The roles of exercise-induced lipolysis in promoting tissue repair and regeneration. Exercise-induced lipolysis may play diverse roles in different stages of wound healing. In the early stage of wound healing, exercise might cause catabolism of dermal white adipose tissue to facilitate M1 macrophage infiltration in the wound site and release proinflammatory cytokines to clear damaged tissue from the wound through phagocytosis. In the later stage of wound healing, exercise might stimulate dermal white adipose lipolysis to induce dermal adipocytes to dedifferentiate and to generate diverse myofibroblasts that produce extracellular matrix (ECM) in the wound bed. Moreover, exercise potentially enhance lipolysis to support M2 macrophage recruitment, which involves in promoting migration and proliferation of fibroblasts, keratinocytes, and vascular endothelial cells by producing and releasing anti-inflammatory cytokines and growth factors. The dashed lines indicate the potential effects await further investigation. The graph was created with biorender.com (agreement number: GC27LQNJI5).

Non-classical effects of key enzymes involved in exercise-induced lipolysis

In addition to its TG hydrolase activity, ATGL exhibits some other non-classical functions. The Barbara Kahn laboratory utilized lipidomics to compare the lipid profiles in mice with adipose-specific overexpression of Glut4 (AG4OX) to those in control wild-type mice, identifying a significant increase in a novel class of branched fatty acid esters of hydroxy fatty acids (FAHFAs) in AG4OX mice. Subsequent studies revealed that FAHFAs are evolutionarily conserved, with palmitic acid esters of hydroxy stearic acids (PAHSA) serving as a representative, capable of lowering blood glucose levels, promoting insulin secretion, and inhibiting the secretion of inflammatory factors in macrophages, thereby exhibiting anti-inflammatory properties and the effects of improving glycemic homeostasis [229]. It has been found that ATGL can synthesize FAHFAs by utilizing transacylation reactions to esterify hydroxy fatty acids (HFA) with fatty acids derived from TG or DG. In vivo experiments confirmed that overexpression of ATGL enhances FAHFA synthesis, while suppression or knockout of ATGL reduces the levels of FAHFAs in mice. This highlights the important biological function of ATGL-mediated transacylation activity beyond its lipase activity, establishing ATGL as a key catalytic enzyme in the biosynthesis of FAHFAs [230]. What is more, a recent study confirmed that ATGL functions as a negative regulator for lipopolysaccharide (LPS)-mediated inflammation in cells. The transfection of LPS into cells triggers the activation of the noncanonical inflammasome, a process facilitated by mouse caspase-11 or its human caspase-4. Upon activation, caspase-11/caspase-4 mediate the cleavage of gasdermin D (GSDMD), leading to the formation of pores in the cell membrane. This pore formation initiates pyroptosis, a form of inflammatory cell death characterized by the release of pro-inflammatory cytokines and cellular contents. Cells deficient in adipose triglyceride lipase (ATGL) demonstrate augmented immune reactions upon encountering intracellular LPS, characterized by an increased secretion of interleukin-1β, reduced cellular viability, and heightened cytotoxicity. ATGL-knockout mice exhibited aggravated responses to endotoxin challenges, underscoring the role of ATGL in controlling immune sensitivity to bacterial stimuli. Further investigation revealed that ATGL can hydrolyze the lipid A component of LPS. Through mass spectrometry, it was demonstrated that ATGL catalyzes the degradation of LPS side chains. Then, the role of ATGL in regulating inflammation was also assessed in an LPS-induced sepsis mouse model. It was found that the absence of ATGL exacerbated the toxic response to LPS, resulting in decreased survival rates and increased serum levels of the inflammatory cytokine IL-1β. Conversely, adenoviral-induced overexpression of ATGL protected mice from severe inflammation and significantly improved the survival rates [231]. In this case, the effects of exercise-induced lipolysis may extend beyond the process of lipolysis itself. The lipolytic enzymes upregulated in response to exercise may also exert non-classical functions that further facilitate the role of exercise in the maintenance of metabolic and inflammatory homeostasis, thereby delaying the progression of some diseases. Further studies are needed to corroborate the above hypothesis.

Advices for exercise programs to promote lipolysis

Increased lipolysis could be primarily attributed to the elevated plasma concentrations of pro-lipolytic hormones during extended periods of exercise and the secretion of catecholamines showed an increase that correlates with the duration of exercise [126]. Regarding the type of exercise, analysis of untargeted metabolomics profiles of plasma collected from human subjects who performed endurance or resistance exercise revealed that glycerol (an indicator of lipolysis) was one of the dominant metabolites that sharply increased in the plasma immediately after endurance exercise, suggesting the priority of endurance exercise in promoting lipolysis post-exercise [232]. In addition, the efficiency of lipolysis in WAT was gradually elevated by exercise with low to moderate intensities, but decreased after high intensity exercise [126]. Similar outcome was evidenced in the condition of exercise-induced intramuscular triacylglycerol hydrolysis. During moderate exercise, phosphorylation of HSL, ATGL and perilipin collectively enhanced the lipolytic rates in skeletal muscle, while at higher power outputs, AMPK phosphorylates additional sites on HSL, which inhibits the typically lipolytic activity of HSL to blunt lipolysis [233]. Based on the evidence presented above, endurance exercise of longer duration and low to moderate intensity appears to be an optimal option for activating the lipolytic pathways and achieving the lipolytic effect. In fact, in most pathological conditions, high-intensity exercise protocols have not been thoroughly investigated due to potential risks, while the effects of relatively lower-intensity exercise are gradually being recognized. Current exercise prescriptions for diseases such as heart failure proposed that patients with stable heart failure should initially engage in aerobic exercise for 45–60 min at a moderate exercise intensity 3–5 days per week [234,235]. Such exercise approach helps to produce a sufficient stimulus for promoting beneficial physiological adaptations including the stimulation of lipolysis to bring about the improvements in exercise capacity, symptoms of diseases and prognosis. Notably, due to differences in pathophysiology, comorbidities, medications, and prior exercise experience, patients may differ in their ability to tolerate the exercise programs even at low to moderate intensity, thus more precise and individualized exercise prescriptions are required for vulnerable populations, such as the elderly or those with chronic conditions.

Conclusion

Overall, exercise has been well-established as an effective intervention that influences various physiological processes and exerts different effects on curbing the onset and progression of diseases. Nonetheless, molecular targets of exercise effects are not well defined, which limits the maximization of these benefits. Lipolysis is an important physiological process and is well-characterized to be regulated by exercise. Emerging researches underscore the role of exercise in promoting lipolysis across various tissues. Factors like cytokines, lipolytic enzymes, co-factors of lipase, miRNAs, lncRNAs, hormones, and β-adrenergic receptors in canonical lipolysis pathway and lipophagy-induced acid hydrolysis of lipid are implicated in facilitating this process. Exercise-mediated lipolysis plays important roles in multiple physiological and pathological processes, including regulating immune system, facilitating bone formation, meliorating MASLD, fighting against obesity, inhibiting cancer development, improving cardiac function, and promoting tissue repair and regeneration. But how exercise-induced lipolysis contributes to the above processes is not fully understood. In-depth understanding of the role and mechanism of lipolysis in exercise-mediated beneficial effects would pave the way for formulating safe and effective exercise programs for the promotion of health and the control of diseases. Furthermore, exercise-induced expression and activation of lipolytic effectors may encompass more than just the lipolytic process. Upregulated key enzyme during the process of exercise-induced lipolysis may also yield other benefits via their non-classical effects, which deserves further investigation. Thus, as one of the critical procedures in fat metabolism to increase the lipid flux, lipolysis could be a break-in point to better understand the influence of exercise on health improvement.

Lipolysis stimulation in response to exercise may play important parts in alleviating various pathological processes. We have summarized the direct roles of exercise-promoted lipolysis in enhancing the production of common lymphoid progenitors (CLPs), facilitating osteoblast differentiation, improving obesity-related metabolic disorders, and alleviating fatty liver diseases. Additionally, some indirect evidence suggests that exercise-mediated lipolysis may also contribute to the improvement of some diseases, which sheds light on the research interest in the future. There are some research gaps that warrant fully investigation in the future, including whether exercise can straightly regulate the expression of Cdo1, IRE1α, and PAK4 in adipose tissue to bring about the benefits mediated by lipolysis; the exact role of lysosomal lipophagy-induced FAO in the regulation of immune system by exercise; whether exercise can promote the release of PUFAs and activate hepatic Sirt1 to alleviate MASLD by inducing lipolysis; the direct contribution of lipolysis to exercise-mediated tumor cell apoptosis and inhibition of tumor growth; and whether exercise can improve cardiac function and facilitate tissue repair by activating lipolysis.

Moreover, lipolysis is most abundant in adipose tissues, but it can also occur in other tissues. The mechanisms described in this review may apply to not only in adipose tissue, but also in other tissues. Besides, it is promising to demonstrate whether the heterogeneity, location and composition of adipose tissue determine the variety of lipolytic response to physical exercise intervention, which helps to unveil a more precise landscape of exercise effects.

CRediT authorship contribution statement

The search and collection of literatures was performed by J.-Y.Z. and L.G. The first draft of the manuscript was written by J.-Y.Z. and L.G. co-wrote the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethics requirement

This review article has fully complied with research ethics.

Declaration of competing interest

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

Acknowledgments

This work was supported by The Program for Overseas High-level talents at Shanghai Institutions of Higher Learning (TP2022100 to L.G.), the National Natural Science Foundation of China (No. 32070751 and 31871435 to L.G).

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