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Exercise Training Activates AMPK to Improve Metabolic-Associated Fatty Liver Disease: Research Progress

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Abstract

Metabolic-associated fatty liver disease (MAFLD) is a metabolic disorder characterized by excessive hepatic lipid accumulation and is closely associated with insulin resistance, chronic low-grade inflammation, and mitochondrial dysfunction. Exercise training is a key non-pharmacological strategy that improves the hepatic metabolic milieu and may slow disease progression, yet the underlying molecular mechanisms remain incompletely clarified. This review aims to synthesize, from the perspective of energy metabolism regulation, the potential mechanisms by which exercise ameliorates MAFLD through activation of AMP-activated protein kinase (AMPK), thereby providing a theoretical basis for optimizing exercise-based interventions. A literature review approach was adopted. Systematic searches were conducted in major English-language academic databases, including Web of Science and PubMed, using keywords related to exercise training, MAFLD, and AMPK. Representative recent basic and clinical studies were screened and integrated to summarize relevant signaling pathways and physiological outcomes. The evidence indicates that exercise-induced AMPK activation suppresses de novo lipogenesis while promoting fatty acid oxidation, thereby reducing intrahepatic lipid deposition. Exercise may also improve mitochondrial function and enhance mitophagy, lowering oxidative stress and modulating inflammation-related signaling to attenuate chronic hepatic inflammation. Collectively, AMPK serves as a central regulatory node linking exercise stimuli to coordinated restoration of metabolic and inflammatory homeostasis in MAFLD. Future well-designed human studies and multidimensional evidence are warranted to clarify the pathway-specific effects of different exercise prescription components on AMPK signaling networks.

Keywords: *AMPK, Exercise, Metabolic-Associated Fatty Liver Disease*

A. Introduction

Metabolic-associated fatty liver disease (MAFLD), previously termed non-alcoholic fatty liver disease (NAFLD), was renamed because it offers more concise and explicit diagnostic criteria, more diversified diagnostic approaches, and better reflects the metabolic nature and severity of the disease(Eslam, Sanyal, et al., 2020; Gofton et al., 2023). An international expert panel proposed the nomenclature change in 2020 (Eslam, Newsome, et al., 2020), and the Chinese Society of Hepatology subsequently adopted the term after a formal vote in 2021 (Nan et al., 2021). Although several international liver associations proposed a new definition in 2023, namely metabolic dysfunction-associated steatotic liver disease (MASLD)(Rinella et al., 2023), which aims to encompass the full spectrum of hepatic steatosis and to some extent avoid disease-related stigma, it still lacks broad applicability and wide recognition(Alboraie et al., n.d.; Chen,

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2023). Moreover, multiple studies have shown that the MAFLD diagnostic criteria more accurately identify clinically relevant conditions such as hepatic fibrosis than the MASLD criteria(Pan, Al-Busafi, et al., 2024; Pan, Derbala, et al., 2024); therefore, the validity and practicality of this new definition remain to be further evaluated. Notably, there is substantial overlap between NAFLD and MAFLD, with an overall very high concordance (Cohen's kappa = 0.92)(Targher, 2020), indicating that NAFLD-related data can largely be regarded as applicable to MAFLD. Before domestic and international consensus statements were released, most studies focused on NAFLD; accordingly, many NAFLD-related studies are cited in this review.

MAFLD is the most prevalent chronic liver disease worldwide, affecting approximately one-third of the global population, and its prevalence continues to increase, posing serious threats to human health and imposing a substantial socioeconomic burden(Chan et al., 2022). It is projected that by 2030, the number of individuals with NAFLD in China will exceed 300 million, representing the fastest growth rate globally, and MAFLD will become a major challenge for the control and prevention of chronic diseases(Estes et al., 2018). MAFLD comprises a spectrum of liver disorders ranging from early simple steatosis to intermediate non-alcoholic steatohepatitis (NASH). Without timely treatment, NASH may progress to liver fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC). Therefore, timely intervention at the early stage of MAFLD to reduce hepatic lipid accumulation and reverse disease progression remains a major challenge for public health. At present, apart from lifestyle and dietary modification, pharmacological therapy, and bariatric surgery in selected cases, no effective medical intervention has been identified that can completely reverse MAFLD (Pafili & Roden, 2021).

From a lifestyle modification perspective, maintaining regular physical activity can effectively prevent the development of MAFLD, slow its progression, reduce liver fat content, and alleviate hepatic steatosis and liver aging (Thyfault & Rector, 2020). Exercise is an effective way to increase whole-body energy expenditure. It promotes phosphorylation of downstream substrates by activating a key energy-regulating enzyme, AMP-activated protein kinase (AMPK), thereby modulating energy metabolism, inhibiting hepatic lipid accumulation, and attenuating hepatic steatosis. These effects collectively contribute to the improvement and potential reversal of MAFLD. Therefore, with AMPK as the central focus, this review summarizes the pathophysiological mechanisms of MAFLD, exercise-induced activation of AMPK, and the mechanisms by which exercise ameliorates MAFLD via AMPK signaling.

B. Methods

This study employed a narrative literature review design with a mechanistic focus on energy metabolism regulation. The review was designed to synthesize and critically analyze existing basic and clinical research on the role of exercise training in ameliorating metabolic-associated fatty liver disease (MAFLD) by activating AMP-activated protein kinase (AMPK). By integrating findings from molecular, physiological, and clinical perspectives, this approach aimed to construct a comprehensive theoretical framework explaining how exercise-induced AMPK signaling contributes to improvements in hepatic lipid metabolism, mitochondrial function, and inflammatory regulation in MAFLD.

The research procedure consisted of several systematic stages. First, the research scope and conceptual framework were defined, emphasizing the interaction between exercise interventions, AMPK activation, and MAFLD-related metabolic pathways. Second, a structured literature search was conducted to identify relevant studies. Third, retrieved articles were

screened according to predefined inclusion criteria, focusing on relevance, methodological rigor, and their contribution to understanding AMPK-mediated mechanisms. Finally, selected studies were organized and synthesized to identify consistent patterns, key mechanisms, and research gaps related to exercise-induced metabolic regulation in MAFLD.

Data were collected through systematic searches of major international academic databases, including Web of Science and PubMed. Keywords and combinations of terms related to "exercise training," "metabolic-associated fatty liver disease," and "AMP-activated protein kinase" were used to ensure comprehensive coverage of the topic. Priority was given to recent peer-reviewed basic and clinical studies that examined molecular signaling pathways, metabolic outcomes, and physiological responses to exercise in the context of MAFLD. Relevant information extracted included study design, exercise modalities, AMPK-related signaling mechanisms, and reported hepatic metabolic outcomes.

Data analysis was conducted using a qualitative synthesis approach. The selected studies were analyzed thematically to identify recurring mechanisms and signaling pathways associated with exercise-induced AMPK activation. Comparative analysis was applied to integrate findings across different experimental models and clinical populations. The synthesized evidence was then interpreted to elucidate how AMPK functions as a central regulatory node linking exercise stimuli to reduced hepatic lipid accumulation, improved mitochondrial function, enhanced fatty acid oxidation, and modulation of inflammation in MAFLD. This integrative analysis also highlighted limitations in the existing evidence and informed recommendations for future multidimensional, human-based research.

C. Results and Discussion

Pathophysiological Mechanisms of MAFLD

MAFLD is a multifactorial metabolic disease driven by a combination of genetic and environmental factors, insulin resistance (IR), oxidative stress, and inflammation. A key pathological feature is that IR increases the influx of free fatty acids into the liver and promotes triglyceride (TG) breakdown in adipose tissue, leading to excessive lipid accumulation through the actions of triglyceride lipase and hormone-sensitive lipase(Banerjee et al., 2024; Tarantino et al., 2010). Disease progression typically begins with hepatic lipid deposition, corresponding to the stage of simple steatosis, which is primarily attributable to insulin resistance and disordered lipid metabolism. As excessive lipid accumulation triggers oxidative stress and inflammatory responses, the disease can progress to non-alcoholic steatohepatitis (NASH). Persistent inflammation further activates hepatic stellate cells, driving the development of liver fibrosis and ultimately cirrhosis, in which extensive fibrotic tissue replaces normal hepatic parenchyma, resulting in severe impairment of liver structure and function. On the basis of cirrhosis, ongoing hepatocellular injury and compensatory regeneration increase the risk of hepatocellular carcinoma (HCC)(Nassir, 2022).

Beyond liver-related morbidity and mortality, MAFLD is also strongly associated with a high prevalence of metabolic syndrome, type 2 diabetes mellitus, and atherosclerotic cardiovascular disease. The pathogenesis of MAFLD is complex. In the "two-hit" hypothesis proposed by Day and colleagues (Day & James, 1998), insulin resistance is regarded as the first hit, followed by oxidative stress, lipid peroxidation, and mitochondrial dysfunction as subsequent hits. With advances in research, it has become evident that this hypothesis cannot fully explain the diverse molecular and metabolic alterations observed during MAFLD development. Accordingly, the "multiple parallel hits" hypothesis proposed by Tilg and colleagues (Tilg et al., 2021) emphasizes the multifactorial nature of MAFLD. Factors, including

but not limited to insulin resistance, dysregulated lipid metabolism, oxidative stress, inflammation, and genetic susceptibility, may act in parallel or synergistically at different stages to drive disease evolution. Although substantial progress has been made in recent years, the precise roles and interrelationships of these factors at the cellular and molecular levels remain incompletely understood and warrant further investigation.

Effects of Exercise Training on MAFLD

Physical inactivity is a major contributor to MAFLD. Studies have shown that increased sedentary time significantly elevates the prevalence of MAFLD, and both pediatric and adult patients with MAFLD commonly exhibit low levels of physical activity (Zhang et al., 2023). Regular exercise training, however, has demonstrated beneficial effects in the prevention and management of MAFLD. These benefits are partly attributable to the anti-inflammatory properties of exercise, which can reduce systemic and hepatic inflammation, thereby slowing the progression of liver injury and fibrosis. In addition, exercise training can modulate the gut microbiota, improve metabolic health, and mitigate hepatic inflammation and injury associated with gut dysbiosis. Moreover, exercise enhances lipid metabolism and reduces hepatic fat accumulation, thereby lowering the risk of hepatocellular steatosis. It may also promote autophagy of visceral adipose tissue, contributing to weight reduction and, consequently, decreased liver fat content. Therefore, exercise training should be considered a core component of comprehensive MAFLD management to achieve more durable, holistic therapeutic benefits. Research on optimal exercise modalities, individualized prescriptions, and the underlying mechanistic pathways remains ongoing.

MAFLD is closely associated with obesity. Evidence indicates that, compared with individuals of normal weight, those with obesity have a 3.5-fold higher risk of MAFLD (Polyzos et al., 2019). For each 1-kg increase in body weight, the prevalence of MAFLD increases by approximately 3%, and individuals who gain more than 20 kg have a fourfold higher prevalence of MAFLD compared with those whose weight remains stable(Wang et al., 2023). Mechanistically, obesity-induced insulin resistance contributes to hepatic steatosis, lipotoxicity, inflammation, and fibrosis. Exercise training enhances whole-body and hepatic fat oxidation efficiency, enabling more fatty acids to be metabolized as energy and thereby reducing lipid accumulation in both the body and the liver. Regular moderate- and high-intensity exercise can also markedly reduce visceral adiposity, which is associated with a lower risk of MAFLD. By increasing energy expenditure and elevating basal metabolic rate, exercise effectively reduces body weight; sustained exercise further helps individuals maintain a healthy weight and prevent weight regain, thereby reducing the long-term incidence and progression of fatty liver disease. With respect to insulin metabolism, exercise training—particularly aerobic and resistance exercise—can improve insulin signaling, substantially reduce insulin resistance, enhance insulin sensitivity in skeletal muscle, improve whole-body glucose metabolism, and lower blood glucose levels. Overall, by reducing fat accumulation, lowering body weight, and improving insulin sensitivity, exercise training can significantly decrease the risk of MAFLD and improve clinical outcomes. Accordingly, exercise represents an essential strategy for MAFLD prevention and treatment, and its multifaceted benefits play a pivotal role in improving patient health status and preventing disease progression.

Notably, studies have also shown that even in the absence of substantial weight loss, engaging in 150 minutes per week of moderate- to vigorous-intensity aerobic exercise can significantly reduce triglycerides, low-density lipoprotein cholesterol, aspartate aminotransferase, alanine aminotransferase, and hepatic fat content(Babu et al., 2021; Stine et al., 2023). Therefore, regardless of whether body weight decreases, exercise training can effectively reduce hepatic fat accumulation. The mechanisms underlying these improvements

likely involve multiple coordinated effects, including reductions in intrahepatic lipid content, increases in fatty acid oxidation, induction of hepatoprotective autophagy, attenuation of oxidative stress and inflammation, enhancement of insulin sensitivity, and modulation of the gut microbiota. Exercise may also further promote liver health by improving systemic metabolic function and cardiovascular health.

Potential Mechanisms by Which Exercise-Induced AMPK Activation Improves MAFLD

Enhancement of AMPK Activity by Exercise Training

AMPK is a cellular energy-sensing enzyme widely expressed in mammalian tissues, including the liver, skeletal muscle, and brain. As a key metabolic regulator, AMPK senses and maintains energy balance, inhibits fatty acid and cholesterol synthesis, promotes glucose uptake and fatty acid (FA) oxidation, and facilitates mitochondrial biogenesis and cellular autophagy. AMPK is a heterotrimeric complex composed of a catalytic α subunit and two regulatory subunits, β and γ. The γ subunit contains four cystathionine β-synthase (CBS) domains that form two Bateman modules responsible for binding adenine nucleotides (ATP, ADP, and AMP); AMPK activity is modulated through the binding of AMP, ADP, and ATP.

Under energy-replete conditions, ATP occupies the binding sites on the γ subunit, and the Thr-172 residue on the α subunit remains unphosphorylated; AMPK therefore remains inactive. During exercise, ATP is substantially consumed, and AMP and ADP competitively replace ATP at the γ subunit, inducing a conformational change that exposes Thr-172 on the α subunit for phosphorylation, thereby activating AMPK. The extent of AMPK activation varies with exercise intensity. Evidence indicates that both prolonged low-intensity exercise and moderate-intensity exercise performed at approximately 60% of maximal oxygen uptake can significantly increase AMPK activity(Wojtaszewski et al., 2002). Once activated, AMPK phosphorylates multiple downstream targets, markedly enhancing ATP production, improving the efficiency of glucose uptake and utilization, promoting the translocation of glucose transporter type 4 (GLUT4), thereby improving energy supply in skeletal muscle and the heart, and enhancing insulin sensitivity. In addition, activated AMPK promotes FA oxidation and reduces lipid accumulation in the liver and throughout the body. In adipose tissue, AMPK facilitates lipolysis and induces browning of white adipose tissue, increasing energy expenditure. In skeletal muscle, AMPK improves metabolic capacity and fatigue resistance by regulating mitochondrial biogenesis and mitochondrial function(Spaulding & Yan, 2022; Steinberg & Hardie, 2023).

Effects of Activated AMPK on Hepatic Lipid Metabolism

Following exercise-induced activation, AMPK acts through multiple mechanisms—including regulating signaling pathways and key enzymes involved in lipid metabolism—to suppress hepatic lipid synthesis and accumulation while promoting FA oxidation, thereby contributing to the amelioration of MAFLD.

Inhibition of Hepatic Lipid Synthesis and Accumulation

De novo lipogenesis (DNL) is a major pathway for hepatic lipid synthesis, particularly for triglyceride (TG) production. DNL primarily uses carbohydrates as substrates and generates long-chain fatty acids through sequential reactions involving acetyl-CoA and malonyl-CoA, the latter produced by acetyl-CoA carboxylase (ACC). DNL has been reported to be approximately threefold higher in patients with MAFLD than in healthy individuals. In an in vitro model simulating DNL activation as observed in MAFLD, TG accumulation on day 7 increased by 476.8% ± 17.3% compared with day 1(Kim et al., 2023). These findings suggest that enhanced DNL contributes, at least in part, to MAFLD development.

Activated AMPK can inhibit ACC activity by phosphorylating ACC, thereby reducing malonyl-CoA production, attenuating DNL, and decreasing hepatic lipid synthesis. An animal study showed that during the recovery period, 2 hours after acute exercise, increased AMPK activity was accompanied by elevated ACC phosphorylation(Diniz et al., 2019).

In parallel, insulin enhances DNL by promoting nuclear translocation of sterol regulatory element-binding protein-1c (SREBP-1c), a major transcription factor driving DNL, thereby increasing SREBP-1c activity and upregulating lipogenic gene expression, which in turn promotes fatty acid and TG synthesis(Belew & Jones, 2022). By contrast, exercise-activated AMPK increases ACC phosphorylation and phosphorylates SREBP-1c at Ser372, thereby suppressing SREBP-1c maturation and activity, preventing its entry into the nucleus, and reducing its capacity to bind DNA and initiate transcription of lipogenic genes. Collectively, these findings indicate that exercise-induced AMPK activation suppresses hepatic lipid synthesis via the AMPK/ACC axis.

In addition to inhibiting lipogenesis by directly or indirectly reducing ACC activity, activated AMPK can exert similar effects by activating silent information regulator 1 (SIRT1). SIRT1 is a NAD+-dependent histone deacetylase that removes acetyl groups from multiple proteins, thereby modulating their functions. This mechanism plays important roles in cellular metabolism, stress responses, and gene expression. SIRT1 suppresses hepatic lipid synthesis primarily through deacetylation of two key targets: first, by deacetylating SREBP-1c, which impairs its ability to bind promoter regions of DNA and reduces the expression of lipogenic genes; and second, by deacetylating liver kinase B1 (LKB1), enabling its activation and subsequent phosphorylation of AMPKα at Thr-172, thereby activating AMPK and reducing lipid synthesis.SIRT1 activity is also dependent on the intracellular NAD+/NADH ratio. When NAD+ levels increase, SIRT1 activity is enhanced. AMPK promotes NAD+ production by upregulating the expression and activity of nicotinamide phosphoribosyltransferase (NAMPT), a rate-limiting enzyme in the NAD+ salvage pathway. Increased NAMPT activity generates substantial amounts of NAD+, thereby indirectly enhancing SIRT1 activity(Jin et al., 2023; Tian et al., 2024). In other pathways, AMPK can also reduce ATP consumption by inhibiting gluconeogenesis and lipogenesis, thereby improving cellular energy status and indirectly increasing the NAD+/NADH ratio and enhancing SIRT1 activity. Collectively, these studies suggest that AMPK and SIRT1 form a positive feedback loop through mutual activation, jointly maintaining energy balance and metabolic homeostasis to suppress hepatic lipid synthesis. Thus, exercise-induced AMPK activation may ameliorate MAFLD through the AMPK/SIRT1/SREBP-1c pathway.

Promotion of Fatty Acid Oxidation

Reduced FA oxidation and dysregulation of the oxidation process are important contributors to MAFLD progression, and enhancing FA oxidation is a key strategy to improve MAFLD (Fang et al., 2022). Carnitine palmitoyltransferase 1 (CPT1) is a pivotal enzyme in fatty acid metabolism that catalyzes the first step of mitochondrial β-oxidation. Elevated malonyl-CoA concentrations inhibit CPT1 activity, thereby reducing FA oxidation and promoting lipid synthesis. Because AMPK activation inhibits ACC and decreases malonyl-CoA production, reducing malonyl-CoA concentration can relieve CPT1 inhibition and facilitate the entry of fatty acids into mitochondria for oxidation. In addition, peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) plays an important role in regulating mitochondrial gene expression and function. In a 12-week high-intensity running intervention, activation of the AMPK–SIRT1–PGC-1α signaling pathway regulated fatty acid metabolism-related genes, including CPT1, thereby promoting mitochondrial biogenesis, FA oxidation, and energy expenditure(Khalafi et al., 2020). Exercise-activated AMPK can induce NAD+-dependent SIRT1-mediated

deacetylation of PGC-1α, enhancing lipid oxidation rates and energy metabolism. Moreover, activated AMPK can directly phosphorylate PGC-1α and increase its expression(Jäger et al., 2007). Both mechanisms act synergistically to upregulate CPT1 expression and promote FA oxidation.

Effects of Activated AMPK on Inflammation

Inflammation plays a critical role in the progression of MAFLD. Excessive hepatic accumulation of TG and free fatty acids (FFA) can trigger oxidative stress and endoplasmic reticulum stress, leading to mitochondrial dysfunction and excessive production of reactive oxygen species (ROS). These stress responses activate pro-inflammatory signaling pathways, such as nuclear factor κB (NF-κB) and the NLRP3 inflammasome, thereby stimulating the release of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β. Meanwhile, immune cells such as macrophages and neutrophils are recruited to infiltrate the liver, thereby establishing a chronic low-grade inflammatory milieu. This inflammatory response not only directly induces hepatocyte apoptosis and necrosis but also promotes hepatic stellate cell (HSC) activation, leading to collagen deposition and accelerating the development of liver fibrosis. AMPK also exerts multiple effects on the regulation of inflammation (Cacicedo et al., 2004). Through direct and indirect mechanisms, AMPK can attenuate inflammation, reduce the generation of inflammatory mediators and oxidative stress-related products, and suppress the low-grade chronic inflammation induced by hepatocellular lipotoxicity and insulin resistance. These multilayered regulatory actions not only alleviate local hepatic inflammation but may also help improve systemic metabolic disturbances, providing potential therapeutic targets for MAFLD.

Suppression of Inflammatory Responses

NF-κB is a family of transcription factors widely expressed in eukaryotic cells and regulates the expression of multiple genes involved in inflammation and cell proliferation. Under resting conditions, NF-κB typically exists in an inactive form in the cytoplasm, bound to its inhibitor, inhibitor of κB (IκB). Upon external stimulation, IκB kinase (IKK) is activated and phosphorylates IκB, leading to IκB degradation and release of NF-κB. NF-κB subunits subsequently translocate to the nucleus, bind specific DNA sequences, and initiate the transcription of pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β.

After 8 weeks of moderate-intensity aerobic exercise, AMPK in MAFLD mice suppressed excessive inflammatory cytokine release by inhibiting NF-κB activity(Diniz et al., 2021). Specifically, AMPK phosphorylates IKK, thereby preventing NF-κB nuclear translocation and reducing the expression of TNF-α, IL-6, IL-1β, and other pro-inflammatory cytokines. In addition, AMPK reduces ROS accumulation by optimizing mitochondrial dynamics and initiating mitophagy, thereby attenuating NF-κB-mediated inflammatory signaling. A study reported that following an 8-week swimming intervention, AMPK levels in rats exposed to nicotine stress recovered markedly toward normal, and the ratio of phosphorylated NF-κB to total NF-κB significantly decreased to 1.01(Lin et al., 2020).

Furthermore, there is antagonistic crosstalk between SIRT1 and NF-κB. Activated SIRT1 directly suppresses NF-κB activity by deacetylating the p65 subunit of NF-κB, and it can also inhibit IκB degradation and reduce TNF-α and IL-6 expression, thereby maintaining NF-κB in an inactive cytoplasmic state and indirectly suppressing its activity (Yang et al., 2022). Accordingly, exercise-induced AMPK activation may suppress NF-κB signaling and alleviate hepatic inflammation through IKK phosphorylation and/or the AMPK/SIRT1/NF-κB pathway.

In addition, studies have indicated that increased SIRT1 and AMPK activity can synergistically inhibit NLRP3 inflammasome activation. Together, they regulate both NF-κB

and NLRP3 pathways, reduce the secretion of pro-inflammatory mediators by M1 macrophages, and promote polarization toward the M2 phenotype, which exerts anti-inflammatory and tissue-repair functions.

Enhancement of Hepatocellular Mitochondrial Function and Mitophagy

Plasma FFA is a major contributor to excessive hepatic lipid accumulation in patients with NAFLD. Mitochondrial function in adipose tissue is crucial for regulating FFA release into the circulation, and maintenance of mitochondrial function relies on the dynamic balance between mitochondrial biogenesis and degradation. Studies have shown that 8 weeks of moderate-intensity exercise, combined with controlled intake of fat and other nutrients, significantly increased AMPK activity and PGC-1α levels, an important regulator of mitochondrial biogenesis, in mice. A study in a MAFLD zebrafish model likewise reported that, compared with controls, high-fat diet–fed MAFLD zebrafish that performed 4 hours of swimming daily for 12 weeks exhibited more stable hepatic mitochondrial quality and function, whereas AMPK activity and PGC-1α expression were significantly reduced in the control group (Zou et al., 2023).

ROS is a major driver of NLRP3 inflammasome activation. Mitochondrial dysfunction leads to excessive ROS production, thereby promoting oxidative stress and inflammation. Conversely, AMPK is a key regulator of both ROS generation and clearance. AMPK activation can reduce ROS accumulation under hyperglycemic or metabolic stress conditions by promoting the expression of antioxidant enzymes. Experimental evidence shows that in mice subjected to 12 weeks of aerobic exercise, activated AMPK markedly reduced ROS levels(Liu et al., 2023). Moderate exercise can trigger antioxidant responses while increasing ROS production, thereby maintaining a dynamic balance. However, excessively high-intensity or prolonged exercise may result in ROS generation exceeding cellular antioxidant capacity, leading to oxidative stress; in the absence of AMPK activation, ROS levels may increase from a baseline of 100 to 240 (Craige et al., 2024).

In the context of mitophagy, AMPK directly phosphorylates the autophagy-initiating kinase Unc-51-like autophagy activating kinase 1 (ULK1) at specific sites (Ser555), thereby activating ULK1 and initiating mitophagy. After aerobic exercise, AMPK levels increased by approximately twofold, and ULK1 phosphorylation increased synchronously by approximately 1.8-fold(Drake et al., 2021). In a high-fat diet model, AMPK activation increased the protein expression of PTEN-induced putative kinase 1 (PINK1) and Parkinson protein 2, E3 ubiquitin protein ligase (PARKIN) by approximately 1.8-fold and 2.1-fold, respectively, promoting stabilization of PINK1 accumulation on the outer mitochondrial membrane and further recruitment of PARKIN to damaged mitochondria, thereby tagging mitochondria for autophagic degradation. After exercise, phosphorylation of dynamin-related protein 1 (DRP1) increased by approximately 1.6-fold. AMPK promotes selective mitochondrial fission by phosphorylating DRP1, facilitating the segregation of damaged mitochondrial components and thereby enhancing mitophagy efficiency. Concurrently, the ratio of the autophagy marker LC3-II to LC3-I increased by approximately twofold(Liu et al., 2023). Therefore, exercise-induced AMPK activation may improve mitochondrial function in hepatocytes and promote mitophagy via multiple pathways, thereby attenuating MAFLD progression.

D. Conclusion

This review focuses on the key pathological processes of metabolic-associated fatty liver disease (MAFLD) and systematically synthesizes current evidence on how exercise training influences disease progression through an AMPK-centered metabolic regulatory network. Collectively, the available data indicate that AMPK serves as a pivotal hub in exercise-mediated

improvements in MAFLD. By suppressing de novo lipogenesis and promoting fatty acid oxidation, AMPK reduces intrahepatic lipid accumulation and the lipotoxic burden, thereby alleviating hepatic steatosis at its metabolic source and improving insulin resistance.

Beyond lipid metabolism, exercise-induced AMPK activation may couple with mitochondrial quality-control pathways to promote mitochondrial biogenesis and mitophagy, enhance energetic efficiency, and attenuate oxidative stress, thereby weakening inflammation amplification and the risk of fibrosis progression driven by mitochondrial dysfunction. In parallel, AMPK exerts important negative regulatory effects on inflammatory signaling. Current studies suggest that exercise-activated AMPK can inhibit NF-κB signaling and the expression of downstream pro-inflammatory mediators, and can act synergistically with energy-sensing factors such as SIRT1 to reduce chronic low-grade hepatic inflammation, establishing a dual improvement pathway targeting both metabolic and immune homeostasis. Overall, AMPK can be regarded as a key molecular node linking exercise stimuli to hepatic metabolic restoration, providing a clear mechanistic rationale for optimizing exercise prescriptions and developing targeted intervention strategies.

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