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Review

Metabolic roles of PGC-1α and its implications for type 2 diabetes

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Abstract

PGC-1α is a transcriptional coactivator expressed in brown adipose tissue, liver, pancreas, kidney, skeletal and cardiac muscles, and the brain. This review presents data illustrating how PGC-1α regulates metabolic adaptations and participates in the aetiology of type 2 diabetes (T2D). Studies in mice have shown that increased PGC-1α expression may be beneficial or deleterious, depending on the tissue: in adipose tissue, it promotes thermogenesis and thus protects against energy overload, such as seen in diabetes and obesity; in muscle, PGC-1α induces a change of phenotype towards oxidative metabolism. In contrast, its role is clearly deleterious in the liver and pancreas, where it induces hepatic glucose production and inhibits insulin secretion, changes that promote diabetes. Previous studies by our group have also demonstrated the role of PGC-1α in the fetal origins of T2D. Overexpression of PGC-1α in β cells during fetal life in mice is sufficient to induce β-cell dysfunction in adults, leading to glucose intolerance. PGC-1α also is associated with glucocorticoid receptors in repressing expression of Pdx1, a key β-cell transcription factor. In conclusion, PGC-1α participates in the onset of diabetes through regulation of major metabolic tissues. Yet, it may not represent a useful target for therapeutic strategies against diabetes as it exerts both beneficial and deleterious actions on glucose homoeostasis, and because PGC-1α modulation is involved in neurodegenerative diseases. However, its role in cellular adaptation shows that greater comprehension of PGC-1α actions is needed.

Keywords: Adipose tissue; Beta cells; Diabetes; Liver; Metabolism; PGC-1α

1. Introduction

Nuclear receptors and their transcriptional coregulators have drawn interest in the field of metabolic diseases as they are responsible for activation and inhibition of metabolic cell adaptations. Among these proteins, peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) belongs to a superfamily of transcriptional coregulators associated with transcription factors, mostly nuclear receptors that do not directly bind to DNA. It is expressed in brown adipose tissue, liver, pancreas, kidney, skeletal and cardiac muscles, and the brain. It plays a major role in the control of energy and glucose metabolism by strongly modulating the biogenesis and activity of mitochondria, but it also initiates significant tissue-specific functions, including fibre-type switching in skeletal muscle, neoglucogenesis and fatty acid oxidation in liver. This review presents data illustrating how PGC-1α is a key regulator of metabolic adaptations and also participates in the aetiology of diabetes.

In nucleated cells, nuclear receptors participate in the signalling pathways of many biomolecules, mostly hormones. More commonly, after fixing the ligand, these receptors dimerize, migrate to the nucleus and bind to specific regions of DNA. They modulate gene transcription in response to binding of a specific ligand. Interaction with the ligand leads to receptor conformational change, allowing the recruitment of transcriptional

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coactivators such as the family of steroid receptor coactivator-1 (SRC1) proteins and transcription intermediary factor 2 (TIF2) [1]. These coactivators contribute significantly to transcriptional control through regulation of chromatin remodelling (to increase accessibility of the genome), recruitment of other transcriptional cofactors and adequate activation of the transcriptional machinery.

Most coactivators are ubiquitously expressed, but not PGC-1α, which is expressed in a limited number of tissues. PGC-1α was first identified in 1998 in a two-hybrid screen in yeast as a protein that interacts with peroxisome proliferator-activated receptor (PPAR) transcription factors in brown, but not white, adipocytes [2]. It is now clear that PGC-1α is an important modulator of metabolism. This review discusses the molecular mechanisms of PGC-1α activation, and then summarizes its main roles and specific implication in type 2 diabetes.

2. Insights into the structure and regulation of PGC-1α

PGC-1α is a 91-kDa nuclear protein belonging to a small family of coactivators with a high degree of homology at their N- and C-terminal ends. The family includes two other members: PGC-1β (or PERC: PGC-1-related oestrogen receptor coactivator) and PRC (PGC-1-related coactivator) [3]. PGC-1β and PRC were identified after PGC-1α on the basis of its primary sequence homology [2,4,5]. PGC-1α protein has an LXXLL motif at its N-terminal end (a contiguous sequence of five amino acids, where 'L' is leucine and 'X' is any amino acid, and referred to as a 'nuclear receptor box'), allowing it to bind to a large number of nuclear receptors (Fig. 1). The pattern is repeated three times in the sequence of PGC-1α (termed L1, L2 and L3) [6], which also contains sequences for interactions with transcription factors, such as myocyte enhancer factor 2C (MEF2C), associated with PGC-1α and located between amino acids 400 and 550 [7]. In addition, PPARγ is an important partner of PGC-1α and binds to the L2 pattern, or a region completely independent of this site between amino acids 200 to 400 [8]. PGC-1α has, within its structure, an inhibitory domain that suppresses its own transcriptional activity [9]. This domain comprises the L3 pattern, allowing binding to one or more repressor proteins [6,10], such as p160/MBP protein, in cultured myoblasts. In these cells, the p38 mitogen-activated protein (MAP) kinase (MAPK) pathway recruits p160/MBP and stabilizes PGC-1α, which then interacts with transcription factors [6,10,11]. Recruiting p160/MBP with PGC-1α suppresses mitochondrial respiration in these cells. Another known example of PGC-1α suppression involves oestrogen receptor-related receptor-alpha (ERRα). Overexpression of this receptor inhibits PGC-1α transcriptional activity, a mechanism that does not appear to involve p38 MAPK [12]. However, some authors have shown that PGC-1α increases levels of ERRα mRNA, and PGC-1α itself interacts with ERRα to coactivate transcription of genes involved in mitochondrial energy metabolism [13–15]. Thus, ERRα could be a feedback element of PGC-1α, depending on the metabolic state of the cell.

SIRT1 protein (sirtuin 1) can also activate PGC-1α by deacetylation [16] while, in hepatocytes, GCN5 protein inhibits PGC-1α activity by acetylation [17]. A large number of hormones that increase intracellular cAMP or calcium concentrations can generally induce PGC-1α expression [18]. PGC-1α activity is regulated through other post-transcriptional modifications such as phosphorylation (Fig. 1) [19], methylation [20] and small ubiquitin-like modifier (SUMO)-ylation [21].

PGC-1α is involved in chromatin remodelling, transcription activation and regulation of mRNA splicing [3]. As its activity lacks histone acetyltransferase (HAT) activity, when recruited by a transcription factor, it mobilizes other coactivators with HAT activity at its N-terminal end. Thus, PGC-1α allows modifications of chromatin structure through histone acetylation [3], which facilitates access of transcriptional machinery to gene promoters where PGC-1α was recruited. In addition, it has also been found that PGC-1α is associated with RNA polymerase II (Pol II) and the TRAP/220 subunit of the TRAP/mediator complex (thyroid hormone receptor-associated proteins) in the preinitiation transcription complex. PGC-1α is also able to bind to elongation and splicing factors in the elongation complex through its C-terminal end, comprising two important areas: a domain of pattern-recognition receptors and RNA-binding proteins; and an enriched serine/arginine domain characteristic of splicing regulators [8].

3. Regulation of PGC-1α transcription

To coactivate gene transcription, PGC-1α has to be recruited by a transcription factor that binds to the relevant gene promoter. PGC-1α interacts with several nuclear receptors, including PPARγ, glucocorticoid receptors (GRs), oestrogen receptor-alpha (ERα), liver X receptor-alpha (LXRα), retinoic acid receptor-alpha (RXRα) and thyroid hormone receptor (TR) [22]. It may also interact with the orphan farnesoid X receptor (FXR), ERRα and ERRγ [23,24]. More specifically, the three members of the PGC-1 family can induce every gene of mitochondrial biogenesis and oxidative phosphorylation to variable degrees, depending on the tissue [2,4,25–29]. PGC-1α activates the expression programme by binding to ERRα or to nuclear respiratory factors (NRFs) [30,31]; similarly, several other genes involved in mitochondrial biogenesis and oxidative phosphorylation have binding sites for NRFs and ERRα [13]. The PGC-1 family can also induce, in addition to nuclear genes, the expression of mitochondrial genes that are mainly controlled by two transcription factors with nuclear expression: transcription factor A, mitochondrial (TFAM); and transcription factor B (TFB) [31,32]. As well as regulating genes involved in mitochondrial biogenesis and oxidative phosphorylation, the PGC-1 family also regulates the expression of genes involved in fatty acid oxidation (FAO) [33].

Other transcription factors can interact with PGC-1α. Among them, hepatocyte nuclear factor 4-alpha (HNF4α) [29], an orphan nuclear receptor, and Forkhead box protein O1 (FOXO1) [34] are involved in gluconeogenesis in liver. However, neither PGC-1β nor PRC interacts with these transcription factors [29,34,35]. It is also worth noting that PGC-1 family members are not induced by the same signals within a tissue. For example, glucagon induces PGC-1α expression in liver via transcription