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VISIONS AND REFLECTIONS

PGC-1α: a master gene that is hard to master

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Abstract Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) is a transcriptional coactivator that favorably affects mitochondrial function. This concept is supported by an increasing amount of data including studies in PGC-1α gene-deleted mice, suggesting that PGC-1α is a rescue factor capable of boosting cell metabolism and promoting cell survival. However, this view has now been called into question by a recent study showing that adeno-associated virus-mediated PGC-1α overexpression causes overt cell degeneration in dopaminergic neurons. How is this to be understood, and can these seemingly conflicting findings tell us something about the role of PGC-1α in cell stress and in control of neuronal homeostasis?

Keywords PGC-1α · Mitochondria · Dopaminergic neurons · Transgenic animal · Adenovirus · Parkinson's disease

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The current interest in peroxisome proliferator-activated receptor-γ (PPARγ) coactivator-1α (PGC-1α) stems from the fact that oxidative stress and mitochondrial dysfunction are known to play a key role in the pathogenesis of many degenerative disorders including Parkinson's disease (PD) [1, 2]. Mitochondria are not only the energy powerhouse of the cell, producing ATP via oxidative phosphorylation, but mitochondria are also involved in the control of apoptosis, in oxidative free radical (ROS) production, and in cell calcium homeostasis. Mitochondria are considered to play a decisive role in the pathogenesis of PD, and respiratory chain dysfunction is a major culprit in both familiar and sporadic forms of PD [3]. Studies employing PGC-1α knockout mice revealed an increased sensitivity of dopaminergic neurons to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP) [4]. MPTP enhances ROS production leading to inhibition of complex I of the respiratory chain that is also often dysfunctional in patients with PD. Furthermore, meta-analysis of genes altered in PD revealed decreased levels of PGC-1α and its mitochondrial target genes [5]. This points to a role for PGC-1α in disease pathogenesis, suggesting that it could be a promising target for early intervention in PD.

In cells, the levels of PGC-1α are tightly regulated and influenced by both environmental (e.g., cold, fasting, physical activity) and cell-specific signals (e.g., growth factors, hormonal signaling, cell energy levels) [6, 7]. The effect of these signals converge on at least two transcription factors that ultimately determine the expression level of PGC-1α in the cell: (1) the cAMP response element binding protein (CREB), which promotes PGC-1α expression [4] and (2) the recently discovered Parkin-interacting substrate (PARIS) which acts as a repressor of PGC-1α expression [8]. Interestingly, PARIS itself is regulated via ubiquitination by the E3-ubiquitin ligase Parkin that is also

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mutated in a familial type of PD [3, 8]. Apart from transcriptional regulation, PGC-1α is subject to extensive posttranslational modifications, including phosphorylation by various protein kinases and deacetylation caused by the NAD-dependent silent information regulator T1 (SIRT1) [7]. These modifications can increase the inherent activity of PGC-1α on downstream genes and they may be quantitatively more important in the physiological setting than the mere upregulation of PGC-1α.

Adding to the physiological roles of PGC-1α in the nervous system it was recently reported that an inactivation of PGC-1α specifically in brain neurons using a calcium/calmodulin-dependent protein kinase IIα-Cre construct protected mice against diet-induced obesity and impaired the expression of nutrition-induced genes in the hypothalamus [9]. These observation lend credence to the view that neuronal expression of PGC-1α is important also for the control of energy balance at the whole body level. Apart from this, the neuronal inactivation of PGC-1α produced degenerative lesions in the brain and particularly in the striatum [9]. These lesions were similar to those observed previously in the whole-body PGC-1α-deficient mice [4].

In their study of PGC-1α overexpression in the rat nigrostriatal system using AAV vectors, Ciron et al. [10] reported an unexpected degeneration of dopaminergic neurons. The decrease in cell viability caused by PGC-1α overexpression was observed in the substantia nigra pars compacta (SNp), harboring the cell bodies of the dopaminergic neurons, and this effect was accompanied by the loss of nerve terminals in the striatum and with the depletion of dopamine and its metabolites. Behavioral analysis and tracing studies of neuronal connectivity further supported the conclusion that prolonged overexpression of PGC-1α in the SNp severely impairs the function of the dopaminergic neurons without major effects on other neuronal systems. Studies of embryonic mouse ventral midbrain neurons in culture showed that the number of mitochondria was increased after AAV-PGC-1α infections resulting in an enhanced cell respiration, increased ATP production, and a depolarization of the mitochondrial membrane potential. Furthermore, transcriptome analysis showed significant changes in several mitochondrial-linked genes in line with the observed increase in mitochondrial biogenesis and respiratory capacity induced by PGC-1α [10]. Notably, no single gene could be directly linked to the loss of dopaminergic neurons induced by PGC-1α overexpression, suggesting that the mitochondrial changes were due to alterations in gene regulatory networks affecting fundamental processes in cell homeostasis. What could then be the reasons for these dramatic effects observed with PGC-1α and are these effects restricted to brain and neuronal cells?

In considering the latter point, the finding that PGC-1α can have an unfavorable impact on cell physiology is not without precedent. In the heart, PGC-1α is a key regulator of mitochondrial biogenesis and energy-producing capacity, as determined by the ATP production. As shown by Lehman et al. [11], overexpression of PGC-1α in cardiac myocytes of transgenic mice leads to mitochondrial proliferation with dilated cardiomyopathy, which correlates with the expression level of PGC-1α. Similar adverse effects following PGC-1α overexpression were also reported for the heart [12], and for the skeletal muscle with and ensuing muscle atrophy [13] and insulin resistance [14].

Ciron et al. [10] also noted that the degree and time of onset of the degeneration of dopaminergic neurons correlated with the dose of AAV injected into the brain. The PGC-1α-mRNA levels in this study ranged from an about 5- to 300-fold increase compared to controls. Although no data on the actual protein levels were given, it is likely that they far exceed the normal levels in the neurons. This situation, in turn, may lead to a metabolic perturbation characterized by a mitochondrial hyperactivity with increased oxygen consumption resulting in anoxia and, subsequently, to energy depletion thereby overriding regulatory pathways necessary for neuronal survival. Furthermore, an increased mitochondrial respiratory capacity is intimately linked to an increased production of ROS that may further repress survival pathways, hence promoting apoptosis signaling. This effect may be especially prominent in dopaminergic neurons that are known to be particularly vulnerable cells and are sensitive to various types of oxidative [2] and endoplasmic reticulum stress [15]. Another possibility is that the increased number of mitochondria in PGC-1α-overexpressing neurons influences the axonal transport of these organelles [16] thereby perturbing their normal turnover. It is known that mitochondria are degraded via the process of selective autophagy called mitophagy, and a block at this stage could conceivably influence the turnover of proteins important for cell survival. It is also conceivable that PGC-1α, being part of different transcriptional active complexes in high abundance, may influence some genes and pathways that are not regulated by PGC-1α under normal circumstances. Many of the nuclear proteins interacting with PGC-1α, such as PPARγ, are themselves tightly regulated and they control various aspects of cell metabolism and inflammation. Particularly in neurons the precise genes and transcriptional pathways influenced by PGC-1α are not fully clarified.

Recently, Mudò et al. [17] reported that transgenic overexpression of PGC-1α in neurons increased the capability of the dopaminergic cells to tolerate MTPT-induced neurotoxicity. This finding contrasts with the results by Ciron et al. [10] but may be explained by the different

methods used to elevate PGC-1α in the brain. In this respect, the transgenic overexpression of PGC-1α during a longer time period may better model the physiological regulation of the protein than the acute high-level overexpression of PGC-1α brought about using AAV viruses. In line with this, transgenic overexpression of PGC-1α in mice was shown to significantly improve motoneuron functions and increase life span in the SOD1-G93A mouse model of amyotrophic lateral sclerosis (ALS) [18]. Beneficial effects of PGC-1α on motor neurons were observed also in another ALS mouse model and using transgenic mice with PGC-1α expression in all cells including motoneurons and glial cells [19]. This is important to note as it has been shown that glial cells can influence motoneurons and the disease pathogenesis of ALS [20, 21]. It would be highly interesting to study whether PGC-1α has a role in the interplay between glial cells and neurons as observed in ALS, and which probably occurs in other neurodegenerative diseases as well.

Comparing experimental models of neuroprotection, the viral and the transgenic approaches have shown to be rather similar in efficacy, as exemplified by the anti-apoptotic X chromosome-linked inhibitor of apoptosis protein (XIAP) in brain ischemia, using either AAV-XIAP expression [22] or transgenic XIAP mice [23]. In many cases, the viral approach has clear advantages in the study of brain diseases with the fast and effective delivery of the gene in question and with a high level of protein expression in the nervous system. In addition, the generation of transgenic mice takes time, it is expensive, and the exact site of integration of the transgene is usually not known, and may vary between mouse lines. In recent years, one has learn to control better the toxicity of the virus itself in brain by using different substrains of AAVs.

However, as shown here by the work of Ciron et al. [10] on PGC-1α, one drawback of the AAV-mediated overexpression is that the normal constrains and regulatory pathways of the protein in question can be changed resulting in deleterious effects on cell metabolism and viability. One way out of this dilemma is to consider ways to modulate the biological activity of PGC-1α to meet the actual requirement of the cell for energy production and cell metabolism. The levels and activity of PGC-1α in the cell are subjected to fine-tuned regulation by various biochemical substances and signals that can also be influenced pharmacologically by different drugs. Notably, in the study by Mudò et al. [17], the activation of PGC-1α by using the small-molecule compound, resveratrol produced almost a similar degree of neuroprotection of dopaminergic neurons as that observed with the transgenic overexpression of PGC-1α. The development of better drugs targeting PGC-1α may give us new possibilities to boost mitochondrial activity in a more controlled manner. Along this line, a better understanding of the physiological regulation of PGC-1α and its signaling cascades in neurons is a prerequisite for future therapies using this master gene in brain disorders, including PD.

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