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Mini Review

Lipid Metabolism and Mitochondrial Biogenesis in Septic Liver – A Mini Review Focused on PGC-1α expression

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Abstract

Decreased fatty acid (FA) oxidation and oxidative phosphorylation are observed in many tissues and organs during sepsis. The suppression of catabolism appears to lead to an insufficient supply of energy and is associated with multiple organ failure. In septic models that utilize endotoxemia or live bacteria, FA oxidation is generally suppressed. Furthermore, peroxisome proliferator-activated receptor gamma-coactivator 1 alpha (PGC-1α), which induces mitochondrial biogenesis and promotes FA oxidation, is typically downregulated. However, despite similar experimental settings, increased mRNA expression of PGC-1α has been found in some studies, implying the restoration of mitochondrial functions. Such finding might indicate that PGC-1α gene expression can be rapidly controlled by subtle differences in the dose and time course of septic insult. In this review, we aimed to discuss liver and hepatocyte studies that assessed PGC-1α expression. Although the cause-and-effect relationship between decreased mitochondrial function and multi-organ failure is still debatable, recent evidence favors the view that the overexpression of PGC-1α can promote the restoration of the mitochondria following sepsis-induced damage.

Introduction

In sepsis, an excessive level of systemic inflammation caused by infection often leads to progression to multi-organ dysfunction. This organ dysfunction is characterized by decreased oxidative phosphorylation and catabolism, including fatty acid (FA) oxidation and the down regulation of enzymes in the tricarboxylic acid (TCA) cycle. Decreased mitochondrial functions (mitochondrial dysfunction) must be assessed as such dysfunctions are mainly observed in individuals who do not survive septic shock, compared to survivors or controls [1].

Exaggerated inflammation affects the mitochondria in the following ways [2]: it induces tissue hypoxia, which results in insufficient production of ATP; it increases nitric oxide (NO), reactive oxygen species (ROS), and other small reactive molecules that inhibit mitochondrial functions; it exerts hormonal effects, such as low T3 syndrome, that negatively impact mitochondrial activities; and it downregulates the genes encoding mitochondrial proteins [2,3]. Despite the above findings, the link between mitochondrial dysfunction and multi-organ failure is still not well understood. As a results, several hypotheses have been considered. However, those concerned with the mechanisms or cause-and-effect relationship have not been supported by convincing experimental or clinical evidence [4]. There are many challenges to exploring mitochondrial dysfunction and multi-organ failure; this is because inconsistent results can arise from dependence on species and tissues/organs, as well as technical issues [4].

In this article, we sought to briefly discuss lipid metabolism in sepsis, with emphasis on its potential evolutionary advantage in the suppression of FA oxidation. Thereafter, we discussed the controlled expression and activity of peroxisome proliferator-activated receptor gamma-coactivator 1 alpha (PGC-1α, a key molecule for mitochondrial biogenesis) in the liver. Even in similar experimental settings, inconsistent results have been reported for PGC-1α transcript levels. Such feature is intriguing considering the evolutionarily conserved low metabolic state in critical illness. Although we are aware that many important studies have addressed mitochondrial biogenesis in sepsis outcome, we opted to mainly refer to review articles, instead of original articles, to discuss mitochondrial and multi-organ failure. We suggest referring to several review articles for more information [2,4-6].

Hypertriglycemia associated with inflammation

In this section, we briefly review the changes in lipid metabolism during infection and inflammation. Evidence from clinical and model-based studies has led to a consensus that a wide range of disturbances in lipid metabolism occur during infection and inflammation [5]. Although large variances due to species-dependency and methodological differences (e.g., administration of lipopolysaccharide [LPS] vs. live bacteria) are known, commonly observed disturbances include increased levels of triglycerides (TG) and FA in plasma, reduced levels of high-density lipoprotein, increased lipolysis in adipose tissue, and decreased beta-oxidation in multiple organs. The potential benefits of dyslipidemia have been proposed as lipoproteins were previously found to bind to and neutralize LPS and lipoteichoic acid; these potential benefits were also observed *in vitro* [5]. It is thus possible that the hyperlipidemia induced by infection is part of the body's defense mechanisms [5]. For example, Read et al. reported that chylomicron and synthetic TG-rich lipid emulsion infusion significantly improved survival in cecal ligation and puncture (CLP) rat models

[7,8]. The article by Khovidhunkit et al.contains experimental evidence of the lipoprotein-mediated protection from LPS and/or bacterial challenge [5].

The elevated concentrations of TG might be caused by increased recycling (re-esterification) of non-esterified FA to TG, which occurs in parallel with increased lipolysis [9,10]. However, the inhibition of lipoprotein lipase and decreased low-density lipoprotein clearance might contribute to the increase in TG increase. Increased hepatic FA synthesis induced by tumor necrosis factor-alpha (TNF-α) or interleukin-1 (IL-1) might be mediated by the increased level of hepatic citrate. This increase in turn activates acetyl-CoA carboxylase, a rate-limiting enzyme for FA synthesis [11]. The mechanisms underlying the increase in citrate levels in hepatocytes have not been investigated. However, an increase in glycolysis and a decrease in gluconeogenesis may contribute to citrate increase. In fact, isolated hepatocytes treated with TNF-α for 3 h showed a dose-dependent decrease in gluconeogenesis [12].

The liver is the organ that controls metabolism throughout the entire body. Thus, the situation in the liver is known to be different from that in other organs. An earlier study reported the results of experiments involving cytokine- or LPS-injected rodent models as well as *in vitro* experiments. According to the researchers, the administration of LPS, TNF, or IL-1 caused adipose tissue lipolysis and suppressed FA oxidation in multiple tissues, but enhanced hepatic lipogenesis and re-esterification [13]. These findings highlight the unique features of the liver in FA uptake. In multiple organs/tissues, FA uptake and oxidation are reportedly decreased during sepsis. Consistent with these findings, FA transport protein (FATP) and FA translocase (FAT)/CD36 mRNA expression were found to be decreased in multiple organs. However, in the liver, LPS injection decreased FATP mRNA levels but increased FAT/CD36 mRNA levels by 4- to 5-fold. Such finding led us to hypothesize that FATP-mediated influx of FA may be used for mitochondrial oxidation, whereas FAT/CD36 transports FA to the cytosol for re-esterification. Further findings were revealed to support this hypothesis [13-15]. In sepsis, hepatic TG formation is increased, whereas hepatic FA oxidation is decreased. Notable studies in the 1980s and 1990s studies have been reviewed [9]. Most studies utilizing animal models of severe sepsis have revealed decreased FA oxidation ability in most of the organs examined. This reduction may help to increase FA in the blood, which in turn assists in the increased re-esterification into TG in plasma.

Of note, the systemic activity of FA oxidation might be a dominant energy supply in the acute phase. For example, indirect calorimetry respiratory gas analysis was used to determine the energy substrate metabolism in an LPS mouse model [16]. Based on their findings, the researchers reported a marked decrease in carbohydrate oxidation and an increase in FA oxidation. This was particularly evident in the acute phase at approximately 24 h. This metabolic switch from carbohydrates to lipids might help to meet the increased energy demand required during inflammation. In addition, a significant decrease in plasma FFA and an increase in liver free FA (FFA) and TG levels at 24 h were found, which suggest the transport of lipid to the liver for storage.

Mitochondrial dysfunction and biogenesis

After the initial exaggerated inflammation, the immunosuppressive phase ensues, which tends to be associated with multi-organ failure. Multi-organ failure is a major determinant of survival in patients with sepsis. Although the cause-and-effect relationship remains controversial [2,4], there is evidence of the importance of mitochondrial dysfunction during sepsis [6]. Initial organ dysfunction in sepsis has been associated with decreased oxidative phosphorylation [6,17]. For example, electron transport chain complexes are less abundant in cells from patients with sepsis. Mitochondrial dysfunction occurs because of the overproduction of cytokines, ROS, and NO, which inhibit the respiratory chain [3,18]. As the TCA cycle and FA oxidation are important functions of the mitochondria, mitochondrial dysfunction results in the dysregulation of metabolism. A notable study in this regard was carried out to perform a metabolome analysis of the plasma of patients with sepsis. The researchers observed that individuals who did not survive had elevated plasma levels of acyl-carnitines, suggesting poorer uptake of FAs by the mitochondria [19]. Furthermore, the plasma levels of common metabolites, such as citrate, malate, glycerol, and glucogenic and ketogenic amino acids, were higher in non-survivors than survivors, suggesting impaired mitochondrial aerobic catabolism for energy generation in non-survivors.

Currently, it is unclear whether the mitochondria play a causative role in tissue dysfunction, or whether mitochondrial changes represent a downstream marker of tissue damage [2,18]. Decreased expression levels of respiratory complexes have been reported using several animal model studies. In fact, a study that employed a preclinical model of sepsis (peritoneal transplantation of 10^6 colony forming units of *Staphylococcus aureus*) reported that normal oxidative respiration was concomitantly restored with mitochondrial biogenesis [20]. The time course of recovery of the number and density of the mitochondria can be regarded as the recovery from septic conditions [21]. Following mitochondrial dysfunction, several transcriptional coactivators and nuclear transcription factors that include nuclear respiratory factor-1 (NRF-1), NRF-2, and PGC-1α coordinate mitochondrial biogenesis [22]. This process is considered to involve mitochondrial quality control and the regulation of genes required for biogenesis. The importance of mitochondrial biogenesis in the recovery from sepsis has also been highlighted in a study that demonstrated that PGC-1α mRNA level was only elevated in survivors and the decreased transcription of the respiratory chain subunits was milder in survivors than non-survivors [23].

The presence of mitochondrial dysfunction in sepsis remains controversial. An analysis of 76 papers based on endotoxemia or inflammation models, or clinical cases observed that mitochondrial dysfunction was not a feature consistently observed in the models/cases with multi-organ failure in severe sepsis and septic shock. Compared to rodent

endotoxemia models, porcine sepsis models exhibited minor changes in mitochondrial respiration in the liver, heart, and brain samples [24]. In addition to such between-species differences, methodological issues also present challenges [4,24]. For example, even control animals can display pronounced variability in mitochondrial respiration [24]. Therefore, it could be safer to consider that the degree of mitochondrial dysfunction can be highly variable and organ-specific, and can change over the course of sepsis.

It is important to consider that the suppression of mitochondrial activity may have protective effects in some critical situations. Findings relevant to this issue include the depletion of ATP to 20% to 30% in the liver owing to fructose injection to protect against TNF-induced liver damage [25].

Sepsis and PGC-1α

In several animal models of sepsis, following acute inflammation and an initial decrease in mitochondrial function and ROS-induced damage, mitochondrial biogenesis is activated [22]. In this section, we briefly discuss the functions of PGC-1α, a key molecule in mitochondrial biogenesis. Further, we aim to discuss conflicting findings regarding the regulation of PGC-1α expression levels after septic stimulation. A more comprehensive discussion of PGC-1 is presented in several review articles [26-28].

PGC-1α belongs to the PGC-1 family, which is a well-studied family of transcriptional coactivators that integrate signaling pathways in the control of cellular and systemic metabolism [26,27]. PGC-1 coactivators act as docking platforms for other proteins that possess histone acetyltransferase activity. Additionally, they facilitate the assembly of the basal transcription machinery [27]. The PGC-1 family consists of PGC-1α, PGC-1b, and PGC-1-related coactivator (PRC) [27]. Although these members share the function of mitochondrial biogenesis, each regulates a distinct process. In addition to mitochondrial biogenesis [29], PGC-1α promotes hepatic fasting responses, including gluconeogenesis, FA beta-oxidation, ketogenesis, and bile-acid homeostasis [26,30]. Accordingly, PGC-1 regulates many genes important for metabolism, including *peroxisome proliferator-activated receptor alpha* (*PPARα*). In the liver, *PPARα* governs the expression of genes involved in FA oxidation and gluconeogenesis from glycerol [31]. For example, PGC-1α activates the transcription of phosphoenolpyruvate carboxykinase or glucose 6-phosphatase. However, unlike PGC-1α, PGC-1β controls hepatic lipid synthesis and lipoprotein production [26], and is constitutively expressed [27]. This review does not focus on PGC-1β and PRC.

PGC-1α expression is dynamically regulated in a tissue-specific manner, such as cold temperature in brown adipose tissue, fasting in the liver, or exercise in skeletal muscle [27]. Transcriptional networks by the PGC-1α system now seem to be more complex than initially thought [32]. Evidence for this complexity is due to recent discoveries of alternatively spliced isoforms, including NT-PGC-1a, PGC-1a1 (the originally described isoform), PGC-1a2, PGC-1a3, and PGC-1a4 [28,32]. At present, these isoforms are being intensively investigated. However, they have been found to show distinct degradation dynamics and can even shift the splicing patterns of target genes.

PGC-1α activity is extensively regulated by various modalities. Although these modalities are not considered in detail in this mini-review, post-translational modifications that include phosphorylation and methylation acetylation/deacetylation have been well documented [28]. SIRT1 is an NAD+-dependent protein deacetylase and a key metabolic sensor. Ample evidence supports the function of SIRT1 in deacetylating PGC-1α to promote its transcriptional activity. *In vitro* findings support the view that AMPK, another metabolic sensor, directly phosphorylates and activates PGC-1α [33]. Furthermore, recent studies have drawn attention to the intracellular localization of PGC-1α. Although full-length PGC-1α resides in the nucleus, NT-PGC-1α resides in the cytoplasm and is translocated to the nucleus upon protein kinase A-mediated phosphorylation [34].

PGC-1α levels in animal models of sepsis and acute inflammation

In cooperation with transcription factors, such as PPARα, PGC-1α is crucial in lipid and carbohydrate metabolic processes. PPARα is an important target of PGC-1α and is considered to be the master regulator of lipid metabolism, particularly FA oxidation. Consistent with the suppression of FA oxidation in sepsis, decreased levels of PPARα expression have been consistently reported in many septic models and humans. In this section, we detail the conflicting results regarding the changes in PGC-1 expression levels in animal models. Intriguingly, although most studies have reported that septic stimulation (LPS or CLP challenge) markedly lowers PGC-1α levels in different tissues, including the liver [30], several studies have reported remarkable increases in PGC-1α. Furthermore, the regulation of PGC-1α levels by pathways involved in innate immunity appears to be highly tissue-specific and a complex temporal pattern of development with tissue specificity has been described.

In the muscle, PGC-1 mRNA reportedly exhibited a transient increase, peaking at 2 h after LPS administration; however, a decrease to approximately 20% of the basal level was evident in the liver until approximately 16 h after recovery [35]. Other authors have reported that in cytokine- or LPS-injected rodent models, as well as *in vitro*, all RXRα, PPARα, LXRα, and PGC-1α transcripts were decreased in the liver at 16 h after TNF or IL-1 injection. After LPS injection, the mRNA levels of PGC-1α and SRC-1, an acetyltransferase that interacts with PGC-1α, decreased in the liver at 16 h. In this experiment, the researchers administered an intraperitoneal injection of 100 μg of LPS, 100 ng TNF, or 80 ng of IL-1 per mouse [36].

Another study demonstrated that mitochondrial damage is prevalent in the liver during the subacute phase of CLP

sepsis in mice. The authors used a CLP model that resulted in 60% mortality within 6 days, with most deaths occurring within 72 h. Further, mitochondrial damage was evident as represented by carbamoyl-phosphate synthetase 1 (CPS-1) in plasma from 8 to 48 h after CLP [37]. Interestingly, the plasma CPS-1 level peaked at 24 h, whereas the alanine aminotransferase (ALT) level peaked at 48 h, suggesting that mitochondrial damage occurred earlier than the peak of hepatocyte damage. PGC-1 as well as mitochondrial transcription factor A (Tfam) were increased at 24 h, but decreased to levels below the control at 48 h and 6 days. Such transient increase and return to less than normal level might be a remarkable feature of the regulation of PGC-1 expression. Mitochondrial oxidative stress, as measured by increased protein carbonylation, was first evident at 8 h and peaked at 24 h. Ultrastructural mitochondrial damage was also observed, and its timing coincided with CPS-1 release. Overall, these results suggest that mitochondrial biogenesis accounts for the restoration of mitochondrial mass in the liver of CLP mice surviving for 6 days.

Most of the relevant studies simply showed decreased levels of PGC-1α in the liver. In one study, LPS treatment resulted in decreases in the PGC-1α and PPARα protein levels to 15% and 20% of the levels in control mice, respectively, at 16 h. In the study, a lethal dose of LPS (25 mg/kg body weight) was administered, which led to 50% mortality at 30 h [38]. In a more recent study, 16 h after the administration of 5 mg/kg LPS, marked decreases in hepatic transcripts for PGC-1α, PPARα, and estrogen related receptor α (ERRα) were observed [39].

Similarly, other authors observed that the administration of 10 mg/kg body weight LPS suppressed FA oxidation as measured at 16 h, with a marked decrease in PGC-1α mRNA in the liver [40]. Intriguingly, exercise led to a dramatic increase in the PGC-1α transcript level at 16 h in the liver.

In some studies, PGC-1α transcripts or proteins have been reported to increase despite the use of experimental protocols similar to those discussed above. One study focused on metabolic recovery with the possible requirement of mitochondrial biogenesis and used a model featuring the peritoneal transplantation of 10^6 colony forming units of *Staphylococcus aureus*, which led to 80% survival on day 7 [20]. In the model, progressive increases in the mRNA levels of NRF-1, PGC-1α, and Tfam were observed in the liver from day 0 to 2 (NRF-1, Tfam) or day 0 to 3 (PGC-1α). As a result, the researchers concluded that mitochondrial biogenesis occurred on day 2 and metabolism recovered on day 3.

Generally, mild or gradual septic insult (low-dose LPS or a relatively small number of live bacteria) may result in a transient increase in PGC-1α expression. However, after a bolus injection of high-dose LPS, strong suppression of PGC-1α expression appears to be predominant. Although such findings were not derived from a study involving hepatocytes, the idea is supported by a study [41] that used a model of acute kidney injury (AKI) induced by *Hemiscorpius lepturus* venom. The researchers reported a dose-dependent pattern of PGC-1α expression. After a lethal dose of venom, the induction of apoptosis was associated with decreased PPAR-α, PGC-1α, and NRF-2 transcripts in the kidney. However, after a challenge with lower doses of the venom, significant recovery accompanied by PGC-1α upregulation was observed after acute kidney infection.

LPS stimulation of hepatocytes *in vitro* may thus cause a marked increase in the PGC-1α transcript. Notably, hepatocytes express TLR4; however, purified hepatocytes are basically free from immune cells and might differ *in vivo* where pro-inflammatory cytokines are produced by immune cells. An *in vivo* CLP mouse model and *in vitro* LPS treatment (100 ng/mL) of hepatocytes revealed very pronounced increases in PGC-1α, Tfam, and NRF-1 mRNAs [21]. The mitochondrial density decreased in LPS-treated hepatocytes or CLP mice until 8 h and returned to normal within 24 to 48 h. Strikingly, treating primary mice and human hepatocytes with LPS (100 ng/mL) led to increased levels of PGC-1α, NRG1, and Tfam mRNA at 8 h.

Of note, the expression level of the PGC-1α protein might differ from its mRNA level, despite only a limited number of studies rigorously comparing the two. Diao et al. [42] reported that the PGC-1α mRNA increased in mice subjected to burn and mice subjected to burn plus LPS insults. However, the PGC-1α protein level showed a rather small increase and the 38-kDa PGC-1α was found to decrease. Similar to other studies, PGC-1α mRNA was quickly and transiently regulated. Notably, careful analysis of the PGC-1α transcript and its isoforms was required in the study.

Overall, the collective findings demonstrate that PGC-1α expression dynamics are often transient [43].

Perspectives of the mitochondria and PGC-1a in sepsis

Mitochondrial dysfunction in sepsis has attracted extensive attention. However, technical problems have complicated research on the mitochondrial activity in sepsis. As discussed by Jeger et al. [24], technical problems in the measurement of mitochondrial function, duration of sepsis, and the choice of model (CLP, live bacteria injection, LPS) can introduce variability. Thus, it may be beneficial to focus on biochemical markers or more correctly, the dynamics of mRNA and protein expression as well as protein post-translational modification of proteins. These aspects collectively represent the mitochondrial activities and regulation of mitochondrial biogenesis and quality control.

PGC-1α is recognized as a key molecule in the study of the mitochondria in sepsis. PGC-1α is unique in its organ-dependent manner of expression as well as the rapid changes in its expression level. The organ-dependent time course of mitochondrial functions may be partly explained by the fact that the time course of PGC-1α mRNA expression level is quite different among tissues and organs. As explained earlier, in an LPS mouse model, the level of PGC-1α mRNA in the liver decreases up to 8 h and then recovers, while in the skeletal muscle, a transient rise is evident at 2 h, with the levels remaining higher than the control until 16 h after LPS injection [35]. The regulatory network for the expression

level of PGC-1α has evolved, thereby enabling a rapid and drastic change. PGC-1α is a short-lived protein whose degradation is mediated by the ubiquitin-proteasome system [44]. Studies and discussions concerning the evolutionary significance of such complex networks will help to clarify the role of mitochondrial biogenesis in sepsis. It is interesting to envision that PGC-1α expression at least two irreconcilable needs. In sepsis, systemic suppression of FA oxidation (which helps to increase TG in plasma) and the downregulation of PPARα and PGC-1α has an evolutionary advantage. However, in tissue injury associated with mitochondrial dysfunction, mitochondrial biogenesis is temporarily important, with the need for high PGC-1α activity. From the perspective of metabolic changes in sepsis, a recent notable study reported that PGC-1α undergoes a metabolic switch from glucose utilization to lipid utilization [45]. Such finding is consistent with the roles of PGC-1α in increasing gluconeogenesis and FA oxidation. In immune cells, lipid utilization leads to a more pronounced immunosuppressive function of immune cells.

Another important factor influencing PGC-1α expression and control is age. LPS-induced expression of induced NO synthase in the lung was reportedly more pronounced in 18-month-old rats than 3-month-old rats [46]. In addition, higher serum levels of ALT and total bilirubin levels were found in the aged rats compared to the young rats. Other researchers have demonstrated increased nuclear levels of PGC-1α in young mice, and a decrease after sepsis in mature mice [47].

It is important to determine whether the activation of mitochondrial biogenesis is beneficial in the treatment of sepsis. In general, probing the causality of mitochondrial dysfunction in multi-organ failure is challenging, partly because of the difficulty in determining causality from simple associations. It has been hypothesized that the temporal decrease in mitochondrial function may represent an adaptive response, which slows energy-utilizing processes, limits ROS production, and prevents cell death [18].

Nonetheless, in several recent studies, the expression of PGC-1α improved the health conditions of sepsis models. In one study, mildly increased expression of PGC-1α in skeletal muscle was found to be protective against sarcopenia and metabolic disease during aging, which was evident from the improved insulin sensitivity [48]. Furthermore, the therapeutic potential of PGC-1α in Duchenne muscular dystrophy was demonstrated in experiments using dystrophin-deficient mice [49]. Of note, this gene transfer experiment was conducted partly because mitochondrial dysfunction is known to occur in dystrophic skeletal muscle. Intriguing results regarding muscle activity and PGC-1α expression have been reported by Irahara et al. [45]. Strikingly, neuromuscular electrical stimulation applied once at low frequency and low voltage, or applied twice at low frequency and high voltage increased PGC-1α mRNA expression in skeletal muscle, caused a switch in energy metabolism, and suppressed inflammation [45]. These findings are interesting, given that the researchers previously reported similar beneficial effects of exercise. As proposed by the researchers, improving metabolism in muscles may have beneficial systemic effects. Although we did not discuss insulin sensitivity, the forced expression of PGC-1α may benefit the therapeutic modulation of insulin resistance. Intriguingly, decreased mitochondrial activity reportedly correlated with the degree of insulin resistance and correlates with decreased mitochondrial activity. These events in turn correlate with decreased expression of PGC-1α [27]. In a recent study on the effect of PGC-1α overexpression, a rat model of cardiomyopathy was employed to demonstrate mitochondrial damage [50]. Although PGC-1α transcript and protein levels increased at 3 h, the protein level returned to normal at 6 h and the transcript level was lower than the normal level. Although the authors did not assess the *in vivo* effect of PGC-1α overexpression, analysis using H9c2 rat cardiac myoblast cells showed that either PGC-1α activation by ZLN005 or PGC-1α overexpression reduced apoptosis in myocardiocytes after exposure to LPS. Further, PGC-1α gene overexpression alleviated LPS-induced mitochondrial damage in cardiomyocytes. Another recent study used a rat model of burn-induced cardiac dysfunction to demonstrate that the administration of ZLN005 during post-burn resuscitation restored left ventricular systolic function [51].

The collective findings indicate the therapeutic potential of PGC-1α gene transfer, at least in skeletal muscle and cardiomyocytes. However, only few studies have addressed whether PGC-1α gene transfer aids in the recovery from sepsis. In the near future, several studies will explore the possibility that the activation of PGC-1α or the pathway that activates PGC-1α, such as the AMPK/SirT/PGC-1α pathway, may improve the prognosis of patients with sepsis. As PGC-1α signaling is linked to several pathways in cellular signaling, the regulatory signals and complexes that regulate PGC-1α activity is very complex [33]. Therefore, a therapeutic strategy targeting PGC-1α in the liver may disrupt function and result in harm. Understanding the regulatory network of PGC-1α is important for efficient targeting of PGC-1α and its associated molecules for improved treatment of patients with sepsis.

Conflict of Interest

Authors declare that they have no conflict of interest.

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