

The Role of PGC1 α in Cancer Metabolism and its Therapeutic Implications

Zheqiong Tan^{1,2,3}, Xiangjian Luo^{1,2,3}, Lanbo Xiao^{1,2,3}, Min Tang^{1,2,3}, Ann M. Bode⁴, Zigang Dong⁴, and Ya Cao^{1,2,3}

Abstract

PGC1 α is a transcription factor coactivator that influences a majority of cellular metabolic pathways. Abnormal expression of PGC1 α is associated with several chronic diseases and, in recent years, it has been shown to be a critical controller of cancer development. PGC1 α acts as a stress sensor in cancer cells and can be activated by nutrient deprivation, oxidative damage, and chemotherapy. It influences mitochondria respiration, reactive oxygen species defense system, and fatty acid metabolism by interacting with specific transcription factors. The characteristic traits of PGC1 α in maintaining metabolic homeostasis promote cancer cell survival and tumor metastasis in harsh microenvironments. Not only does PGC1 α act as a coactivator, but is also itself

controlled by oncogenes and transcription factors. PGC1 α and these molecules can form signaling axes that include PML/PGC1 α /PPAR α , MTF/PGC1 α , and PGC1 α /ERR α , which are important in regulating metabolic adaptation in specific cancer types. Some of these PGC1 α -associated pathways are inherently activated in cancer cells, and others are induced by stress, which enable cancer cells to acquire resistance against therapy. Notably, certain therapeutic-resistant cancer cells are addicted to PGC1 α -dependent metabolic activities. Suppression of PGC1 α expression resensitizes these cells to therapeutic treatments, which implicates PGC1 α as a promising target in cancer molecular classification and therapy. *Mol Cancer Ther*; 15(5); 774–82. ©2016 AACR.

Introduction

Metabolic reprogramming is considered to be a hallmark of cancer (1). Glycolysis, mitochondrial respiration, glutaminolysis, and fatty acid metabolism are important participants in cancer development (2–6). These processes provide cancer cells with an adaptable metabolic feature and afford survival opportunities for cancer cells undergoing stress (7–9). Among the numerous regulators or mediators of cancer metabolism, PPAR γ coactivator-1 alpha (PGC1 α) is emerging as an essential controller of multiple metabolic pathways (10, 11).

PGC1 α is strongly activated by conditions causing energy limitation, including cold, exercise, and fasting, and is particularly abundant in tissues demanding large energy consumption (12–14). Once activated, PGC1 α interacts with several transcription factors and affects various biologic activities under normal physiologic conditions (15). Induced by exercise, PGC1 α can promote a functional fiber switch toward more oxidative types in skeletal muscle cells by interacting with muscle-specific myocyte enhancer factor 2 family transcription factors (16, 17). PGC1 α also facilitates

mitochondrial oxidative phosphorylation (OxPhos) by coactivating nuclear respiratory factor 1 and estrogen-related receptors (ERR; refs. 18, 19). It has been identified to stimulate fatty acid oxidation (FAO) through interactions with several transcription factors including sirtuin 1 (SIRT1), PPARs, and hepatocyte nuclear factor 4 (20–25), and PGC1 α also increases autophagy and thermogenesis through transcription factor EB and uncoupling protein-1, respectively, under stress condition (26–30). In addition, it has been shown to protect cells against oxidative damage through nuclear factor erythroid 2 (Nrf2) and forkhead box O3 (31–33).

In all of these instances, PGC1 α functions as a necessary adaptor for cells to maintain metabolic balance under harsh situations, and it plays a protective role in preventing chronic disease, such as skeletal muscle atrophy, heart failure, neurodegeneration, obesity, diabetes, and hepatic steatosis, and some of these diseases are predisposing factors for cancer initiation (10, 11, 34, 35). Recently, several advances have shown that PGC1 α expression is tightly associated with cancer progression (10, 11). The exceptional ability of PGC1 α in manipulating cellular metabolism enables cancer cells to thrive under a constantly fluctuating energy status, and highlights the importance of PGC1 α in effective cancer therapy (36).

Structure and Regulation Mechanism of PGC1 α

The *PGC1 α* gene is located on chromosome 4 in human and encodes a protein containing 798 amino acids (29). When activated, PGC1 α can be recruited as a transcriptional coactivator to subsequently dock or bind with transcription factors or nuclear receptors (NR; refs. 15, 37). The N-terminal activation domain and LXXLL motifs of PGC1 α interact with various transcription factors (19, 37, 38). Proteins, such as CREB-binding protein, p300 and steroid receptor that acetylate histones, can be sequentially

¹Cancer Research Institute, Xiangya School of Medicine, Central South University, Hunan, China. ²Key Laboratory of Chinese Ministry of Education, Central South University, Hunan, China. ³Key Laboratory of Carcinogenesis of Chinese Ministry of Public Health, Central South University, Hunan, China. ⁴The Hormel Institute, University of Minnesota, Austin, Minnesota.

Corresponding Author: Ya Cao, Cancer Research Institute, Xiangya School of Medicine, Central South University, Xiangya Road 110, Changsha 410078, China. Phone: 860-731-8480-5448; Fax: 860-731-8447-0589; E-mail: ycao98@vip.sina.com

doi: 10.1158/1535-7163.MCT-15-0621

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recruited to the PGC1 α transcriptional activator complex, to remodel the chromatin structure and provide optimal biochemical conditions for target gene transactivation (39). The C terminal of PGC-1 α is believed to recruit the thyroid receptor-associated protein/vitamin D receptor-interacting protein/mediator complex that facilitates transcription initiation and interferes with RNA processing through Ser/Arg-rich or RNA-binding domains (40, 41).

Notably, PGC1 α is controlled by several posttranslational modifications. Because PGC1 α is markedly sensitive to cellular energy status, it is tightly regulated by stress sensors such as AMP-activated protein kinase (AMPK) and SIRT1. Both AMPK-mediated phosphorylation and SIRT1-mediated deacetylation activate PGC1 α under energy deprivation conditions (42, 43). In addition, the p38 MAPK stabilizes the PGC1 α protein by increasing its phosphorylation state (44). On the other hand, methylation of the arginine residues at the C-terminal region by protein arginine methyltransferase 1 (PRMT1) decreases PGC1 α stability whereas phosphorylation of PGC-1 α by Akt/protein kinase B and SUMOylation at the conserved lysine residue 183 attenuate PGC1 α activity (44–46). These diverse posttranslational modifications direct PGC1 α to different target genes. In addition to posttranslational modifications, PGC1 α is also influenced by cellular calcium (Ca²⁺) and cyclic adenosine monophosphate signaling (47, 48). Notably, some transcription factors coactivated by PGC1 α can, in turn, regulate PGC1 α , comprising autoregulatory loops that augment target gene transcription (17).

PGC1 α and Cancer Metabolism

PGC1 α has been shown to be a promoter of carcinogenesis in chemical-induced colon and liver carcinoma mouse models (49).

Ectopic expression of PGC1 α has been observed in several cancer types (50–53), and it is regulated by several oncogenes and signaling pathways (Fig. 1; refs.54–57). Similar to its normal physiologic functions, PGC1 α primarily regulates mitochondrial respiration and detoxification of reactive oxygen species (ROS) in cancer cells through specific signaling pathways and transcription factors (Table 1). In addition, the involvement of PGC1 α in regulating FAO and glucose- or glutamine-derived lipogenesis in cancer cells has become clearer in recent years (Fig. 2; refs.49, 51, 58).

MITF/PGC1 α Axis in Melanoma

Among all its functions, PGC1 α -dependent regulation of OxPhos is best studied in cancer, especially in melanoma. On the basis of PGC1 α expression levels, melanomas have been defined into two subsets with different biologic phenotypes (53, 59, 60). The PGC1 α -positive cells exhibit elevated mitochondrial oxidative metabolism and substantial ROS detoxifying capacities. In contrast, the PGC1 α -negative cells are dependent on glycolysis for survival and are more sensitive to ROS-induced apoptosis (53). In this context, PGC1 α is transactivated by the oncogenic melanocyte lineage-specification transcription factor (MITF), and the PGC1 α -negative cells seldom express MITF (57, 61). These findings indicate that melanomas classified by the expression of MITF/PGC1 α have different metabolic capacities, resulting in distinct destinies following ROS-inducing treatments (53, 57).

The V600E BRAF mutation plays a critical role in melanoma-gensis by constitutively activating the MAPK signaling pathways (62, 63). Although the BRAF inhibitor, vemurafenib, and the MEK inhibitor, selumetinib, have achieved superior clinical effects to treat BRAF V600E-positive individuals, *de novo* and acquired

Figure 1. Regulation mechanisms of PGC1 α in cancer. Oncogenes such as *MITF*, *P53* enhance the transcriptional activity of PGC1 α , whereas *MYC* and *HIF* suppress it. PGC1 α can also be activated by posttranslational modifications. It is deacetylated by PML or SIRT1, and is phosphorylated by AMPK in cancer cells.

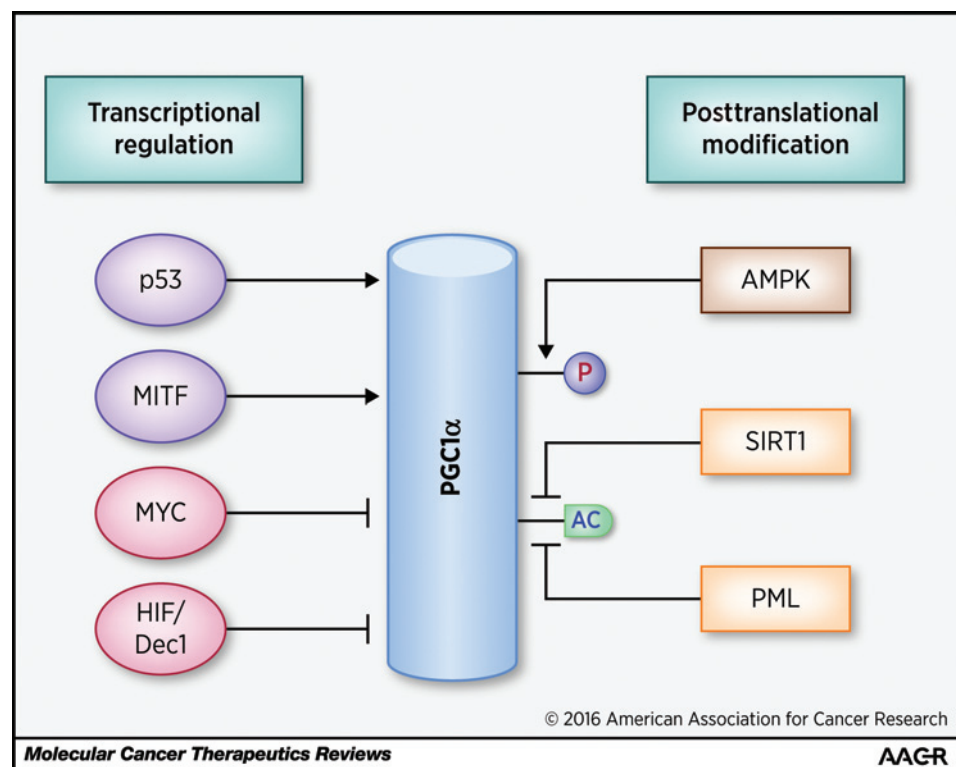


Table 1. A summary of PGC1 α -dependent signaling in cancer

Signaling axis	Cancer type	Metabolic pathways	Function	References
MITF/PGC1 α	Melanoma	OxPhos; ROS clearance	Resistance to BRAF or MEK inhibitors	(53, 57, 68)
PGC1 α /ERR α	Breast cancer	OxPhos; Glycolysis	Support anchorage independent growth	(70)
PGC1 α /ERR α	ERBB2/Neu-induced breast cancer	Glutamine-derived lipogenesis	Promote cell growth in hypoxia	(51)
PML/PGC1 α /PPAR α	Breast cancer	FAO	Promote cell growth and luminal filling	(58)
Androgen/AR/AMPK/PGC1 α	Prostate cancer	OxPhos; Glucose and FAO	Promote cell growth	(52, 93, 94)
p53/PGC1 α	Lung and liver cancer	OxPhos; ROS clearance	Contribute to p53 target selection; Resistance to transient starvation	(96)
SIRT1/PGC1 α /Nrf2	Breast, ovarian, colon, and lung cancer	ROS clearance	A target axis of miR-34 and metformin	(102)
RIP1/PGC1 α	Lung cancer	OxPhos; Glycolysis	Maintain DNA integrity and promote cell growth	(98)
PGC1 α /ACLY-FASN	Colon and liver cancer	Glucose-derived lipogenesis	Promote tumor growth	(49)
MYC/PGC1 α ^a	PDAC	OxPhos; glycolysis	Resistance to metformin	(56)
HIF/Dec1/PGC1 α ^a	ccRCC	OxPhos; ROS	Promote tumor growth	(55)

^aPGC1 α is suppressed by the oncogene or signaling pathway in this context.

resistance are still prevalent (64–67). PGC1 α and MITF are induced in both melanoma cell lines and patient biopsies following BRAF or MEK inhibition (57). MITF/PGC1 α signaling promotes OxPhos and protects drug-resistant cells from BRAF inhibitor-induced apoptosis. Encouragingly, a genome-wide siRNA screen and mRNA expression profile of resistant melanoma cell lines showed that resistance can be abrogated by inhibiting mTORC1/2 (68). Inhibition of mTORC1/2 decreases MITF nuclear localization and PGC1 α expression. The combination inhibition of MEK and mTORC1/2 markedly reduces xenograft tumor proliferation in MEK inhibitor-resistant mice (Fig. 3). This finding supports the idea that PGC1 α could be a candidate biomarker to determine therapeutic strategies. At the very least, blocking mitochondria respiration genes or mTORC1/2 signaling could resensitize cancer cells to BRAF or MEK inhibition in melanomas harboring activated MITF/PGC1 α /OxPhos signaling.

PGC1 α /ERR α axis in breast cancer

ERR α is a ligand-independent NR that regulates a number of metabolic genes in the presence of a coactivator, such as PGC1 α (69). PGC1 α and ERR α are both downstream proteins of the kinase suppressor of RAS1 (KSR1), a molecular supporting Ras-induced transformation in breast cancer (70). The interaction of PGC1 α and ERR α is required to promote OxPhos and glycolysis in an H-Ras^{V12}/KSR1-dependent manner to support anchorage-independent growth. Besides glucose use, glutamine utilization is also a characteristic feature of cancer metabolism (71), and the PGC1 α /ERR α axis was reported to regulate glutaminolysis in the ErbB2/Neu-induced breast cancer model (51). This axis increases the expression of glutamine metabolism genes and manipulates glutamine-derived carbon flux into lipogenesis, which favors the proliferation of breast cancer cells in hypoxia. On the other hand, the axis was also reported to increase angiogenesis by promoting VEGF secretion in the same model (72). Indeed, the hypoxia-inducible factor 1 (HIF1)-independent regulation of VEGF by PGC1 α /ERR α signaling was already reported in muscle cells under nutrient-deprivation conditions (73). These observations indicated that this signaling axis is responsive to microenvironmental stress and can be a promoter of cancer metastasis.

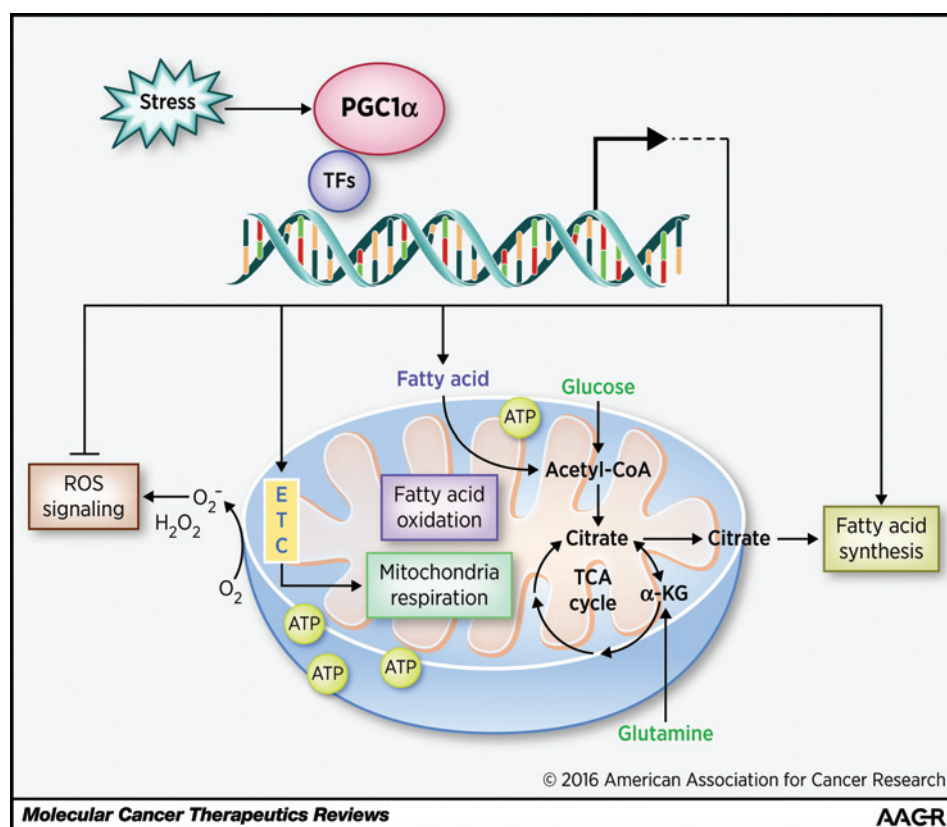
Another group demonstrated that PGC1 α and ERR α are over-expressed in brain metastatic breast cancer cells, with enhanced mitochondria respiration, FAO, glycolysis, and elimination of ROS (74). These changes give brain metastatic cells a considerable growth advantage, which is accompanied by resistance to therapeutic drugs. Recently, a study also confirmed that PGC1 α expression is markedly upregulated in circulating cancer cells (CCC) in a breast cancer metastatic mouse model (75). These cells relied on PGC1 α to maintain mitochondria activity during their transition to target organs. Clinical analysis in this research also indicated that PGC1 α is enriched in invasive ductal breast cancer patients with bone marrow dissemination, and illustrated a significant negative correlation between PGC1 α expression and patient outcome. Even though this study did not identify the target transcription factor of PGC1 α in CCCs, the data illustrated that PGC1 α is essential in cancer metastasis.

Overall, the PGC1 α /ERR α signaling axis is responsible for altering cellular metabolic status and guarantees cancer cell survival under limited nutrient supply and high-energy demanding microenvironments (76). Disruption of PGC1 α , ERR α , or OxPhos genes could abrogate these malignant properties of cancer providing valuable strategies to achieve better, more effective, therapeutic effects.

MYC/PGC1 α axis in pancreatic ductal adenocarcinoma

MYC-driven metabolic reprogramming is critical for cancer cell survival and proliferation (77, 78). Most recently, MYC has been confirmed to be a direct regulator of PGC1 α in pancreatic ductal adenocarcinoma (PDAC; ref. 56). It binds to the promoter of PGC1 α and has an inhibitory effect on PGC1 α at transcriptional level. The MYC/PGC1 α ratio was reported to be a main controller of metabolic phenotype in PDAC cells. In this study, high PGC1 α expression was found in pancreatic cancer stem cells, which was allowed by MYC suppression (56). Although the MYC^{low}PGC1 α ^{high} status is essential to maintain mitochondrial respiration, stemness, and tumorigenicity of pancreatic CSCs, it also makes CSCs more vulnerable to metformin treatment than more differentiated PDAC cells. With low MYC expression, CSCs are unable to activate glycolysis under metabolic stress (56). Even so, a subset of metformin-resistant pancreatic CSCs can

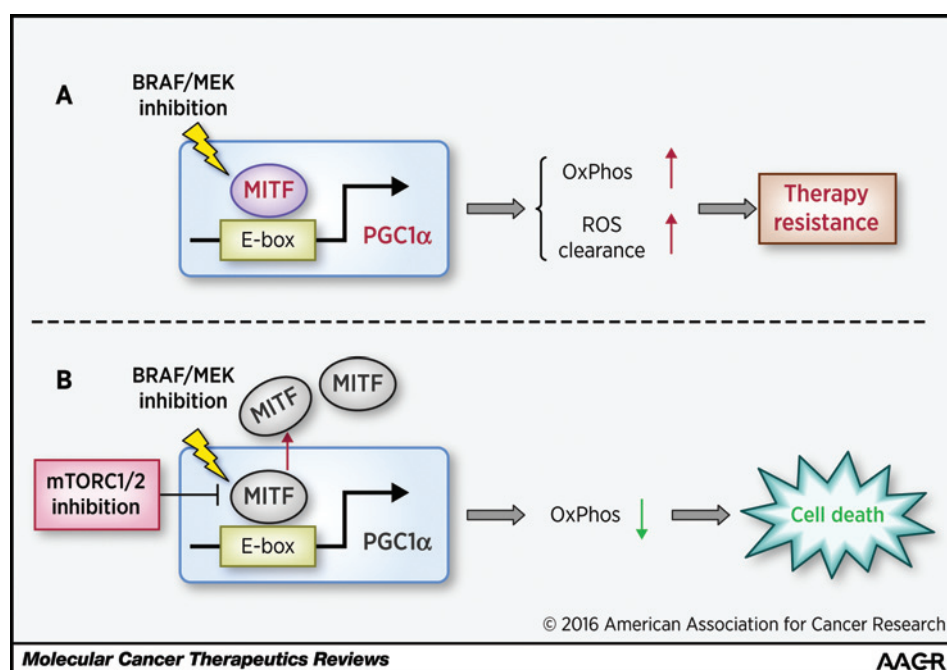
Figure 2. Biologic function of PGC1 α in cancer cells. Once induced by stress, PGC1 α interacts with specific transcription factors and promotes mitochondrial respiration, fatty acid metabolism, or ROS detoxification, which facilitates cancer metabolic adaptation.



emerge during treatment. The resistant cells display an intermediate metabolic phenotype with reduced OxPhos but enhanced glycolysis, as a result of increased MYC/PGC1 α ratio, compared with metformin-sensitive CSCs (56), and MYC inhibi-

tion increases the sensitivity to metformin in resistant CSCs. These data indicated MYC/PGC1 α balance determines the metabolic plasticity and sensitivity to metformin of pancreatic CSCs.

Figure 3. Involvement of the MITF/PGC1 α signaling in melanoma therapy. A, mechanism of the MITF/PGC1 α signaling axis in melanoma therapeutic resistance. MITF can be activated by BRAF or MEK inhibition and then transactivate PGC1 α , which promotes mitochondrial respiration and ROS detoxification, leading to drug tolerance of BRAF/MEK inhibition. B, combinatory suppression of BRAF/MEK and mTORC1/2 contributes to melanoma cell death. mTORC1/2 inhibition can decrease nuclear localization of MITF, then suppress PGC1 α expression and mitochondrial respiration, which resensitizes melanoma to BRAF/MEK inhibition.



Another research study performed in a mouse model of pancreatic tumor also highlighted the importance of PGC1 α in PDAC therapeutic resistance. Tumor cells which survive the genetic or pharmacologic ablation of *KRAS*, overexpress PGC1 α (79). Although PGC1 α expression is closely related to therapeutic resistance of PDAC in both models, mechanisms of how PGC1 α influences tumor relapse are different. The former study emphasized the regulation of MYC on PGC1 α in a KRas-independent manner (56). It is the increased MYC/PGC1 α ratio reduces the reliance of CSCs on OxPhos, leading to metformin resistance. While, in KRas ablation-resistant mouse model, it is the strong reliance on OxPhos ensures resistant cells survival (79), and this phenomenon might be restricted to KRas-ablated dormant pancreatic tumor cells.

PML/PGC1 α /PPAR α axis in breast cancer

Even though mitochondrial respiration has been considered as the main biologic function of PGC1 α , the crucial role of PGC1 α in regulating FAO has received more attention in recent years. FAO is activated in several type of cancers, and the transcription factor, PPAR α , is the main regulator of this process (80–83). PPAR α can be activated by endogenous fatty acid, fatty acid derivatives or fibrates, and is coregulated by PGC1 α (84, 85). In breast cancer cells, PGC1 α is controlled by the promyelocytic leukemia (*PML*) gene which is enhanced in a subset of breast cancers and especially enriched in triple-negative cases (58, 86). PGC1 α is deacetylated by PML, leading to transactivation of PPAR α and FAO activation. The PML/PGC1 α /PPAR α /FAO signaling pathway provides ATP to promote cell survival and luminal filling in breast cancer (58). Furthermore, this pathway is also involved in hematopoietic stem cell maintenance (87, 88). Although only a small number of studies reported the involvement of PGC1 α in cancer stem cells, the metabolic profile of hematopoietic stem cells and cancer stem cells could have some common traits in stemness maintenance (79, 89–91). These studies provided evidence indicating that PML/PGC1 α /PPAR α signaling is essential for maintaining cellular metabolic homeostasis with potential therapeutic implications.

AR/PGC1 α axis in prostate cancer

The androgen receptor (AR) is a ligand-activated transcription factor that is substantially modulated by coregulators (92). Among the coactivators, PGC1 α interacts with AR to orchestrate central metabolism and cell survival in prostate cancer (93). PGC1 α can bind to the N-terminal domain of the AR and promote the formation of AR homodimer, which increases the transcription of AR target genes, such as *PSA* (52). Inhibition of PGC1 α causes cell-cycle arrest at the G₁-phase and suppresses growth of either AR-positive or castration-resistant prostate cancer cells. These findings indicated that disruption of PGC1 α expression could be useful for treating AR-positive prostate cancer and also might be more efficient in castration-resistant prostate cancer, which depends more on AR signaling (52).

More than a coactivator of AR, PGC1 α can be simultaneously regulated by AR signaling. Both mRNA and protein levels of PGC1 α can be induced by androgens in prostate cancer in an AMPK-dependent manner (94). The androgen/AR/AMPK/PGC1 α signaling axis increases mitochondria biogenesis, glucose oxidation, and FAO to generate building blocks and ATP for cancer cell growth. The positive feedback regulation provides a great advantage to sustain PGC1 α expression and augment its influence on cancer metabolism.

p53/PGC1 α axis in cell fate determination

P53 can either be a tumor suppressor or an oncogene in cancer. Its biologic function is tightly regulated by translational modifications and interaction with other proteins (95). PGC1 α acts as a contributor to wild-type p53 target selection in cancer cells in response to glucose deprivation (96). When PGC1 α is induced by transient starvation and binds to p53, Lys120 acetylation of p53 is prevented, and p53 preferentially transactivates genes associated with ROS clearance and mitochondrial metabolism. However, in prolonged or chronic starvation, PGC1 α undergoes degradation by ring finger protein 2-mediated ubiquitin–proteasome pathway. This process facilitates Lys120 acetylation of p53, leading to p53-dependent apoptosis (96). In this case, p53 has both cytoprotective and cytotoxic functions under nutrient-limited conditions. PGC1 α performs as an essential switch in modulating stress-dependent transcription of p53, and directs the stress response of p53 toward prosurviving outcomes (97).

In addition to the interaction of PGC1 α and wild-type p53, other studies suggested that PGC1 α expression can be influenced by wide-type p53. Gene expression analysis in 28 human lung adenocarcinoma cell lines with different p53 mutational status showed that the mRNA level of *PGC1 α* is higher in p53 wild-type cell lines compared with cell lines with p53 loss or missense mutation (50). Suppression of PGC1 α inhibits the growth of p53 wild-type lung adenocarcinoma cells, implicating that PGC1 α might be a potential target of wild-type p53 in lung adenocarcinoma, and the direct transcription regulation of wild-type p53 on PGC1 α has been demonstrated in neuroblastoma cells and myoblasts (54). Similar to the AR/PGC1 α axis, an autoregulatory loop might also exist between p53 and PGC1 α .

As well as the direct regulatory mechanism between PGC1 α and p53, the receptor-interacting protein 1 (RIP1)/PGC1 α signaling axis indirectly affects the control of p53-dependent cell proliferation (98). This signaling pathway maintains metabolic homeostasis in lung cancer cells. Loss of RIP1 suppresses PGC1 α expression and OxPhos, resulting in accelerated glycolysis. However, excessive glycolysis decreases cellular NAD⁺ levels and impairs DNA repair, which activates p53-mediated cell growth inhibition (98, 99). These data provide additional evidence supporting a reciprocal regulation between metabolic adaptation and wild-type p53 in cancer cell fate determination.

SIRT1/PGC1 α axis in stress adaptation

SIRT1 is the main regulator of PGC1 α and activates PGC1 α through the deacetylation of PGC1 α at specific lysine residues (20). SIRT1/PGC1 α signaling is required to transactivate FAO genes under nutrient restriction in skeletal muscle cells (100). The switch from glucose to fatty acid utilization benefits cell survival under stress conditions, and SIRT1/PGC1 α signaling also mediates Nrf2 expression to antagonize oxidative damage (101). It was identified as a targeted pathway of metformin in p53 wild-type cancer cells (102). Metformin suppresses this signaling through miR-34a in a p53-dependent manner and then sensitizes cancer cells to oxidative stress. These research findings provide new evidence for the effectiveness of metformin in cancer therapy (103).

Therapeutic Implications

As noted above, cells with high expression of PGC1 α have an advantage to survive under metabolic stresses, including oxidative

damage, energy deprivation, and even cancer therapy. The therapeutic resistant cancer cells especially have a strong reliance on metabolic activities mediated by PGC1 α . On the basis of the evidence, PGC1 α is believed to have an emerging role in cancer therapeutic resistance (57, 68, 75).

Whereas specific inhibitors of PGC1 α are not yet available, the major methods to disrupt PGC1 α signaling have been focused on suppressing key enzymes of PGC1 α -dependent metabolic pathways or targeting-related transcription factors. OxPhos, FAO, or ERR α inhibitors were all observed to reduce cell growth in PGC1 α -positive cancer cells (51, 68, 75, 87).

Metabolic intervention significantly limits adaptive responses in cancer therapy as discussed above. However, suppressing a single metabolic node might not be fatal to certain cancer cells, because alternative metabolic paths still could be engaged to compensate for the deficiencies. In melanoma, suppressing PGC1 α expression or OxPhos resensitize therapeutic-resistant cells to oxidative damage (53). However, these treatments simultaneously activate alternate metabolic fluxes in a small set of cancer cells (104). The increased ROS production caused by PGC1 α inhibition stabilizes HIF1 α protein, and HIF1 α induces a metabolic switch from OxPhos to glycolysis which promotes cell survival (105). Surprisingly, even a combinatory suppression of PGC1 α and HIF1 α could not eradicate tumors in mice. Instead, this process promotes glutamine utilization to offset the energy crisis. Only blocking all of these pathways can maximize tumor-suppressing efficiency. Another study also indicated that robust mitochondria respiration activity strongly relied on autophagy and FAO, which provide nutrients to mitochondria (79). Suppression of the compensatory fluxes could greatly increase the sensitivity of melanoma cells to OxPhos inhibition (79, 105). These data highlight the metabolic flexibility of cancer and emphasize the demand for a multitargeted therapeutic strategy to reduce or avert the treatment resistance.

The Paradoxical Role of PGC1 α in Cancer

In contrast to most studies, a few studies reported that PGC1 α was a tumor suppressor in some cancer types (55, 106–109). For instance, low expression of PGC1 α is associated with poor survival in VHL-deficient clear cell renal cell carcinoma (ccRCC) and breast cancer (55, 110). In VHL-deficient ccRCC, PGC1 α is suppressed by HIF-dependent activation of transcriptional repressor Dec1 (55). Overexpression of PGC1 α protects mouse intestinal epithelium against colon cancer formation (111). Mechanically, induction of cell death is the major cause associated with PGC1 α -mediated tumor suppression. PGC1 α acts as a stabilizer of a tumor suppressor mitostatin, which triggers mitophagy in breast cancer (112). It also enhances Bax-mediated apoptosis in colorectal and ovarian epithelial carcinoma cells (109, 113).

The paradoxical role of PGC1 α in cancer is caused by several factors. As PGC1 α is highly sensitive to environmental stimulation, thus methods include gene interference and the discrepancy between *in vitro* cell culture and tumor microenvironments technically can influence the expression of PGC1 α (11). As a tran-

scriptional coactivator, the tissue specificity of corresponding transcription factors can significantly contribute to the variability of PGC1 α expression (35). The diverse upstream signals of PGC1 α also correspond to its dynamic role in tumor development based on activation by different oncogenes and changes in the metabolic mode.

Conclusion and Further Perspectives

According to the abovementioned discussion, PGC1 α facilitates a flexible metabolic profile in cancer cells and contributes to cancer survival and therapeutic resistance. (15, 114, 115). Even though mitochondrial respiration is identified as a predominant biologic function of PGC1 α in cancer, a few studies also underscore PGC1 α as a promoter of FAO and glucose- or glutamine-derived lipogenesis in recent years (49, 51, 58). The discoveries indicated that PGC1 α can not only enhance ATP production, but also affect carbon flux. On the basis of a deeper understanding of FAO and autophagy in cancer therapy, more attention should be paid on the role of PGC1 α in the regulation of lipid metabolism in the future (116–119).

Despite PGC1 α can interact with various transcription factors under physiologic conditions, research studies focusing on PGC1 α -targeted transcription factors in cancer cells are still limited, and mechanisms of the interactions are also elusive. Moreover, except for *PML* and *MYC*, few oncogenes have been reported conclusively to regulate PGC1 α (56, 58). Whether changes in PGC1 α expression are due to oncogene control or a nongenetic metabolic adaptation might depend on cellular context. Elucidating these issues would be very helpful in understanding the function of PGC1 α in cancer.

For the reason that certain chemotherapeutically resistant cancer cells are extremely addicted to PGC1 α -dependent metabolic activities, targeting PGC1 α -associated pathways could be a desirable means to resensitize cancer cell to therapy. However, even more than chemotherapy, radiotherapy is also a necessary strategy against some tumor types. The relationship between radiotherapy and PGC1 α needs to be further studied. According to the evidence discussed earlier, disruption of PGC1 α target genes and the potential compensatory pathways, combined with traditional chemotherapy/radiotherapy should be the best strategies to achieve maximized therapeutic efficiency in the future.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

Y. Cao is a recipient of the National Basic Research Program of China, grant no. 2011CB504305 and the National High Technology Research and Development Program of China, grant no. 2012AA02A501. X.J. Luo is a recipient of the National Science Foundation of China, grant no. 81573014. M. Tang is a recipient of the National Science Foundation of China, grant no. 81402250.

Received September 10, 2015; revised January 13, 2016; accepted January 29, 2016; published OnlineFirst April 15, 2016.

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