

Review Article

The metabolic modulator PGC-1 α in cancer

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Abstract: The peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1 α) is a central modulator of cell metabolism. It regulates mitochondrial biogenesis and oxidative metabolism. Modifications and adaptations in cellular metabolism are hallmarks of cancer cells, thus, it is not surprising that PGC-1 α plays a role in cancer. Several recent articles have shown that PGC-1 α expression is altered in tumors and metastasis in relation to modifications in cellular metabolism. The potential uses of PGC-1 α as a therapeutic target and a biomarker of the advanced form of cancer will be summarized in this review.

Keywords: PGC1 alpha, prostate cancer, melanoma, breast cancer, pancreatic cancer, metabolism, mitochondria

Introduction

Modifications and adaptations in cellular metabolism are hallmarks of cancer cells. After the pioneering discovery, made by Otto Warburg, showing that cancer cells preferentially use glycolysis to meet their energetic needs, several studies have shown that cancer cells have an altered metabolism compared to normal cells. Recent findings have elucidated the metabolic changes, also termed metabolic reprogramming, occurring in cancer cells in response to environmental challenges such as hypoxia, nutrient scarcity, increased radical oxygen species (ROS), or pH modifications [1, 2]. These metabolic adaptations confer resistance to apoptosis and are required to sustain rapid cell proliferation, migration and invasion. Thus, interfering with cancer cell metabolism with drugs such as metformin (an inhibitor of the complex 1 of the mitochondrial respiratory chain), or 2-deoxyglucose (2-DG; an inhibitor of glycolysis), has been shown to decrease tumor growth and induce apoptosis in several cancer cells types [3-7].

One of the major and well-described modulators of cell metabolism is a member of the peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1) transcriptional co-activator family: PGC-1 α . PGC-1 α is implicated in mitochondrial biogenesis and oxidative metab-

olism. It is therefore not surprising that alterations in the activity and expression of PGC-1 α are associated with many diseases in different tissues. It is well established that PGC-1 α is implicated in diabetes, neurodegeneration and cardiovascular disease [8, 9], but several recent articles, discussed below, have also revealed that PGC-1 α plays an important role in cancer. In this review, after an overview of PGC-1 α , we will discuss the latest results concerning the role of this coactivator in tumorigenesis and the formation of metastases.

PGC-1 α is a transcriptional coactivator and a member of the PGC-1 protein family

The PGC-1 family is composed of three members, PGC-1 α , PGC-1 β and PRC (PGC-1-related coactivator), which share common structural features and modes of action (**Figure 1**). The first member of the PGC-1 family, PGC-1 α , was identified in the late 1990s and found to interact with the peroxisome proliferator-activated receptor- γ (PPAR γ) transcription factor in brown adipose tissue, a tissue rich in mitochondria and specialized in thermogenesis [10]. PGC-1 α is a transcriptional coactivator whose expression is induced in response to cold exposure in brown adipose tissue, and in skeletal muscle in association with the expression of decoupling mitochondrial proteins (UCPs: un-

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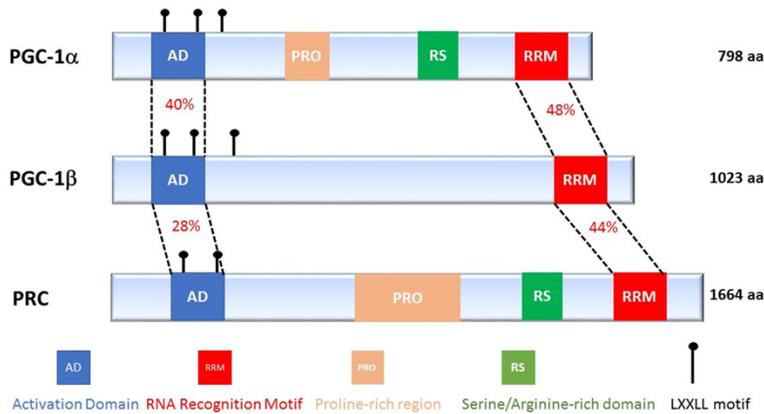


Figure 1. The PGC-1 protein family members. Schematic representation of the three members of the PGC-1 family, indicating their different regions and the % of homology between each member in the N and C-terminal region of the co-activators.

coupling proteins). PGC-1 β is the closest homologue of PGC-1 α . They share high sequence identity [11, 12], especially across several distinct domains including an N-terminal activation domain (40% homology), a central regulatory domain (35%) and a C-terminal RNA binding domain (48%). Both coactivators are highly expressed in oxidative tissues such as brown adipose tissue, heart, kidney, skeletal muscle and brain [13]. PRC is ubiquitously expressed and shares lower levels of homology with the two other members of the family (Figure 1) [14]. Of note, splice variants of PGC-1 α (NT-PGC-1 α and PGC-1 α 1-4) have been identified in skeletal muscle and their role and function remain poorly described [15].

The N-terminus of these coactivators contains a transcriptional activation domain as well as an important motif for interactions with nuclear receptors: the leucine-rich LXXLL motif [16]. The C-terminal domain has the highest homology between the three PGC-1 coactivators and includes an RNA recognition and binding site (RRM, RNA recognition motif) and a domain rich in serine and arginine (RS, serine/arginine-rich domain) [11, 12]. These two domains are known to be involved in post-transcriptional modifications of RNA [17]. Sequence analyses revealed that the PGC-1 family is conserved in many species, including primates, rodents, ruminants, birds, amphibians and fish.

PGC-1 coactivators act as transcriptional regulators but do not have a DNA-binding domain.

They bind to various transcription factors and nuclear receptors that recognize specific sequences in their target genes. While other transcriptional coactivators possess intrinsic histone acetyltransferase activity that facilitates chromatin remodeling and gene transcription, members of the PGC-1 family lack enzymatic activity. Therefore, PGC-1 coactivators exert their modulatory function on gene transcription by acting as an anchor platform for other proteins with histone acetyltransferase activity and by promoting the assembly of transcriptional machinery to trigger gene transcription.

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The N-terminal region of PGC-1 α has several LXXLL leucine-rich motifs, also called NR boxes, which are crucial for interactions between PGC-1 α and a wide variety of nuclear receptors and transcription factors (Figure 1). Among these transcription factors, PPAR α [18], the estrogen receptor (ER) [19], retinoid X receptor α (RXR α) [20], the glucocorticoid receptor (GR) [21], the hepatocyte nuclear factor-4 α (HNF4 α), nuclear respiratory factor 1 and 2 (NRF1/NRF), and sterol regulatory element-binding proteins 1 and 2 (SREBP1/2) are known to regulate the expression of genes implicated in several functions of cellular metabolism (Table 1).

PGC-1 α is a metabolic sensor of environmental stresses

The expression and activity of PGC-1 α are controlled by environmental and physiological stimuli. Temperature, more specifically the response to cold, is a major inducer of PGC-1 α expression in brown adipose tissue and muscle via the cAMP signaling pathway and activation of protein kinase A (PKA) [10]. The expression of PGC-1 α is also increased in muscle after exercise, via activation of Ca²⁺/calmodulin-dependent protein kinase IV (CaMKIV) and calcineurin A. Another mechanism known for regulating the expression of PGC-1 α in muscles after exercise involves the p38 mitogen-activated protein kinase (p38 MAPK protein) and phosphoryla-

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Table 1. Main transcription factors interacting with PGC-1 α

Transcription Factor	Function, Role	References
NRF1/NRF2	Mitochondrial biogenesis	[104, 105]
PPAR α /PPAR β	Mitochondrial biogenesis; Fatty acid oxidation	[106, 107]
PPAR γ	Mitochondrial biogenesis; UCP1 expression	[10, 57, 108-110]
ERR α /ERR β	Mitochondrial biogenesis	[111, 112]
TR β	CPT1 expression	[113, 114]
FXR	Triglyceride metabolism	[115]
LXR α /LXR β	Lipoprotein secretion	[116, 117]
GR; HNF4 α ; FOXO1	Neoglucogenesis	[11, 12, 28, 118]
MEF2	Muscle fiber type1 gene regulation	[59, 119]
Er α /Er β ; PXR	Unknown	[11, 120]
SREBP1/SREBP2	Lipogenesis; Lipoprotein secretion	[116]
Sox9	Chondrogenesis	[121]

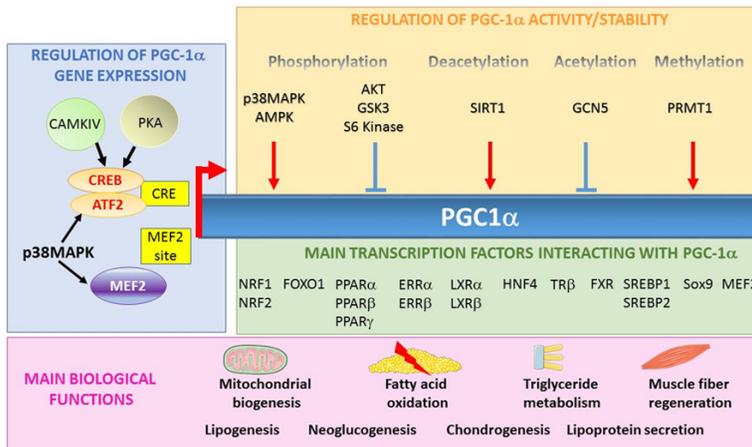


Figure 2. PGC-1 α , a co-activator implicated in several biological functions. PGC-1 α gene expression is mainly regulated by three transcription factors (CREB, ATF2 and MEF2) that bind to the CREB-responsive element (CRE) and myocyte enhancer factor-2 (MEF2). The protein is also regulated by post-translational modifications such as phosphorylation, deacetylation, acetylation and methylation. PGC-1 α interacts with numerous transcription factors and is implicated in several biological functions.

tion of the myocyte enhancer factor-2 (MEF2) and activating-transcription factor 2 (ATF2) transcription factors [22-24].

PGC-1 α is very sensitive to the energy status of the cell. It is finely regulated by the AMP-activated protein kinase (AMPK), a sensor of cellular AMP levels. AMPK is activated in muscle tissue during exercise and increases mitochondrial biogenesis and metabolism. The mitochondrial activation that is mediated by AMPK requires PGC-1 α activity [25, 26]. Similarly, fasting is another environmental signal that is known to regulate the expression of

PGC-1 α . In liver, the expression of PGC-1 α is increased in response to glucagon, a pancreatic hormone that induces activation of cAMP and CREB [27]. This induction of PGC-1 α in the liver during fasting leads to an increase in the expression of gluconeogenesis genes that promotes the production of hepatic glucose and maintains glucose homeostasis [28] *via* the association of PGC-1 α with transcription factors, such as HNF4 α [29] or forkhead box protein O1 (FOXO1) [30].

The transcriptional activity of PGC-1 α can also be modulated by post-translational modifications that positively or negatively affect its ability to

recruit complexes capable of remodeling chromatin and activating gene transcription. These post-translational modifications include phosphorylation, acetylation, methylation and ubiquitination and are able to not only modulate the intensity of the response mediated by PGC-1 α , but also to determine which transcription factor will interact with PGC-1 α .

PGC-1 α is phosphorylated on serine and threonine residues at different sites by several kinases. The most well characterized of these kinases are p38 AMPK [26, 31, 32], AKT [33], AMPK [34], S6 kinase (ribosomal protein S6

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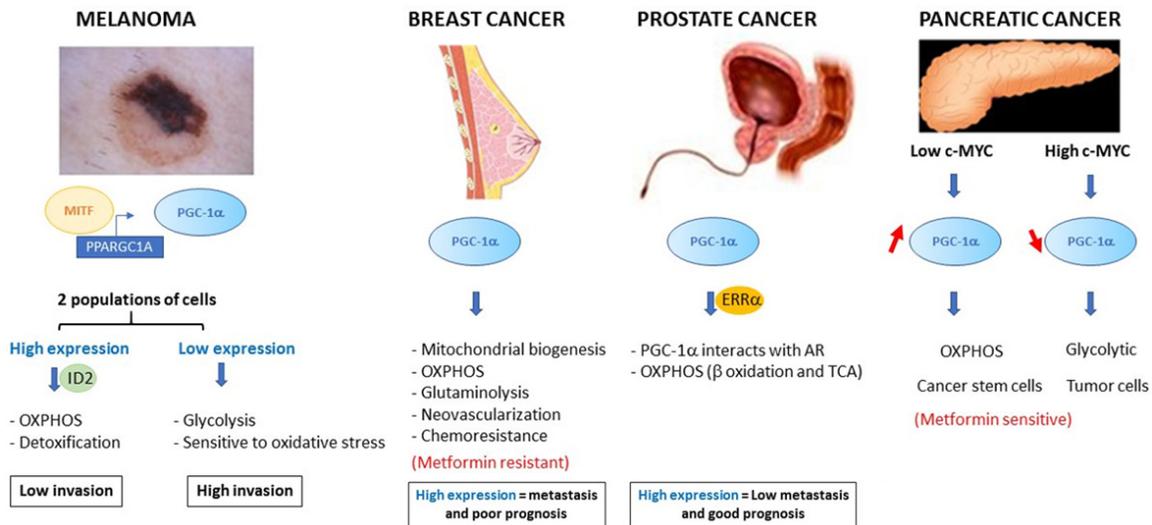


Figure 3. PGC-1 α and cancer. Schematic summary of the different roles of PGC-1 α in melanoma, breast and pancreatic cancer. The expression of PGC-1 α is associated with modifications to cancer cell metabolism, different phenotypes associated with the aggressiveness of the cancer and patient survival.

kinase) [35] and GSK3 β (glycogen synthase kinase 3 β) [36]. The phosphorylation of these specific residues can lead to the activation of PGC-1 α , as is observed for p38 MAPK and AMPK, which stabilize or activate PGC-1 α , respectively [26, 34]. In contrast, they can also induce the inhibition of PGC-1 α , for example, Akt inhibits PGC-1 α activity and GSK3 β increases the proteasomal degradation of PGC-1 α [36]. Finally, phosphorylation by S6 kinase prevents the interaction between PGC-1 α and HNF4 α (Figure 2) [35].

PGC-1 α is also regulated by the action of deacetylases and acetylases. For instance, sirtuin 1 (SIRT1) activates PGC-1 α by the deacetylation of the lysine residues [37, 38] and GCN5 (lysine acetyltransferase 2A) acetylates and inactivates PGC-1 α [39]. PGC-1 α is also activated following the methylation of arginine residues in the C-terminal position by PRMT1 (protein arginine methyltransferase 1) [40].

PGC-1 α is a master regulator of oxidative metabolism

One of the main functions of PGC-1 α is the control of energy metabolism, which is achieved by acting both on mitochondrial biogenesis and oxidative phosphorylation. This is confirmed by numerous *in vitro* and *in vivo* studies that have demonstrated that PGC-1 α is involved in mitochondrial biogenesis. In fact, overex-

pression of PGC-1 α in adipocytes, muscle cells, cardiac myocytes and osteoblasts leads to an increase in the amount of mitochondrial DNA [41-44]. PGC-1 α initiates mitochondrial biogenesis by activating transcription factors that regulate the expression of mitochondrial proteins that are encoded by nuclear DNA [45]. Mitochondrial DNA encodes some protein subunits of the mitochondrial respiratory chain and proteins that are required for mitochondrial protein synthesis. All other mitochondrial proteins are encoded by nuclear DNA and therefore, mitochondrial biogenesis requires coordination between these two genomes. This coordination is orchestrated by PGC-1 α , which activates transcription factors that control the expression of mitochondrial genes encoded by the nucleus [16, 46]. For example, PGC-1 α activates NRF1 and NRF2 [44, 47-49], thus triggering the expression of several proteins: the β -ATP synthase, cytochrome c, cytochrome c oxidase subunits, transcription factor A mitochondrial (TFAM) [44, 50], and transcription factor B1 M and B2 M (TFB1M, TFB2M) [51]. Interestingly, NRFs induce TFAM, a transcriptional activator, which translocates to the mitochondrion and plays an essential role in the replication, transcription, and maintenance of mitochondrial DNA [52, 53]. By regulating the expression level of TFAM, PGC-1 α controls the expression of proteins encoded by mitochondrial DNA.

The induction of PGC-1 α correlates with physiological situations such as cold, prolonged exercise or fasting (see above). In these circumstances, fatty acids become the preferred energy substrate for the cells. Thus, PGC-1 α controls expression of genes involved in fatty acid oxidation [54] via PPAR α [55]. PGC-1 α induces expression of the fatty acid transporters CD36 and carnitine palmitoyltransferase I (CPT1), which allow fatty acids to enter into the cell (CD36) and then inside the mitochondria (CPT1), where they are ultimately oxidized. Two transcription factors have been identified as partners of PGC-1 α for the regulation of β -oxidation: PPAR α [18, 41, 56] and estrogen-related receptor alpha (ERR α) [57, 58].

In addition to its roles in mitochondrial biogenesis and oxidative phosphorylation, PGC-1 α is also involved in the regulation of glucose metabolism. Induction of PGC-1 α in skeletal muscle activates the expression of glucose transporter 4 (GLUT4), via activation of the MEF2 transcription factor, which increases glucose uptake in these cells [59]. This increase in intracellular glucose concentration is coupled with a decrease in glycolysis and an increase in glycogen storage [60]. Indeed, the induction of PGC-1 α leads to the expression of PDK4, via ERR α . This enzyme inhibits glucose oxidation via inhibition of PDH and thus promotes glycogen synthesis [61, 62]. Any increase in oxidation via the mitochondrial respiratory chain is associated with the consequent production of ROS. Increased levels of ROS can lead to genotoxic stress and cell death. As a result, cells have developed defense mechanisms against these potentially toxic species. PGC-1 α is involved in the regulation of ROS levels by inducing the expression of several enzymes involved in the detoxification of ROS, such as the superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) [63, 64]. The ability of PGC-1 α to induce these antioxidant enzymes are essential for the protection against ROS-induced cell damage and cell death [65].

Why is PGC-1 α suspected to play a role cancer biology?

Cancer cells face numerous stresses and environmental conditions and PGC-1 α may play a role in their response to this environment. Firstly, nutrient and oxygen supplies fluctuate in

tumors and cancer cells must therefore adapt their metabolism, alternatively relying on glycolysis or oxidative phosphorylation (OXPHOS). These variations will modify the energy status of cancer cells and interfere with signaling pathways (AMPK, mTORC1), transcription factors (hypoxia-inducible factor 1 alpha HIF1 α), protein expression (glucose transporter GLUT) that are known to interact with PGC-1 α .

Secondly, cancer treatments such as radiation and chemotherapy have been shown to induce oxidative stress in tumors [66, 67]. ROS production can either induce cell death or resistance to treatments through mechanisms implicating anti-oxidant enzymes [68]. Oxygen species are mainly produced by the mitochondria. Thus, regulation of mitochondrial biogenesis and PGC-1 α may interfere with the responses to treatments.

Finally, recent studies have shown that lipids are a source of energy for cancer cells. Adipocytes are important members of the tumor microenvironment as they promote cancer cell aggressiveness through the release of cytokines (adipokines), such as Interleukin 6, to increase the invasive properties of breast cancer cells, or chemokine (C-C motif) ligand 7, to promote local dissemination of prostate cancer cells [4, 69]. Additionally, adipocytes release fatty acids from lipid droplets, which are oxidized by fatty acid β -oxidation in cancer cells. This metabolic crosstalk between adipocytes and cancer cells promotes aggressiveness and the formation of metastasis [70].

Role of PGC-1 α in cancer

PGC-1 α in melanoma

Recent studies have shown that melanoma is comprised of two subpopulations of cells, one expressing high levels of PGC-1 α and a second subpopulation with very low PGC-1 α expression [71-73]. These two populations have different metabolic and phenotypic profiles (**Figure 3**). PGC-1 α -overexpressing melanoma cells have a very high rate of mitochondrial oxidative metabolism and the ability to efficiently detoxify ROS, making them OXPHOS-dependent and resistant to oxidative stress [73, 74]. Overexpression of PGC-1 α confers a significant proliferative and survival potential, but PGC-1 α suppresses the invasive properties of these

cells. Luo *et al.* have shown that PGC-1 α suppresses this pro-metastatic program through the inhibitor of DNA binding 2 protein (ID2) and the TCF4 transcription factor [74]. PGC-1 α induces the transcription of ID2 that subsequently binds to and inactivates the TCF4 transcription factor, preventing it from binding to the promoters of its target genes. Inactivation of TCF4 leads to reduced expression of genes related to the formation of metastases, including integrins, which are known to promote invasion and metastatic spread. In contrast, melanoma cells expressing low levels of PGC-1 α contain few mitochondria, are highly dependent on glycolysis and are highly sensitive to ROS-induced apoptosis [73-75]. However, this subpopulation of cells has a higher expression of the pro-metastatic genes including integrins, transforming growth factor β (TGF β) and Wnt. The low expression of PGC-1 α results in decreased melanoma cell proliferation and strengthened ability to form metastases. Once implanted at the metastatic site, these cells are able to increase their expression of PGC-1 α , which increases growth [73, 74]. Expression of PGC-1 α in these two subpopulations of melanomas is regulated by the oncogenic transcription factor microphthalmia-associated transcription factor (MITF) [73, 76, 77]. Given the cytoprotective properties of PGC-1 α , it is not surprising that it is involved in the response to anticancer treatments. In melanoma, induction of PGC-1 α contributes to chemoresistance by increasing mitochondrial oxidative metabolism [76]. In melanoma cells that strongly express PGC-1 α , depletion of PGC-1 α or inhibition of the respiratory chain increases the efficacy of anti-melanoma chemotherapy by increasing the levels of ROS and apoptosis [73, 76, 78, 79]. In conclusion, PGC-1 α plays a dual role in melanoma by influencing both cell survival and metastatic spread.

PGC-1 α in breast cancer

In breast cancer, PGC-1 α activates nuclear receptors and transcription factors, such as PPAR α , ERR α , NRF1 and NRF2, leading to increased mitochondrial biogenesis and OXPHOS and thus generating the large amounts of ATP required for tumor growth. However, although mitochondrial respiration appears to be the main biological function of PGC-1 α , additional crucial roles have also been described in other

metabolic pathways, including glycolysis, glutaminolysis, regulation of fatty acid oxidation and detoxification [18, 80, 81]. Indeed, the PGC-1 α /ERR α complex modulates the expression of glutamine metabolism enzymes that increase glutamine absorption and thus increase Krebs cycle flux (**Figure 3**) [82]. In addition, the PGC-1 α /ERR α axis co-stimulates expression of genes regulating lipogenesis [82]. Thus, the intermediate metabolites, derived from the catabolism of glutamine, are mainly directed towards the *de novo* biosynthesis of fatty acids. Overexpression of PGC-1 α , and therefore the activation of ERR α , confers growth and proliferation advantages to breast cancer cells, even when nutrients are scarce and/or under conditions of hypoxia. These observations correlate with clinical data showing that overexpression of PGC-1 α and its target glutaminolysis genes are associated with poor prognosis for breast cancer patients. In addition to its intrinsic effects on metabolism, PGC-1 α is also involved in the regulation of angiogenesis in mammary tumors [83]. It enables neovascularization and thus the increase of available nutrients for mammary tumor cells, which leads to tumor growth. The mechanisms by which PGC-1 α induces tumor angiogenesis have not yet been fully elucidated but appear to be regulated by vascular endothelial growth factor (VEGF) independently of HIF-1 [83, 84]. Tumor cells must switch from a state of rapid proliferation to an invasive phenotype in order to be able to metastasize [85]. The pathways and metabolic requirements that allow tumor cells to switch between proliferation and migration/invasion are still largely unknown. Interestingly, a recent study suggested that PGC-1 α may be involved in this mechanism [86]. This study showed that circulating mammary tumor cells express high levels of PGC-1 α and exhibit an increase in mitochondrial biogenesis, resulting in the formation of metastases. In addition, the authors have shown that inhibition of PGC-1 α in these cells inhibits ATP production, reduces actin cytoskeleton remodeling, decreases intravasation and extravasation, and decreases cell survival [86]. Clinical analyzes also showed that PGC-1 α levels are increased in mammary tumors of patients with bone metastases, and revealed a negative correlation between PGC-1 α expression and patient survival [82, 86]. Although this study does not identify the transcription fac-

tor that is targeted by PGC-1 α in circulating cancer cells, these results show that PGC-1 α is essential for the formation of metastases. The role of PGC-1 α in bioenergetic flexibility and thus mammary tumor cell metastasis was confirmed by the study of Andrzejewski *et al.*, which highlights the importance of PGC-1 α in resistance to treatments for this type of cancer [87]. Indeed, activation of several metabolic pathways and detoxification of ROS by PGC-1 α in breast cancer tissue not only confers proliferative advantages but it also leads to metabolic adaptations that can bypass therapies [88]. For example, the use of ERR α antagonists prevents PGC-1 α -mediated metabolic reprogramming and sensitizes mammary tumor cells to therapies [88]. Another study shows that PGC-1 α -mediated bioenergetic capabilities help mammary tumor cells to deal with the metabolic disruptor metformin [87]. In contrast, it has been shown that PGC-1 α -overexpressing mammary tumor cells become dependent on the folate cycle, which is essential for nucleotide synthesis and tumor proliferation, thus these cells are more vulnerable to antifolates, such as methotrexate [89].

PGC-1 α in pancreatic cancer

The c-MYC oncogene causes metabolic reprogramming, which is critical for the proliferation and survival of tumor cells. Recently, it has been shown in pancreatic adenocarcinoma that c-MYC is a direct regulator of PGC-1 α [90]. Indeed, c-MYC binds to the promoter of PGC-1 α and inhibits its transcription. Consequently, it has been shown that the c-MYC/PGC-1 α ratio dictates the metabolic phenotype of pancreatic adenocarcinoma cells [90]. Pancreatic cancer stem cells (CSC) express high levels of PGC-1 α because c-MYC is not expressed and the strong expression of PGC-1 α is essential to maintain mitochondrial respiration. Interestingly, overexpression of PGC-1 α makes CSCs more sensitive to metformin than differentiated pancreatic tumor cells and they are unable to activate glycolysis in instances of metabolic stress because of the very low expression of c-MYC (**Figure 3**). In contrast, differentiated pancreatic tumor cells strongly express c-MYC and have low levels of PGC-1 α . Resistance often appears during treatment with metformin and an intermediate phenotype emerges in the CSCs, with reduced OXPHOS but increased

glycolysis, which is the consequence of the increase in the c-MYC/PGC-1 α ratio. Inhibition of c-MYC in this population of CSCs increases their sensitivity to metformin. These results indicate that the balance between c-MYC and PGC-1 α determines the metabolic plasticity and metformin sensitivity of pancreatic CSCs [90].

PGC-1 α in prostate cancer

The contribution of PGC-1 α to prostate cancer has only recently been considered and few studies address this role [91-93]. The role of PGC-1 α in prostate cancer (PCa) is similar than of melanoma, i.e., subpopulations with different PGC-1 α expression patterns: a sub-population overexpressing PGC-1 α that is proliferative but poorly invasive, and a sub-population with low expression of PGC-1 α that is very aggressive (**Figure 3**). Indeed, Shiota *et al.* show that PGC-1 α promotes tumor growth of a subpopulation of androgen-dependent prostatic cancer cells, *via* activation of the androgen receptor and its target genes [91]. Androgen dependence is a primary characteristic of prostatic tumors and PGC-1 α interacts with and activates the androgen receptor (AR) to modify cancer cell metabolism, leading to an increase in mitochondrial biogenesis and glucose and fatty acid oxidation [91]. In androgen-dependent PCa cells the inhibition of PGC-1 α induces cell cycle arrest in G1 phase and thus suppresses their growth [91]. Moreover, in these cells, expression of PGC-1 α is induced by AMPK in response to androgens [92]. This positive regulation sustains expression of PGC-1 α and increases its influence on tumor metabolism [92]. Recently, Torrano *et al.* identified PGC-1 α as a suppressor of tumor progression based on a bioinformatic analysis of several PCa databases [93]. This observation was confirmed *in vivo* using an androgen-independent prostatic tumor cell line. In fact, injection of cells overexpressing PGC-1 α into a mouse model decreased the progression and the formation of PCa metastases. This tumor suppressor effect of PGC-1 α is mediated by ERR α and regulation of a catabolic transcriptional program. Indeed, the PGC-1 α /ERR α complex increases with β -oxidation and Krebs cycle activity, which weakens the Warburg effect and therefore lowers tumor aggressiveness. In addition, this study shows that, in patients, expression of

PGC-1 α gradually decreases with each increasing grade of tumor, thus highlighting the prognostic value of PGC-1 α in prostate cancer [93].

PGC-1 α in other cancers

The role of PGC-1 α is emerging in other cancers, including hepatocarcinoma [94], colon cancer [95-97], renal cell carcinoma [98] and ovarian cancer [99]. In most of these studies, overexpression of the co-activator in cell lines derived from these cancers inhibits proliferation and/or its low expression is associated with a poor prognosis. However, paradoxically, chemotherapy has been shown to increase PGC-1 α expression in colon cancer and promotes chemoresistance through the activation of sirtuin 1 and oxidative metabolism [100].

Is PGC-1 α a potential theragnosis tool?

Depending on the type of cancer, the expression level of PGC-1 α has an impact on the prognosis: high levels of expression predict a good outcome for patients with prostate cancer and melanoma, whereas it is bad for breast cancer patients. In pancreatic cancer, PGC-1 α is a characteristic of cancer stem cells, which are thought to be at the origin of cancer relapses. Thus, level of expression of PGC-1 α may be a valuable biomarker to diagnose the aggressiveness of cancers and, in some cases, the response to treatment. The metabolic status of cancer cells may affect the response to treatments. For example, one can expect that cells relying on oxidative phosphorylation would be more sensitive to drugs that target the mitochondria. This hypothesis was raised by a recent study performed in non-small cell lung cancer showing that metformin does not affect cells that have been depleted of mitochondrial DNA [101]. Mitochondrial metabolism is fundamental for the maintenance of cancer stem cells, and interestingly, several studies have shown that cancer stem cells are very sensitive to metformin, which specifically targets mitochondrial metabolism [102, 103]. Furthermore, the status of PGC-1 α could also be important given its roles in drug detoxification and the control of antioxidant enzyme expression. Analysis of PGC-1 α expression could therefore provide important information concerning patient prognosis and in selecting which treatments to prescribe.

In conclusion, there is much evidence proving that PGC-1 α plays a role in cancer. However, it is important to elucidate its role in the initiation of tumorigenesis, the progression of tumors, the formation of metastases and the response to treatments. Depending on the tissue, the tumor stage, the microenvironment and certainly the experimental conditions, tumor cells show significant differences in the expression and the activity of PGC-1 α . Unlike oncogenes or tumor suppressor genes, mutations, amplifications or deletions of PGC-1 α are very rarely detected in tumors. Despite the fact that PGC-1 α interacts with a wide variety of transcription factors and is regulated by several signaling pathways, the exact mechanisms that drive the effects of PGC-1 α are still poorly known and require further investigations.

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Disclosure of conflict of interest

None.

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