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The diverse role of the PPAR γ coactivator 1 family of transcriptional coactivators in cancer

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Abstract

The critical role that altered cellular metabolism plays in promoting and maintaining the cancer phenotype has received considerable attention in recent years. For many years it was believed that aerobic glycolysis, also known as the Warburg Effect, played an important role in cancer. However, recent studies highlight the requirement of mitochondrial function, oxidative phosphorylation and biosynthetic pathways in cancer. This has promoted interest into mechanisms controlling these metabolic pathways. The PPAR γ coactivator (PGC)-1 family of transcriptional coactivators have emerged as key regulators of several metabolic pathways including oxidative metabolism, energy homeostasis and glucose and lipid metabolism. While PGC-1s have been implicated in a number of metabolic diseases, recent studies highlight an important role in cancer. Studies show that PGC-1s have both pro and anticancer functions and suggests a dynamic role for the PGC-1s in cancer. We discuss in this review the links between PGC-1s and cancer, with a focus on the most well studied family member, PGC-1 α .

INTRODUCTION

Metabolism is well established for its role in several diseases including diabetes, neurodegeneration, and cardiovascular disease (CVD). In recent years there has also been a resurgence of interest into the role of metabolism in cancer. Tumors show drastic changes in energy homeostasis. Otto Warburg first made this observation more than 80 years ago(1). Warburg observed that even in the presence of oxygen tumor cells produce a significant amount of ATP from glycolysis instead of oxidative phosphorylation (OxPhos) with concomitant production of lactic acid. This is manifested in many cancer cells as an increase in glycolysis and a decrease in OxPhos. This high rate of glucose utilization is coupled with a high rate of glucose uptake, which can be detected in the clinic using ^{18}F fluoro-2-deoxyglucose positron emission tomography (^{18}F FDG-PET)(2). At its most basic, increased glycolysis delivers increased levels of ATP to the rapidly proliferating cells (3). Increased glycolysis also renders cancer cells less dependent on growth factor and nutrient supply (4-7). This is crucial for tumor cells that are often in a nutrient deprived environment and must survive even under reduced oxygen conditions. While a number of studies show that increased glycolysis and decreased OxPhos/mitochondrial function are critical to maintain

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cell growth, more recent studies highlight the crucial role that mitochondria play in promoting cancer (8-10). It is now appreciated that catabolizing glucose to only lactate and ATP leaves nothing left over for one of the crucial requirements of a cancer cell, increased biomass (11-13). Glucose serves as an anabolic precursor for the biosynthesis of molecules involved in generating biomass such as nucleic acids and lipids (ribose and acetyl CoA, respectively). More recent studies suggest a more dynamic role of glycolysis and mitochondrial function in cancer, as opposed to the previous dogma suggesting that glycolysis and OxPhos are mutually exclusive in cancer.

The ability of cells to coordinate metabolism for energy and anabolic purposes during carcinogenesis is a crucial aspect of the cancer metabolism phenotype. This has prompted significant interest in recent years into understanding and targeting key molecules regulating cellular and whole organism metabolism. The PPAR γ coactivators 1 (PGC-1s) are a family of multifunctional transcriptional coactivators that have emerged as playing a central role in cellular and systemic metabolism (14-16). While a role for the PGC-1s is well established in diabetes, neurodegeneration and cardiovascular disease, it is now becoming appreciated that the PGC-1s are playing a major role in cancer. Indeed, many of the functions of PGC-1s in metabolism are also applicable towards a role for PGC-1 in cancer. This review examines some of the recent data linking both pro and antigrowth aspects of PGC-1s in cancer, with a focus on the most well studied member PGC-1 α .

Regulation of cellular metabolism by PGC-1

The first member of the PGC-1 family, PGC-1 α , was initially identified as a transcriptional coactivator driving mitochondrial function and thermogenesis in brown fat (17). The two other family members, PGC-1 β and PGC-1 related coactivator (PRC) were discovered using sequence homology searches (18-21). The PGC-1 family members are similar in their ability to increase mitochondrial function when overexpressed and have a related modular structure (Figure 1). PGC-1 α and PGC-1 β are the most well studied and share the most common homology, which includes several domains that mediate its function. The N terminal activation domain interacts with transcriptional coactivators such as CBP, p300 and SRC1. Adjacent to the N-terminal region is a domain of ~200 amino acids that is involved in inhibition of PGC-1 activity. The N terminal half of the PGCs also mediates interaction with numerous transcription factors via several LXXLL motifs. The C-terminal end of the PGC's interacts with the TRAP/DRIP/Mediator complex. The mediator complex is a multiunit complex that facilitates direct interaction with the transcriptional machinery and is required for transcription. Finally, PGC-1 α has a Ser/Arg rich domain and RNA binding domain that play an important roles in mRNA splicing, although its role in disease is unclear (22).

Although PGC-1 α was initially described as a PPAR γ interacting protein, it is now understood that PGC-1 α can interact with most of the nuclear receptor superfamily of orphan and ligand activated transcription factors. In addition, PGC-1 α can coactivate non-nuclear receptor transcription factors such as Mef2c, SREBP1s and GABPA to name a few (23-27). The multiple protein interaction possibilities of PGC-1 α make it highly versatile and able to control diverse biological programs in different tissues. One of the main functions of PGC-1 α is control of energy metabolism by increasing oxidative metabolism, and in particular mitochondrial oxidative phosphorylation (OxPhos) in muscle, brain, liver and adipose tissue. This includes inducing the expression of most of the genes of the TCA cycle and the electron transport chain, which also promotes mitochondrial biogenesis in many of these tissues. PGC-1 α also plays an important role in glucose metabolism beyond its effects on glucose oxidation. Hepatic glucose out is controlled by PGC-1 α via its control of the gene expression program driving gluconeogenesis (28,29). PGC-1 α also plays an important role in lipid metabolism as will be described below. The ability to take up, metabolize and utilize nutrients is fundamental for normal cellular function. These functions

are even more crucial for a cancer cell, which is under tremendous bioenergetic and anabolic demands. Therefore, the ability of PGC-1s to regulate multiple metabolic pathways has prompted interest into understanding their role in cancer.

REGULATION OF CANCER METABOLISM BY PGC-1 α

An elegant study several years ago showed a dynamic role for PGC-1 α in cancer. Changes to cellular metabolites and gene expression were investigated using fibroblasts serially transformed with different oncogenes (30). At the third stages of transformation, cells showed increased OxPhos gene expression as well as increased TCA cycle intermediates, ATP, glucose uptake, and NADH production. Importantly, there was a significant induction of PGC-1 α expression at this level, suggesting a role for PGC-1 α in mediating these effects at this stage. The increased glucose uptake and oxidative metabolism at this third stage also help to reconcile how increased glycolysis and increased oxidative metabolism coexist. In order for glucose to be used by the mitochondria for oxidative metabolism, increased glucose uptake and flux through glycolysis are required. While PGC-1 α is well established for regulating mitochondrial function, a potential role for PGC-1 α in mediating glucose uptake in cancer is supported by studies in muscle showing that PGC-1 α promotes glucose uptake (25). Therefore, it is likely that PGC-1 α also promotes this effect in a cancer setting.

PGC-1 α and anabolic metabolism

De novo lipogenesis from glucose has become recognized as one of the major metabolic alterations in cancer(12,13,31). While normal cells take up lipids from the extracellular milieu, malignant cells typically synthesize their lipids de novo. This is reflected in the increased expression of several lipogenic enzymes such as acetyl CoA carboxylase (ACC), ATP citrate lyase (ACLY) and fatty acid synthase (FASN), which control de novo fatty acid synthesis and are important for promoting cancer cell growth(32-40). Fatty acids and related lipids are necessary for membrane synthesis in order to generate daughter cells. Lipids are also used for the signal transduction pathways that drive cancer survival and proliferation. For example, lipids play an important role in transmitting signals from the plasma membrane via second lipid messengers. In addition, lipid modification (palmitoylation, myristoylation and isoprenylation) of several oncogenes including WNTs, *RAS* and *AKT*, are required for full oncogenic activation(41,42). Lipids are also precursors for eicosanoids, such as prostaglandins and leukotrienes, which play an important role both in carcinogenesis and progression (43).

Several years ago it was shown that the PGC-1's were capable of promoting lipogenesis in the liver (26). This was in part mediated by coactivating the lipogenic transcription factor, SREBP1. SREBP1 activation is also associated with increased lipogenesis in cancer (44-49). Therefore despite the well-known function of PGC-1 α to promote oxidative metabolism, it also promotes anabolic metabolism. This dual role appears to depend on nutrient conditions. Studies in cultured myotubes under conditions of abundant nutrients showed that PGC-1 α promoted de novo fatty acid synthesis from glucose(50). However, under conditions of nutrient deprivation, PGC-1 α promotes β -oxidation. More recently it was shown that PGC-1 α is playing an important role in lipid homeostasis in muscle using muscle specific PGC-1 α transgenic mice. Similar to the in vitro studies, PGC-1 α promoted de novo lipogenesis from glucose (51). However in muscle, PGC-1 α coactivates the liver X receptor (LXR) as opposed to SREBP1. An important role for PGC-1 α in promoting another anabolic pathway was also demonstrated. The pentose phosphate pathway is another metabolic pathway crucial for cancer cell proliferation (12,13,52). In addition to generating nucleic acids for RNA, DNA and energy generation (ATP), the oxidative branch of the PPP (oxPPP) also produces NADPH, the required reducing agent for biosynthetic reactions such as fatty acid and amino acid synthesis. PGC-1 α promoted oxPPP activity including nucleic

acid and NADPH synthesis. Interestingly, this was a result of increased activity of oxPPP and not the expression of its proteins or RNA. This raises an intriguing idea whereby PGC-1 α can regulate metabolic pathways independent of its ability to coactivate transcription factors.

More recently we showed genetically that PGC-1 α promotes carcinogenesis and tumor growth(53). Loss of PGC-1 α in mice led to increased chemically induced liver and colon carcinogenesis. In addition, while PGC-1 α promoted OxPhos and TCA cycle gene expression, PGC-1 α also increased the expression of enzymes driving lipogenesis. Stable isotope tracer analysis using ^{13}C labeled glucose showed that de novo fatty acid synthesis from glucose was significantly increased in xenografts expressing PGC-1 α . Finally, inhibiting fatty acid synthesis with the FASN inhibitor C75, blocked the ability of PGC-1 α to promote tumor growth. Therefore, these data provide strong evidence for the ability of PGC-1 α to promote cancer by inducing anabolic metabolism.

Reconciling induction of oxidative and anabolic metabolism by PGC-1 α

The fact the PGC-1 can promote BOTH mitochondrial function and lipogenesis should not be all that surprising. Acetyl CoA derived from glucose and glucogenic amino acids such as glutamine, is the key substrate for fatty acid synthesis, and in particular for cancer cells. However, in order for glucose to be used as a substrate for fatty acid synthesis, mitochondrial function and in particular the TCA cycle are required. After glucose is converted to pyruvate, it enters the mitochondria where it is oxidized to acetyl CoA by pyruvate dehydrogenase complex. The acetyl CoA joins with oxaloacetate to form citrate. Citrate is then exported from the mitochondria where it is cleaved to acetyl CoA and OAA again. Acetyl CoA can now go on to participate in fatty acid synthesis. Therefore the ability of PGC-1 α to drive mitochondrial function and the TCA cycle would provide for increased substrate availability for fatty acid synthesis. In further support of this, we also observed an increase in expression of the citrate transporter, Slc25A1, which is required to transport TCA cycle generated citrate into the cytoplasm for lipogenesis (53). Indeed, it appears that PGC-1 α coordinates a gene expression program driving both mitochondrial function and lipogenesis in order to promote cell growth (Figure 2).

The ability of PGC-1 α to promote mitochondrial function serves another purpose. Synthesis of fatty acids is bioenergetically costly which could lead to an energy deficit and subsequent cell death (see below) (13). A single molecule of palmitate, the product of FASN, requires 14 NADPH, 16 carbons (8 acetyl CoA) and 7 ATP. However, one glucose molecule can yield either 12 NADPH via the PPP, 3 acetyl CoA (which still requires mitochondria function) or 2 ATP plus lactate (via glycolysis). Therefore, metabolism of glucose to ATP and lactate leaves nothing over for biosynthetic purposes. Therefore, by using the TCA cycle and OxPhos and truncating the TCA cycle, cells are able to maintain ATP levels. In addition, the TCA cycle serves as an entry point for utilization of glucogenic amino acids such as glutamine which can not only participate in ATP generation, but also lipogenesis. Indeed, in recent years glutamine has been shown to be almost as important for cancer cells as glucose. By coordinating metabolism of glucose, and glucogenic amino acids by the TCA cycle, glycolytic flux and PPP, PGC-1 α enables tumor cells to be more effective in generating biomass while maintaining cellular bioenergetics.

Another paradox related to mitochondrial versus lipogenic effects of PGC-1 is its ability to promote fatty acid oxidation. β -oxidation of fatty acids enables cells to generate significant amounts of energy by generating acetyl CoA which can be used in the TCA cycle and FADH₂ and NADH which can feed into the ETC and generate ATP. Indeed, glucose yields 32 ATP per molecule if completely oxidized, where as one molecule of palmitate generates 106 ATP. Therefore this would seem to generate a futile cycle of lipid synthesis and

degradation. However, it is important to keep in mind that β -oxidation and lipogenesis are not binary processes. Rather they are dynamic and depend on cellular requirements. In addition, the enzymatic reactions of lipogenesis and β -oxidation are spatially separated. Fatty acid synthesis occurs in the cytosol, whereas the β -oxidation of long chain fatty acids occurs in peroxisomes. Medium and short chain fatty acids are oxidized in the mitochondria. Fatty acids do not freely move through cells but rather require transport systems as well that are regulated by nutrient conditions. In addition, the enzymes regulating these processes are subject to growth factor and nutrient control. As mentioned above, in vitro studies show that under conditions of nutrient excess, PGC-1 α promotes lipogenesis (50). In contrast, during reduced nutrient conditions, PGC-1 promotes β -oxidation. This would give cancer cells a survival advantage and metabolic flexibility. Therefore, cellular needs and nutrient and growth factor availability will dictate whether catabolic or anabolic pathways are dominant.

REGULATION OF CELL SURVIVAL BY PGC-1 α

Mitochondria play a central role in energy homeostasis and are control point in cell death cascades (54). Therefore it is not surprising that PGC-1 α plays an important role in cell survival. PGC-1 α protects against apoptosis via a number of mechanisms as discussed below. However, it should be pointed out that many of these studies investigated the role of PGC-1 α in non-malignant/non-transformed settings such as metabolic disease and neurodegeneration. Therefore, it remains to be seen whether similar mechanisms are relevant to cancer as well.

Bioenergetic control of cell survival

When cells experience a bioenergetic crisis, they undergo necrosis or apoptosis depending on the magnitude of the energy deficit. The ability of PGC-1 α to promote ATP production and energy homeostasis enables it to protect against bioenergetic crisis and render cells resistant to necrosis or apoptosis. Neurodegenerative diseases are characterized by neuronal death. The cell death observed in these pathologies is attributed in part to a failure to maintain bioenergetic homeostasis (55). Early studies on PGC-1 α whole body knockout and more recently PGC-1 α neuronal specific knockout mice showed significant cell death in the striatal portion of the brains of mice which leads to neurodegeneration and Huntington Chorea like symptoms (56,57). Neuromuscular disorders and muscle wasting associated with aging have also been shown to be a result of bioenergetic deficit (58). Muscle specific expression of PGC-1 α in mice with mitochondrial myopathy or in aging mice protects against cell death and muscle degeneration in part by maintaining mitochondrial function and cellular bioenergetics(59,60).

Telomeres play a critical role in maintaining chromosome integrity. As cells age, telomeres shorten. Telomere shortening results in the activation of p53, which promotes growth arrest, senescence and apoptosis. The ability of cells to overcome the effects of telomere shortening is important in cancer development(61). It was shown recently that telomere shortening regulates bioenergetic pathways and the transcriptional programs controlling them (62). Telomere dysfunction led to reduced mitochondrial biogenesis and function and increased ROS production (see below). This telomere shortening was also accompanied by a dramatic decrease in PGC-1 α and PGC-1 β expression as a result of p53-mediated repression. Forced expression of PGC-1 α rescued mitochondrial respiration, cardiac function and metabolic activity. Although not examined, these data suggest that PGC-1s might enable cells to overcome cell death associated with telomere shortening, a key mechanism driving cancer development.

Maintenance of cellular bioenergetics and hence protection against cell death by PGC-1 α is also relevant to signal transduction pathways in cancer (63). The PIM kinases (Pim1, Pim2

and Pim3) are a family of serine threonine kinases that play an important role in cancer. Deletion all three Pims (PimTKO) in MEFs leads to significantly lower growth rates compared to wildtype MEFs (64). The presence of just Pim3 was sufficient to restore growth. The energy sensor AMPK is activated when cellular energy levels are decreased. This leads to inhibition of anabolic pathways, which would oppose cell proliferation(65,66). Examination of PimTKO MEFs showed increased levels of activated AMPK which was associated with a significant increase in the AMP/ATP ratio, a measure of energy status in the cells. Importantly, the expression of PGC-1 α was dramatically reduced in PimTKO MEFs, while ectopic expression of PGC-1 α was sufficient to restore ATP levels and reduce the activation of AMPK, although the effect on cell growth was unclear. As a whole these data suggest that by maintaining cellular ATP levels, PGC-1 α can promote cell survival.

PGC-1 α and reactive oxygen species

In addition to bioenergetic crisis, PGC-1 α maintains cell survival via several other mechanisms. The mitochondrial electron transport chain is a major site of reactive oxygen species (ROS) generation. Excess oxidative stress can induce cell death and lead to genotoxic stress. Therefore cells have developed several defenses against these potentially toxic species. PGC-1 α reduces oxidative stress via several mechanisms. PGC-1 α promotes the induction of MnSOD, Cu/ZnSOD, catalase and glutathione peroxidase (GPX1) (67-69). Catalase and glutathione peroxidase are responsible for detoxification of hydrogen peroxide and lipid peroxides, respectively. Mn-SOD and Cu-SOD savaging superoxide radical in the mitochondria or cytoplasm respectively. The ability of PGC-1 α to induce these antioxidant enzymes is critical for protection against ROS induced damage and cell death. PGC-1 α null mice are much more sensitive to the neurodegenerative effects of compounds that induce ROS stress (68). Ectopically expressing PGC-1 α protects neural, endothelial, and muscle cultures against ROS induced cell death(68-72). PGC-1 α can also reduce ROS levels indirectly by inducing the expression of several uncoupling proteins (UCPs). UCPs are inner mitochondrial membrane proteins that dissipate the proton gradient across the inner mitochondrial membrane. This lowers mitochondrial membrane potential, reducing ROS production by the mitochondria. In addition, as discussed above, PGC-1 α promotes NADPH production via the oxPPP. NADPH is required for regenerating reduced glutathione in order to maintain antioxidant defenses in cells. Finally, many chemotherapeutic agents work via induction of oxidative stress. Therefore it is possible that by inhibiting oxidative stress, PGC-1 protects against chemotherapy induced cell death.

PROGRESSION

Angiogenesis

In order for tumors to develop they must establish a blood supply to maintain nutrient levels and metastasize. As it turns out, PGC-1 α plays an important role in this process as well. Several years ago it was shown that PGC-1 α can promote angiogenesis independent of Hif1 α (73). PGC-1 α induced most of the gene expression program of angiogenesis in vitro and in vivo. Although the ability of PGC-1 α to induce angiogenic gene expression is independent of Hif1 α , other studies demonstrated that PGC-1 α regulates Hif1 α activity. Increased expression of PGC-1 α increases oxygen consumption (74). This leads to a decrease in local oxygen tensions, increasing Hif1 α stability. Finally, recent work shows that Hif2 α is a transcriptional target of PGC-1 α although the transcriptional program involved is not clear (75). It should be pointed out that the studies on angiogenesis were done in muscle derived cells. Therefore it is unclear at this point whether the role of PGC-1 α on angiogenesis is relevant with respect to cancer.

Metastasis

Once a blood supply is established, tumors cells will to extravasate from their initial location and invade other portions of the body. However, few tumors cells survive in order to invade into distant sites. Indeed, once cells detach from the basement membrane, they often undergo apoptosis. Recently it was shown that the ability of cells to survive following detachment from the basement membrane is dependent upon its ability to generate energy via β -oxidation and increased antioxidant defense (76). In addition to driving oxidative phosphorylation and the TCA cycle, PGC-1 α promotes β -oxidation of fatty acids (77-79). Although it was not shown whether PGC-1 α is involved in this process, it is entirely possible, that PGC-1 α can promote survival during detachment by promoting β -oxidation. This would lead to an increase in ATP production and protection from bioenergetic stress. PGC-1 α mediated induction of antioxidant defenses described above would also promote cell survival following detachment. Subsequent studies should elucidate whether PGC-1 α or its induction can promote cancer cell survival following detachment from the basement membrane enabling them to migrate into the vasculature or lymphatic system. These data also highlight the dynamic role of PGC-1 α in cancer cell metabolism. Under nutrient stress, PGC-1 α promotes β -oxidation enabling tumor cells to survive during times of energy deprivation. However, under conditions of nutrient abundance, PGC-1 α promotes lipid synthesis as described above.

Once cells survive the initial detachment, tumor cells can now invade into distant sites. An elegant study by Chen et al. examined the gene expression signature of breast cancer cells that metastasize to either bone or brain(80). They then repeated the experiment using the brain-derived metastasis and found that they preferentially went to the brain. The increased propensity to metastasize to the brain in the second round was accompanied by increased expression of PGC-1 α and many of its target genes compared to the parental cells, bone or primary brain metastases. Interestingly, even the primary metastasis from bone and brain had higher PGC-1 α and mitochondrial gene expression than parental cells. This suggests that the PGC-1 α and its ability to control metabolic programs of gene expression is involved in the ability of cancer cells to metastasize to distant sites. In addition, it suggests that PGC-1 α may be involved in tissue specific metastatic involvement.

TRANSCRIPTIONAL PARTNERS OF PGC-1 α IN CANCER

Induction of gene expression by PGC-1 α is mediated by its coactivation of specific transcription factors. It is doubtful that one transcription factor controls the effects of PGC-1 α on survival. Rather the coactivation of different transcription factors by PGC-1 α , leading to changes in energy and metabolic homeostasis, most likely controls cell survival, as described above. In addition, it is not entirely clear how PGC-1 α regulates anabolic metabolism described above. While SREBP1 has been shown to be partially involved in some studies, in others it does not (26,51). Our recent manuscript showing that PGC-1 α promotes tumor growth in part via lipogenesis did not find alterations in SREBP1c expression. However PGC-1 α may still be coactivating SREBP1c without altering its expression. PGC-1 α also promotes lipogenesis in muscle derived cells and tissue by coactivating LXRs. Therefore, LXRs may also be involved in the ability of PGC-1 α to promote cancer growth. The possibility also exists that induction of lipogenesis in cancer is secondary to increased metabolic flux. Future gain and loss of function studies should elucidate whether lipogenic transcription factors are responsible for the effect of PGC-1 α on tumor lipogenesis and growth.

As opposed to PGC-1 α and lipogenesis, the transcription factors mediating the effects of PGC-1 α on oxidative metabolism have been extensively studied. One of the most well characterized transcription factors that interact with PGC-1 α is ERR α (27,81). Coactivation

of $ERR\alpha$ by PGC-1 α induces most of the nuclear encoded genes participating in the TCA cycle and OxPhos in the mitochondria. While the role of PGC-1 α in cancer is only beginning to be explored, a role for $ERR\alpha$ in cancer is well established (82-86). $ERR\alpha$ is overexpressed in many cancers while its inhibition reduces cell proliferation. Recent studies point to an important role for the interaction between PGC-1 α and $ERR\alpha$ in cancer. The Ras oncogene promotes transformation of fibroblasts, which is dependent upon KSR1. Expression of both KSR and H-Ras promotes a gene expression program driving glucose utilization, glycolysis and oxidative metabolism (87). Importantly, PGC-1 α and $ERR\alpha$ were induced by coexpression of KSR and H-Ras. Increasing the interaction between PGC-1 α and $ERR\alpha$ promoted cell growth and anchorage independent growth. Interestingly, $ERR\alpha$ on its own was not able to promote anchorage independent growth, suggesting additional roles for PGC-1 α in this process. A role for $ERR\alpha$ in mediating some of the effects of PGC-1 α in cancer is further supported by data showing that $ERR\alpha$ is responsible in part for the effect of PGC-1 α on angiogenesis.

The nuclear receptor PPAR δ shares a high degree of homology with PPAR γ , the transcription factors used to initially identify PGC-1 α . Chemical and genetic studies demonstrate that PPAR δ , unlike PPAR γ , can promote cell growth and tumorigenesis (88-92). It was recently shown that PPAR δ ligand induced cell proliferation in lung cancer derived cells was associated with induction of PGC-1 α (93). While a direct role for PGC-1 α on cell proliferation was not examined, the data strongly suggest a positive role for PGC-1 α in cell growth.

The androgen receptor (AR) plays an important role in prostate cancer and therapy and mediates some of the anabolic pathways in cancer. Androgen receptor positive (AR+) patients respond well to anti androgen therapies. This raises the question as to how AR functions in cancer. Coactivators are key determinants of AR function. Studies show that PGC-1 α coactivates the AR receptor in prostate cancer (94). In addition, knock down of PGC-1 α inhibited the growth of AR+ prostate cancer cells. In contrast, in AR negative prostate cancer cells, PGC-1 α was unable to affect tumor growth. Currently, the expression of PGC-1 α in prostate cancer is unknown, but this suggests a potential role for PGC-1 α in promoting prostate cancer via the AR.

PARADOXICAL EFFECTS OF PGC-1 α IN CANCER

Cancer is a complex disease. As opposed to diseases where a single alteration can cause a disorder, multiple alterations are required for cancer development(95). Despite the progrowth ability of PGC-1 α described above, other studies suggest that PGC-1 α opposes cancer growth. Studies over the years show a reduction in mitochondrial enzymes promoting OxPhos in a number of different cancers including. In addition, glycolysis and the enzymes of glycolysis are elevated in many cancers. Studies in the last decade have shown that these changes are more than an epiphenomenon. Chemically or genetically inhibiting glycolysis or enhancing OxPhos inhibits cancer cell proliferation. Small molecules such as 2-deoxyglucose, bromopalmitate and dichloroacetate (DCA), which decrease glycolysis, reduce cancer cell proliferation (96-99). In addition, RNAi knockdown of LDH inhibits glycolysis, induces OxPhos and reduces cell growth (100,101). Directly inducing OxPhos also inhibits cancer cell growth. Ectopic expression of the mitochondrial protein frataxin increases OxPhos and reduces tumor cell growth (102). The crucial role that PGC-1 α plays in regulating mitochondrial function and especially oxidative phosphorylation suggest that it might be involved in the metabolic switch in cancer, and hence responsible for the Warburg Effect.

An early study in breast cancer found that PGC-1 α expression did not differ in tumor versus normal adjacent tissue from patients (103). However, a reduction in PGC-1 α was associated with a poorer survival. Another study in colon cancer found that PGC-1 α expression was reduced ~60% in tumors compared to normal tissue (104). However, there was a fair degree of variability in the samples. Tumor PGC-1 α levels were not detected in 12% of patients. In 76% of patients, tumor PGC-1 α expression was reduced and in 12% of patients PGC-1 α expression was elevated. Since no correlation to OxPhos gene expression was performed, the relevance of these studies is unclear. PGC-1 α levels are also reduced in liver tumors compared to adjacent normal tissue (105). However, ectopic expression of PGC-1 α or knockdown of PGC-1 α in liver cancer cell lines did not affect cell growth. This suggests that perhaps the decrease in PGC-1 α is secondary to decreases in OxPhos and mitochondrial function. Another study showed that PGC-1 α expression is reduced in ovarian cancer tissue compared to normal controls (106). Although the sample size was relatively small (N=10 and 7 respectively), adenoviral overexpression in the Ho-8910 ovarian cancer cell line promoted apoptosis.

One caveat that must be kept in mind with regard to PGC-1 α levels in tumors is that its expression is dramatically regulated by environmental signals. Therefore, the heterogeneous local tumor microenvironment can dramatically affect the expression of PGC-1 α . Regardless, some studies have shown increased glycolytic metabolism and decreased OxPhos correlate with PGC-1 α expression related to cancer. Oct1 is a transcription factor that is associated with carcinogenesis. It was shown recently, that loss of Oct1 reduces cell and tumor growth. This effect was accompanied by a shift from glycolytic metabolism to oxidative metabolism with a concomitant induction of PGC-1 α . While it was not shown whether PGC-1 α is required for the metabolic shift controlled by Oct1 or a consequence, the authors showed that the Oct1 oncogene bound to the PGC-1 α promoter and inhibited its expression.

As opposed to a progrowth role described above in colon and liver carcinogenesis, another group recently showed that PGC-1 α is protective against colorectal cancer (107). PGC-1 α expression was reduced in tumors of FAP patients compared to normal adjacent tissue. A similar observation was found in tumors and normal intestine from Apc^{+/min} mice, a mouse model of colorectal cancer that primarily develop small intestinal tumors (a rare event in humans). Injection of PGC-1 α expressing adenovirus directly into established tumor xenografts reduced tumor growth. The role of PGC-1 α on colon carcinogenesis was also examined using transgenic mice. Mice with intestinal specific PGC-1 α over expression were treated with an azoxymethane/dextran sodium sulfate (AOM/DSS) protocol. While AOM induces tumors by itself, when combined with DSS, which acts as a tumor promoter, tumorigenesis is dramatically increased (108). Mice with increased intestinal PGC-1 α were dramatically protected against AOM/DSS induced cancer. Intestinal overexpression of PGC-1 α also protected against small intestine and colon tumor developed in Apc^{min/+} mice. Loss of PGC-1 α in whole body PGC-1 α knockout mice led to increased AOM/DSS induced colon tumorigenesis compared to wildtype mice. Mechanistically, it was shown that PGC-1 α inhibited antioxidant enzyme expression and promoted oxidative stress, leading to increased apoptosis.

RECONCILING THE ROLE OF PGC-1 α IN CANCER

The majority of the published data demonstrates that PGC-1 α inhibits apoptosis. Therefore, the ability of PGC-1 α to promote apoptosis is contradictory to the procancer, pro survival effects of PGC-1 α . One potential explanation is the use of adenoviral PGC-1 α in those studies. Adenovirus itself can promote cell death independent of a transgene, although it is unclear why adenoviral PGC-1 α would promote greater cell death. The studies by Errico et

al also raise questions with regard to the differences in colon carcinogenesis compared to the studies by Bhalla et al. A potential explanation may revolve around the ability of PGC-1 α to reduce inflammation. Inflammation is a powerful promoter of tumorigenesis and tumor growth (95). Although not discussed in this review, PGC-1 α ameliorates inflammation (109). This is believed to be part of the mechanism of how PGC-1 α promotes glucose homeostasis, as well as preserving muscle function in aged animals. The studies showing that PGC-1 α inhibits tumor growth used AOM followed by DSS. DSS exerts powerful proinflammatory effects that are responsible for significantly increasing carcinogenesis induced by AOM. Therefore the presence of PGC-1 α in transgenic and wildtype mice, compared to wildtype and knockout mice respectively, would be expected to reduce inflammation. The reduction in inflammation would in turn reduce the incidence and size of AOM induced tumors. This explanation is also applicable to the differences in xenograft tumor growth observed between studies. The studies showing that PGC-1 α promotes tumor growth were performed using cell lines stably expressing PGC-1 α or shRNA against PGC-1 α . In contrast, the studies showing decreased tumor growth used adenoviral delivery of PGC-1 α directly to established tumors. The presence of PGC-1 α would reduce the adenoviral-associated inflammation and therefore, reduce xenograft growth. An additional question is raised as to how many cells in the tumor actually received virus. Despite these potential explanations, the ability of PGC-1 α to protect against tumorigenesis in *Apc*^{min/+} mice still requires explanation. The *Apc*^{min/+} mice experiment was not performed in PGC-1 α knockout mice. Therefore, the effect may be relevant towards colon specific PGC-1 α overexpression.

Regardless of the differences in pro versus anticancer effects of PGC-1 α , the mechanism of action described for the anti growth effects of PGC-1 α are at odds with the established role of PGC-1 α on oxidative stress. Errico et al demonstrated that PGC-1 α reduced antioxidant enzyme expression and promoted oxidative stress. However, numerous other studies, as described above, demonstrate that many antioxidant enzymes are transcriptional targets of PGC-1 α . Moreover, PGC-1 α potentially protects against oxidative stress. Therefore subsequent studies will be necessary to reconcile these contrary functions of PGC-1 α .

THE ROLE OF THE OTHER PGC-1S IN CANCER

PGC-1 β activates many of the same transcriptional programs as PGC-1 α . Therefore the ability of PGC-1 α to promote lipogenesis in cancer, may also be very relevant for PGC-1 β . Indeed, the studies demonstrating that PGC-1s promote lipogenesis were originally shown for both PGC-1 α and PGC-1 β (26). A recent study found that an interaction between ERR α and PGC-1 β is a key effector of ERBB2 induced tumorigenesis and promotes mammary tumorigenesis (110). Another recent study found that ERBB2 induced the expression of PGC-1 β and a microRNA, miR-378, embedded within the PPARGC1beta locus. miR-378 induction causes metabolic shift of cells from oxidative metabolism towards glycolysis (111). This was in part mediated by a reduction in transcriptional partners of the PGC-1s, GABP and a closely related isoform of ERR α , ERR γ . The differences in transcription factor availability highlight how different transcription factors can direct the function of PGC-1s towards distinct biological functions. While these studies demonstrate a progrowth role of PGC-1 β , like PGC-1 α , PGC-1 β may play a complex role in cancer. Loss of VHL in renal cell carcinomas is associated with reduced mitochondrial function and O₂ consumption (112). Studies show that this is in part due to loss of PGC-1 β . Much less is known about the third member of the PGC family, PRC. However, it does appear to be involved in cell cycle progression as its expression is reduced in quiescent cells and is strongly induced following serum stimulation (20). In addition, RNAi knockdown of PRC decreases G1/S cell cycle progression (113). Finally, thyroid oncocytoomas are characterized by mitochondrial accumulation. PRC expression is elevated in thyroid oncocytoomas and in part responsible

for the mitochondrial proliferation observed in these cancers(114). However, whether this is required for tumor development or growth is unknown. Future studies will elucidate the role of these PGC family members in cancer.

CONCLUSION

The PGC-1's and in particular PGC-1 α have emerged as crucial regulators of cellular and systemic metabolism. These dynamic and versatile coactivators control various aspects of metabolism by posttranslational modifications and interactions with a variety of transcription factors due to nutritional and environmental signals. Recent studies have begun to show how the PGCs are playing a role in the links between metabolism and cancer. PGC-1 α promotes bioenergetic homeostasis and antioxidant defenses, thus protecting against cell death. By promoting anabolic pathways, PGC-1 α enables cells to generate biomass for cell division. In contrast, other studies show that PGC-1 α induces cell death and has anticancer properties. As we begin to understand how PGC-1 α functions based interactions with tissue specific expression of cofactors and nutritional and environmental cues, these contradictory effects of PGC-1 α should be elucidated. Indeed, the ability of PGC-1s to alter growth via different transcriptional partners also suggests a way in which PGC-1s can be targeted in cancer. As we continue to understand the role of PGC-1 α in cancer, it is likely that additional transcription factors and transcriptional regulators will be identified that are responsible for the effects of PGC-1 in cancer. PGC-1 α itself is not at present druggable. However many of its transcriptional partners are, such as ERR α , SREBP1, PPARs and LXRs to name a few. Therefore identifying which partners are responsible for the effects of PGC-1 would enable inhibition of specific pathways controlled by PGC-1 in cancer and in other diseases as well. This would enable the targeting of specific functions of PGC-1s based on its interactions with specific transcription factors. As links between metabolism and cancer begin to be unraveled, studies on the PGCs and their role in cancer will no doubt make a significant contribution to our understanding and targeting of aberrant metabolism in cancer.

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Highlights

PGC1 family of coactivators regulate diverse metabolic functions

Cell metabolism is linked to cancer in part via PGC-1's

PGC1 α promotes survival/progression by inducing cellular antioxidants/bioenergetics

Induction of anabolic metabolism by PGC-1 α promotes cancer growth

Contradictory studies suggest PGC-1 α inhibits tumor growth

Figure 1.

Structure of PGC-1 family of coactivators. PGC-1 α and PGC-1 β share a high degree of homology and share an additional degree of homology in the center region. All three PGCs have a transcriptional activation domain, arginine/serine domain, and RNA binding domain. Only PGC-1 α and PGC-1 β have a transcriptional repressor domain.

Figure 2.

Coordinate regulation of oxidative metabolism and lipogenesis by PGC-1α. PGC-1α promotes energy production via the TCA cycle and oxidative phosphorylation. In addition, the increased TCA cycle flux promotes citrate formation. Citrate is exported from the mitochondria by the citrate transporter SLC25A1. Once in the cytoplasm, citrate is converted to fatty acids by a series of enzymes, induced, either directly or indirectly, by PGC-1α. This provides fatty acids for membrane synthesis and signal transduction pathways driving cancer growth.