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PGC-1alpha, SIRT1 and AMPK, an energy sensing network that controls energy expenditure

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Abstract

Purpose of the review—PGC-1α has been extensively described as a master regulator of mitochondrial biogenesis. However, PGC-1α activity is not constant, and can be finely tuned in response to different metabolic situations. From this point of view, PGC-1α could be described as a mediator of the transcriptional outputs triggered by metabolic sensors, providing the idea that these sensors, together with PGC-1α, might be weaving a network controlling cellular energy expenditure. In this review we will focus on how pathologies such as type 2 diabetes and the metabolic syndrome might be related to an abnormal and improper function of this network.

Recent findings—Two metabolic sensors, AMPK and SIRT1 have been described to directly affect PGC-1α activity through phosphorylation and deacetylation, respectively. While the physiological relevance of these modifications and their molecular consequences are still largely unknown, recent insight from different in vivo transgenic models clearly suggests that AMPK, SIRT1 and PGC-1α might act as an orchestrated network to improve metabolic fitness.

Summary—Metabolic sensors such as AMPK and SIRT1, gatekeepers of the activity of the master regulator of mitochondria, PGC1α, are vital links in a regulatory network for metabolic homeostasis. Together these players explain many of the beneficial effects of physical activity and dietary interventions in our battle against type 2 diabetes and related metabolic disorders. Hence, understanding the mechanisms by which they act could guide us to identify and improve preventive and therapeutic strategies for metabolic diseases.

Keywords

energy expenditure; PGC-1α; SIRT1; AMPK

Introduction

There is an undeniable inner beauty in how intracellular signalling and metabolic pathways respond to environmental challenges as a coordinated network involving distinct cellular compartments to generate an integrated response that allows proper adaptation. A paradigmatic and illustrative example of these coordinated actions can be found in the regulation of energetic metabolism. Energy homeostasis requires the coordinated regulation of energy intake, storage and expenditure. In healthy individuals, fluctuations in any of these processes are normally counterbalanced by regulation of the other two. In contrast, abnormalities in the proper equilibrium of the caloric equation lead to metabolic malfunctions.

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Obesity, type 2 diabetes mellitus (T2DM) and the metabolic syndrome are among the most frequent pathological consequences induced by a misbalance of energy homeostasis. Insulin resistance, defined as the failure to respond to normal circulating concentrations of insulin, constitutes a characteristic hallmark preceding the overt manifestation of the above-mentioned disorders, as evidenced by cross-sectional studies demonstrating insulin resistance in virtually all patients with T2DM [1], as well as prospective studies demonstrating the presence of insulin resistance one to two decades before the onset of the disease [2]. While the exact molecular mechanisms responsible for the development of insulin resistance and how it paves the path to T2DM are enigmas yet to be deciphered, major progress has been achieved in recent years indicating that the regulation of energy expenditure takes center stage in this scenario.

Defective energy expenditure is linked to metabolic disease

Evidence gathered during the last decade indicates that alterations in lipid metabolism may have a central role in the onset of T2DM. First, insulin resistant states are commonly linked with a decreased efficiency to use fatty acids as an energy source in skeletal muscle [3-5]. This, in turn, redirects the fatty acid flux toward storage, leading to the increased ectopic lipid deposition. Evidence for this has been obtained in a wide array of experimental models of human insulin resistance [6-8], to the point that intramuscular triglyceride accumulation has been recognized as one of the most consistent markers of whole-body insulin resistance [9]. Together, these observations led to the hypothesis that defects in mitochondrial oxidative function and the subsequent decrease in energy expenditure may contribute to the metabolic dysfunctions observed both in insulin resistant states, T2DM and aging. Confirming this hypothesis, two seminal studies by Shulman's lab using magnetic resonance spectroscopy to asses mitochondrial function in vivo, demonstrated that two different populations with high susceptibility to develop T2DM, i.e. lean, healthy offspring of type 2 diabetic parents and an elderly population, displayed impaired mitochondrial function in skeletal muscle [10, 11]. Subsequent studies reporting compromised mitochondrial function in T2DM patients further consolidated these observations [12, 13]. To date, however, it is not fully clear whether the impaired mitochondrial oxidative capacity in T2DM is due to diminished mitochondrial content, to intrinsic defects in mitochondrial functionality or both (see [14] for review).

At the molecular level, the oxidative dysfunction displayed in T2DM subjects may find an explanation in a coordinated decrease in the expression of genes involved in lipid oxidation and mitochondrial metabolism in skeletal muscle, as demonstrated by gene-clustering approaches [15, 16]. Furthermore, changes in gene expression are also correlated with changes in muscle fiber-type phenotype [11, 17]. Hence, obese and diabetic individuals display lower ratios of type I muscle fibers, which display high mitochondrial content and oxidative rates, relative to type IIb fibers, which have a glycolytic nature. The latter observation is important since insulin sensitivity is positively correlated with the oxidative capacity of the muscle [18]. Thus, increased glycolytic muscle mass may contribute into decreased whole-body insulin sensitivity, considering that skeletal muscle is responsible for up to 80% of post-prandial insulin-stimulated glucose disposal in healthy individuals [19]. For these reasons, it seems logical that regulation of mitochondrial oxidative capacity may hold promise as a preventive and therapeutic strategy to reduce the burden of T2DM and its associated diseases.

PGC-1α: fueling the oxidative fire

Interestingly, both fiber-type switching and the expression of many genes related to lipid oxidation and mitochondrial metabolism are under the transcriptional control of the

peroxisome proliferator-activated receptor gamma (PPARγ) coactivator-1α (PGC-1α). PGC-1α was originally cloned as a cold-inducible coactivator of PPARγ in brown adipose tissue [20], but it has emerged as a potent coactivator of a plethora of transcription factors impacting on whole body energy expenditure (see [21] for review).

Early studies demonstrated that overexpression of PGC-1α in cultured cells was enough to increase energy expenditure [22-24]. To do so, PGC-1α coordinately increases mitochondrial biogenesis and respiration rates, as well as the uptake and utilization of substrates for energy production. In order to exert such a wide array of functions PGC-1α directly coactivates multiple transcription factors, including nuclear receptors – such as the PPARs [25, 26], or the thyroid hormone receptor (TR) [20], glucocorticoid receptors (GRs) [25], estrogen receptors (ERs) [20, 25] and estrogen-related receptors (ERRs) [27, 28] among others – and non-nuclear receptor transcription factors, such as myocyte enhancer factor-2 (MEF-2) [29] and the family of forkhead O-box (FOXO) transcription factors [30]. By simultaneously coactivating these transcriptional factors PGC-1α can quickly and coordinately modulate a transcriptional program that governs energy metabolism. While PGC-1α coactivation can change in response to different stimuli or in a tissue-specific manner, the molecular mechanisms determining how PGC-1α partners can be selectively targeted are still largely unknown.

Arguably, the most compelling data on the key role of PGC-1α in energy metabolism comes from in vivo studies. PGC-1α is mainly expressed in tissues with high energy oxidative capacity, like heart, skeletal muscle, liver, brown adipose tissue and brain, and is robustly induced in conditions that require energy, such as cold, fasting and exercise [20, 31]. Further evidence supporting a key role of PGC-1α came from tissue-specific genetically engineered mouse models, since germline PGC-1α knock-out mice have pronounced central nervous system perturbations that complicate the interpretation of the phenotype. Muscle-specific PGC-1α transgenic animals display increased mitochondrial number and function, as well as a higher relative amount of type I oxidative fibers [32]. Conversely, mice with a muscle-specific deletion of PGC-1α show abnormal glucose homeostasis linked to a moderate reduction in the number of oxidative type I fibers, decreased endurance capacity and mitochondrial gene expression [33]. Altogether, these data provide compelling evidence that PGC-1α is a key regulator of mitochondrial biogenesis in muscle.

Given the potential action of PGC-1α as a signalling amplifier of specific gene sets, minor disturbances in the activity of this coactivator might strongly impact on whole-body energy homeostasis and on the pathogenesis of the metabolic syndrome. Consistent with the compromised bioenergetic capacity and coordinated reduction in the expression of mitochondrial genes, decreased PGC-1α levels has been reported in skeletal muscle from insulin resistant [34] and T2DM [15, 16] subjects. Similarly, correlations between muscular PGC-1α expression and insulin-stimulated glucose uptake and oxidation have been found in studies on monozygotic and dizygotic twins [35]. PGC-1α expression is also reduced with aging, providing a possible explanation for the link between aging and an increased susceptibility to develop T2DM [35]. Conversely, PGC-1α expression is restored by treatments known to normalize body weight and/or glucose homeostasis [36]

While these findings are mostly corelational, genetic association studies have supported a potential causal role for PGC-1α in the susceptibility to develop T2DM. The PGC-1α gene (PPARGC1A) is localized on chromosome 4p15.1-2 [37], a region that has been associated with basal insulin levels [38], abdominal subcutaneous fat [39] and obesity [40, 41] in different populations. Furthermore, single nucleotide polymorphisms on the PPARGC1A show a strong association to diabetes-related phenotypes [42-44]. Particularly, a possible association of a Gly482Ser PPARGC1A polymorphism with diabetes and its complications

has drawn attention lately. Studies on diverse populations indicated that the Ser variant rendered individuals susceptible to develop T2DM in [42, 43, 45], but, even if in most populations studied there was a tendency to find a higher representation of the Ser variant in type 2 diabetic patients, not all studies have found significant associations [46-48]. The functional meaning of this substitution is currently unknown, even though it has been shown that the Ser variant was associated with an age-dependent reduction in muscle PGC-1α expression [35]. While the genetic evidence collected points towards a potential causal role of PGC-1α in the pathogenesis of T2DM, further research will be required to consolidate this possibility and provide a link between human genetic studies and PGC-1α biology.

Metabolic sensors and PGC-1a: sparks to the fire

The biology of PGC-1α and the regulation of its activity, however, are far from totally understood. The data presented above does not always take into account that PGC-1α activity is not only determined by its expression levels, but also by a number of post-translational modifications, such as phosphorylation [49-51], acetylation [52-54] and methylation [55], amongs others. As recently reviewed [56], these modifications can affect the intrinsic activity of PGC-1α, the stability of the PGC-1α protein or might regulate the interaction with other proteins that determine its activity, such as the corepressor p160MBP [57]. It has also been proposed that PGC-1α might be forming part of different complexes which would provide also ways to influence its activity [58-60]. Hence, understanding this regulatory conundrum of signals and complexes that regulate PGC-1α activity and specificity holds strong promise to improve the pharmacological efficiency in order to selectively target PGC-1α action.

Since PGC-1α has a prominent role in the metabolic adaptations to the energetic status, it should not be surprising that its activity might be targeted by cellular mechanisms capable of sensing perturbations in the metabolic status of the cell as well as the availability of substrates, and transform these inputs into a specific metabolic fate. These sensors would act as integrative nodes of cellular metabolism determining which enzymatic and transcriptional responses will be exerted in order to adapt to the environmental conditions. Such crucial sensing functions are normally performed by enzymes, that are conserved all along the evolutionary scale. Two of them, SIRT1 and AMPK play major roles in metabolic regulation and have recently been shown to impact on PGC-1α to transcriptionally regulate energy expenditure.

SIRT1 and the control of PGC-1α activity

SIRT1 is one of the mammalian homologs of yeast the Sir2 protein, the founding member of the sirtuin gene family. SIRT1 is an enzyme that mediates NAD^+-dependent deacetylation of target substrates. Since the cellular redox balance of NAD^+ and NADH is highly related to catabolic fluxes, it has been postulated that SIRT1 could act as a sensor that directly connects metabolic perturbations with transcriptional outputs, as it was initially characterized as a histone deacetylase [61]. The regulatory role of SIRT1 may, however, be far more complex, as its activity also highly depends on the intracellular levels of nicotinamide, the natural product of the deacetylase reaction catalyzed by sirtuins [62], as well as on post-translational modifications [63] or interaction with other proteins [64-66]. Additionally, the regulation of the intracellular localization of SIRT1 and how NAD+/NADH variations in distinct cellular compartments may affect its activity are issues yet to be fully understood.

While our understanding of mammalian SIRT1 biology is still surprisingly weak, there are a vast number of evidences suggesting that this enzyme has a major role in metabolic homeostasis. First of all, during the last decade, a number of reports have shown that SIRT1

is not just a histone deacetylase. In fact, SIRT1 can directly interact and regulate the activity of transcription factors and coregulators, including PPARγ [67], p53 [68] and the FOXO family of transcription factors [69], all of which are key regulators of metabolism in a variety of tissues. While there is a tendency to associate SIRT1-mediated deacetylation with transcriptional repression, this is not always the case. For example, in the case of FOXO transcription factors, deacetylation by SIRT1 seems to confer target gene specificity [69]. In other cases, such as with Tat-mediated transcription of the HIV long terminal repeats, SIRT1-mediated deacetylation is associated with positive regulation of gene expression [70]. Moreover, the realm of SIRT1 substrates might expand beyond transcriptional regulators, as has been demonstrated by the work showing that SIRT1 can directly regulate the activity of AcetylCoA syntethases through deacetylation [71]. Interestingly, SIRT1 can also directly interact and deacetylate PGC-1α [52].

The regulation of PGC-1α acetylation merits some discussion, as the deacetylation of PGC-1α is tightly linked with enhanced PGC-1α transcriptional activation and mutation of the acetylation sites to arginine, which mimics the deacetylated state, markedly increases basal PGC-1α transcriptional activity [52]. Conversely, acetyltransferase enzymes such as GCN5 [72] and SRC-3 [73] have been demonstrated to inhibit PGC-1α activity by increasing its acetylation. This yin yang between acetyltransferases and deacetylases in the control of PGC-1α activity seems a recurring theme (Figure 1). In fact, the expression of SRC-3 and GCN5 increases upon high fat feeding, while SIRT1 expression diminishes, providing a plausible explanation to why PGC-1α is hyperacetylated and the expression of PGC-1α–dependent genes is downregulated in this state [73]. The converse situation, with an induction of SIRT1 and reduction of GCN5 and SRC3, occurs upon fasting and dietary restriction, now inducing PGC-1α activity [73]. The changes in the expression levels of deacetylases and acetyltransferases will result in a convergent regulation of PGC-1α acetylation status in conditions when energy levels change. Together, these data indicate that acetylation of PGC-1α has a major influence on its activity, and, consequently, the acetyltransferase and deacetylase enzymes modulating this process may heavily impact on whole-body metabolism.

In vivo experiments support a major role for SIRT1 as a metabolic regulator. Several lines of evidence indicate that SIRT1-mediated regulation of PGC-1α activity may play a major role in the metabolic adaptations to energy metabolism in different tissues [52, 54, 74, 75]. In liver, SIRT1 is known to control gluconeogenic activity by modulation of PGC-1α [75] and CREB regulated trancription coactivator 2 (CRTC2) [76], In vivo treatment with SIRT1 agonists promotes deacetylation of PGC-1α in skeletal muscle and brown adipose tissue, which translates into enhanced mitochondrial activity, which, in turn, improves exercise performance and thermogenic activity [54]. Unfortunately, the current SIRT1 knock-out models display several developmental defects [77, 78], they are smaller at birth and show elevated postnatal lethality, making it impossible to evaluate the metabolic role of SIRT1 and its impact on PGC-1α activity and energy expenditure. However, mice models having a mild-overexpression of SIRT1 present ameliorated glucose tolerance when insulin resistance and/or diabetes are induced [79]. A second model mice overexpressing SIRT1 also displayed enhanced glucose tolerance linked to increased metabolic rates [80]. Similarly, treatment with different SIRT1 agonists prevents weight gain and insulin resistance when mice are challenged with high-fat diets [54, 81]. Altogether, these results highlight a role for SIRT1 in the control of metabolic homeostasis. Given that situations of energy deficiency, such as fasting, promote increased intracellular NAD^+ levels [52, 74, 82], it seems plausible that such conditions might affect SIRT1 activity, which would result in the deacetylation of PGC-1α and an increase its transcriptional activity. This mechanism would allow the cell to increase mitochondrial respiration and meet the energetic requirements of the cell in circumstances of energy stress. While the finding of a link between SIRT1 and PGC-1α

represented a promising breakthrough in our understanding of how the cell transcriptionally regulates energy metabolism, the edges of most of the concepts underlying this link need to be mechanistically polished. For example, the SIRT1/PGC-1α axis is not likely to respond similarly in all tissues upon energy stress [82]. Similarly, how SIRT1 interacts with PGC-1α upon energy stress and whether SIRT1 displays any regulation at the level of substrate specificity upon activation, are major issues yet to be solved.

AMPK and the link of PGC-1a activity to energy status

As stated in a recent review [83], AMP-activated protein kinase (AMPK) is a conserved fuel-gauge that has probably played a major role in the maintainance of intracellular energy balance during eukaryotic evolution. Mammalian AMPK is a Ser/Thr kinase that is activated upon alterations in the cellular AMP/ATP ratio. Hence, perturbations in this ratio due to either defects in energy production or increased energy consumption will activate the kinase. Once activated, AMPK switches on catabolic pathways to produce ATP while simultaneously shutting down energy-consuming anabolic processes. In order to perform these actions, AMPK can quickly regulate metabolic enzymes through direct phosphorylation, but, additionally, AMPK also has long-term effects at the transcriptional level in order to adapt gene expression to energy demands. Hence, upon energy deficiency, AMPK will enhance the expression of genes related to glucose transport and glycolysis [83, 84] and mitochondrial respiration [85] while down-regulating lipid synthesis genes [86].

AMPK activation is highly relevant for the transcriptional adaptation to physiological situations of energy demand. Mice expressing a dominant-negative form of AMPK cannot increase mitochondrial biogenesis in response to energy deprivation in skeletal muscle [87]. Similarly, mice where the predominantly muscular γ3 subunit of AMPK has been knocked-out, hence blunting AMPK activation in muscle, show impaired fasting-induced expression of lipid oxidative genes [88], as well as impaired expression of genes induced by exercise [89]. In contrast, in mice overexpressing an activated form of the AMPKγ3 subunit the expression of genes controlling lipid oxidation and mitochondrial activity is induced [88-90]. Furthermore, muscles from mice that overexpress the active form of the AMPKγ3 subunit were protected from diet-induced insulin resistance [91] and fatigue resistance [89]. Finally, it has recently been shown that mice fed with a AMPK agonists display increased oxidative gene expression, enhancement in their endurance capacity and protection against metabolic disease [92, 93]. Therefore, AMPK constitutes a major regulator of basal mitochondrial gene expression as well as mitochondrial gene expression upon energy stress.

Interestingly, there is a strong overlap in the genes transcriptionally regulated by AMPK and those by PGC-1α, hence suggesting that PGC-1α might be an important mediator AMPK-induced gene expression. Supporting this hypothesis, AMPK activation leads to increased PGC-1α expression [94, 95], and AMPK requires PGC-1α activity to modulate the expression of several key players in mitochondrial and glucose metabolism [50]. However, a closer link has been provided by recent findings showing that AMPK can directly interact and phosphorylate PGC-1α [50]. Direct phosphorylation of PGC-1α by AMPK seems to increase transcriptional activity of PGC-1α, even though the reasons why, where, and how that happens are still elusive. Phosphorylation of PGC-1α by AMPK may, hence, be part of the link between the sensing of the energetic status and the induction of transcriptional programs that control energy expenditure, even though how it interacts with other modifications, such as the above-mentioned PGC-1α acetylation, is still unknown.

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Conclusion

A decade after its cloning, and with hundreds of research articles on its back, we might still be at the tip of the iceberg in our understanding of PGC-1α biology. There are major caveats on how PGC-1α transcriptional activity and target gene-sets are specifically regulated upon different circumstances. While a few possible mechanisms have been described, whether and how PGC-1α might act is largely unknown. Nonetheless, the finding that SIRT1 and AMPK impact on PGC-1α furthers our knowledge on how information on the cellular metabolic status is transmitted to PGC-1α and how it adapts transcriptional outputs (Figure 1). Albeit promising, these links are still weak. While there is considerable data supporting that SIRT1 interacts with PGC-1α and promotes its transcriptional activity through deacetylation, the evidence that SIRT1 is a true physiological metabolic sensor is far from conclusive. Furthermore, it is very plausible that additional acetyltransferases and deacetylases, yet to be identified, affect PGC-1α activity. As to AMPK, which is unequivocally defined as a metabolic sensor, the evidence showing that AMPK can activate PGC-1α through direct phosphorylation derives mostly from in vitro assays and further validation in vivo will be important. Given the possible influence of phosphorylation on PGC-1α activity, it will similarly be important to identify the mechanisms governing dephosphorylation of PGC-1α. Additionally, any further implications caused by these post-translational modifications of PGC-1α, such as selective interaction with transcription factors and cofactors or modifying its intracellular localization, still require further study. Similarly, whether perturbations in the acetylation or phosphorylation levels of PGC-1α could be relevant in the development of insulin resistance and T2DM is a question yet to be answered. The combination of such promising links and an exhaustive list of unexplored questions, hence, warrant exciting research for the upcoming years.

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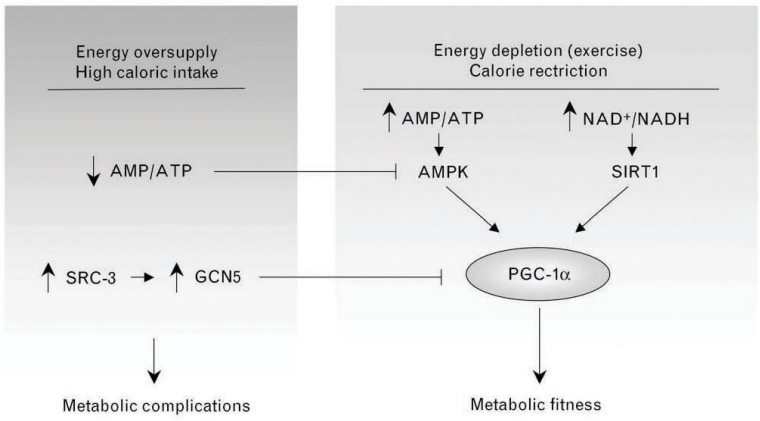

Figure 1. A metabolic sensor network regulating energy expenditure

Situations of energy depletion and/or decreased catabolic rates can be sensed by different enzymes, such as AMPK and SIRT1, whose activation enhance PGC-1α-dependent transcription. Upon calorie rich diets or situations when energy is not limited, AMPK activity is shut down by the high intracellular ATP levels. Similarly, high fat diets increase SRC-3, who positively regulates the protein levels of the acetyltransferase GCN5, which, in turn, plays the opposite role of SIRT1 action on PGC-1α acetylation, hence diminishing PGC-1α transcriptional activity. Perturbations in this metabolic network controlling PGC-1α activity may importantly contribute to whole-body metabolic complications.