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Review

Nutrient-dependent regulation of PGC-1α's acetylation state and metabolic function through the enzymatic activities of Sirt1/GCN5

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ABSTRACT

Mammals possess an intricate regulatory system for controlling flux through fuel utilization pathways in response to the dietary availability of particular macronutrients. Under fasting conditions, for instance, mammals initiate a whole body metabolic response that limits glucose utilization and favors fatty acid oxidation. Understanding the underlying mechanisms by which this process occurs will facilitate the development of new treatments for metabolic disorders such as type II diabetes and obesity. One of the recently identified components of the signal transduction pathway involved in metabolic reprogramming is PGC-1α. This transcriptional coactivator is able to coordinate the expression of a wide array of genes involved in glucose and fatty acid metabolism. The nutrient-mediated control of PGC-1α activity is tightly correlated with its acetylation state. In this review, we evaluate how the nutrient regulation of PGC-1α activity squares with the regulation of its acetylation state by the deacetylase Sirt1 and the acetyltransferase GCN5. We also propose an outline of additional experimental directives that will help to shed additional light on this very powerful transcriptional coactivator.

1. Introduction

The availability of food is one of the most capricious environmental variables that mammals have been subjected to over the course of their natural history. At first glance, an unreliable supply of food would seem to pose a major dilemma for homeothermic organisms like mammals, which have an intrinsically high metabolic rate. Compounding this problem is the metabolic peculiarity that although most mammalian tissues are able to use glucose, fatty acids, or amino acids as fuel substrates there are some tissues, such as the central nervous system, retina, red blood cells, and renal medulla, that rely almost exclusively upon an uninterruptable supply of glucose as fuel. In spite of these existential problems, however, mammals have evolved a highly regulated and effective system of fuel utilization pathways that manages to accommodate the tissue-specific requirements of fuels over a wide range of food and macronutrient availability.

When a mammal is deprived of food, its body undergoes both quantitative and qualitative changes in the way in which stored macronutrients are mobilized and metabolized as fuel. These changes constitute a homeostatic response that ultimately aids in the preservation of a constant supply of circulating blood glucose for those tissues that exclusively require it and in the reduction of overall energy expenditure. Part of this response includes switching to the utilization of free fatty acids as the major macronutrient fuel in peripheral tissues such as muscle as well as increasing the rate of glucose synthesis in the liver and kidney. The coordinated initiation and subsequent maintenance of this remarkable change in fuel utilization is a highly complicated process that requires the integration of many hormonal, transcriptional, translational, and allosteric signals. Identification of the regulatory components in this response has been an important research endeavor for the purpose of aiding not just our understanding of basic biology but also in the development of treatments for pathophysiological conditions where glucose homeostasis has clearly gone awry, such as in obesity and type II diabetes. Elucidation of this regulatory pathway may also help to shed light on the mechanism by which caloric restriction is able to retard or prevent the age-related deterioration of mammalian tissues. One exciting branch of research into this problem over the past 10 years has indicated that a major participant in the physiological process of glucose maintenance and fuel utilization is the protein Peroxisome Proliferator-Activated Receptor Gamma-Coactivator-1 α (PGC-1α). In this review, we discuss the role of PGC-1α in regulating the central pathways of metabolism. We also discuss how the acetyl transferase GCN5 and the deacetylase Sirt1 are capable of changing the acetylation state of PGC-1α in response to nutrient state and reciprocally alter the transcriptional coactivating properties of PGC-1α.

2. PGC-1α and its effects on fuel metabolism in fasting

PGC-1α was first identified as a binding partner and co-activator of the transcriptional activity of PPARγ as part of a study to identify transcriptional components of the pathway responsible for the

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metabolic changes accompanying adaptive thermogenesis [1]. Since that time, however, the list of transcription factors to which PGC-1α is known to bind to and consequently modulate the activity thereof has expanded considerably. This list includes PPARα, glucocorticoid receptor, hepatic nuclear factor-4α, members of the estrogen related receptor (ERR) family, myocyte enhancer factor 2, nuclear respiratory factors 1 and 2, FoxO1, and YY1 [2-6].

The precise mechanism by which PGC-1α is able to enhance the ability of these proteins to initiate gene transcription is not altogether clear, although it is clear that the enhancement of activity is contingent upon the physical interaction of PGC-1α and its cognate transcription factor [7]. Most transcriptional co-activators possess intrinsic enzymatic activity, such as histone acetyltransferase activity, that enables them to modify chromatin to make the genetic locus at which they are located more amenable to transcription. PGC-1α does not appear to possess any enzymatic activity. Its N-terminus, however, is an effective docking site for two well-established histone acetyltransferases, SRC-1 and CBP/p300, which have been shown to be strong enhancers of PGC-1α activity [7]. Although they enhance the activity of PGC-1α, SRC-1 and CBP/p300 do not acetylate PGC-1α. In fact, acetylation of PGC-1α is correlated with a decrease in PGC-1α activity (see below).

It should be noted that although PGC-1α is a co-activator it is not merely a blunt instrument for effecting a wholesale change in the transcriptional activity of its binding partners—its co-activational properties can apparently be selectively tuned for different promoters even when coupled to the same transcription factor. The UCP-1 and aP2 genes, for instance, contain conserved PPARγ binding sites within their promoters but it is only the gene expression of UCP-1 that changes in response to levels of PGC-1α [1]. The mechanism by which this specificity is mediated has not been fully explored.

From a physiological standpoint, the co-activation of a litany of cognate transcription factors by PGC-1α has important metabolic repercussions; collectively, the set of transcription factors to which PGC-1α binds controls the expression of genes involved in gluconeogenesis, glycolysis, lipogenesis, peroxisomal and mitochondrial fatty acid oxidation, and mitochondrial respiration efficiency. Thus, PGC-1α can single handedly coordinate the gene expression of multiple energy pathways. This point is underscored by the PGC-1α knock-out mouse, which shows a reduced respiratory capacity, diminished hepatic TCA cycle flux, reduced rates of hepatic gluconeogenesis and β-oxidation, hepatic steatosis under fasting conditions, and hypoglycemia [8-10].

2.1. PGC-1α function in the liver

In terms of its contribution to the problem of diet-dependent maintenance of energy homeostasis in mammals, there is a body of evidence to suggest that the co-transcriptional activity of PGC-1α is important for the compensatory metabolic responses that occur during food deprivation. The two organs for which this process is best understood are the liver and the skeletal muscle. In the liver during fasting, gluconeogenesis is profoundly upregulated primarily at the level of transcription. A compelling argument can be made for dissecting the upregulation of gluconeogenesis into two temporally distinct phases. In the first and more acute phase (<12–18 h), an increase in the transcription of gluconeogenic enzymes is initiated in part by the activation of cAMP response element binding protein (CREB) and its coactivator CRTC2 (Fig. 1). With prolonged fasting (>12-18 h), however, CRTC2 protein is degraded [11] and its contribution to the fasting transcriptional response is significantly diminished [12]. The initial signal for CRTC2 degradation appears to be deacetylation by Sirt1 [11]. The maintenance of the gluconeogenic response through prolonged fasting is thought to be mediated by PGC-1α and its cognate transcription factors. Indeed, hepatic levels of PGC-1α protein significantly increase under fasting conditions, driven in part by an increase in transcription caused by CRTC2 activation [13] and in part by an increase in the half-life of the protein induced by an attenuation of insulin signaling [14]. The elevated levels of PGC-1α facilitate increased hepatic glucose output by promoting the expression of gluconeogenic genes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase, most likely through the co-activation of HNF4α and FoxO1 [15]. Interestingly, whereas the increase in Sirt1 activity that accompanies prolonged fasting attenuates CRTC2 signaling, it actually improves PGC-1α's ability to increase hepatic gluconeogenesis (see below).

2.2. PGC-1α function in skeletal muscle

In skeletal muscle during fasting, induction of PGC-1α helps to orchestrate a series of metabolic changes that results in muscle tissue using less glucose and more fatty acids for oxidative phosphorylation (Fig. 2). PGC-1α has been shown to increase the expression of the glucose transporters GLUT1 and GLUT4 in muscle tissue [16-18]. In the case of GLUT4, this effect is dependent upon the transcription factor MEF-2c [18]. Although PGC-1α can induce glucose transporter expression, net utilization of glucose by skeletal myocytes is significantly mitigated by an increase in PGC-1α activity. The mechanism by which this occurs involves at least two different processes. The first mechanism is a PGC-1α-induced decrease in the expression of phosphofructokinase and an accompanying diminution in glycolytic flux [16].

The second proposed mechanism involves a PGC-1α-induced increase in the expression of pyruvate dehydrogenase kinase-4 [16,19,20], a negative regulator of pyruvate dehydrogenase, which abates the entry of glucose-derived pyruvate into the TCA cycle. PGC-1α's coactivation of ERRα is responsible for increased PDK4 expression. Higher levels of PGC-1α also permit muscle cells to oxidize more fatty acids. PGC-1α facilitates the delivery of free fatty acids across the cell membrane by increasing the expression of the integral membrane protein CD36, which is capable of binding to long-chain fatty acids and mediates their internalization into the cytosol [16,17]. Transport of free fatty acids from the cytoplasm across the outer mitochondrial membrane is also facilitated by an increase in the expression of the free fatty acid transporter carnitine palmitoyltransferase 1 (CPT-1) [16,20]. The complete oxidation of fatty acids and its coupling to ATP production within the mitochondria are facilitated by an increase in the levels of medium chain acyl CoA dehydrogenase (MCAD), cytochrome oxidases II and IV, isocitrate dehydrogenase 3A, β-ATP synthase, and cytochrome *c* [20].

3. Regulation of PGC-1α co-transcriptional activity: the contribution of acetylation

Given the preponderance of evidence supporting a role for PGC-1α in coordinating the compensatory metabolic responses that accompany food restriction, it is logical to inquire how the biological activity of PGC-1α changes under these circumstances. One conceivable mode of regulation is simply that the absolute concentration of PGC-1α protein is increased under low nutrient conditions and forces, by the principle of mass action, an increase in the activity of its transcription factor binding partners. This is definitely possible within the liver, where the concentration of PGC-1α protein significantly increases during periods of acute fasting [21]. Evaluations of skeletal muscle, on the other hand, have shown that there is no appreciable change in the level of PGC-1α during fasting despite very clear increases in the target genes of PGC-1α [20,22]. Such data strongly suggest the involvement of post-translational regulation of protein activity by covalent modification, allosteric modulation, or changes in intracellular localization/compartmentation.

One proposed mechanistic model for explaining changes in PGC-1α activity under fed and fasting conditions that does not require a