Activation of nuclear receptor coactivator PGC-1 α by arginine methylation

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Peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α), a tissue-specific and inducible transcriptional coactivator for several nuclear receptors, plays a key role in energy metabolism. We report here that PGC-1 α coactivator activity is potentiated by arginine methylation by protein arginine methyltransferase 1 (PRMT1), another nuclear receptor coactivator. Mutation of three substrate arginines in the C-terminal region of PGC-1 α abolished the cooperative coactivator function of PGC-1 α and PRMT1, and compromised the ability of PGC-1 α to induce endogenous target genes. Finally, endogenous PRMT1 contributes to PGC-1 α coactivator activity, and to the induction of genes important for mitochondrial biogenesis.

[**Keywords:** Arginine methylation; coactivator; mitochondrial biogenesis; nuclear receptor; transcription]

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Peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α) is a transcriptional coactivator for many nuclear hormone receptors (NR), such as peroxisome proliferator-activated receptor γ (PPAR γ), the thyroid hormone receptors (TR), retinoic acid receptors, glucocorticoid receptor (GR), and estrogen receptors (ER); it also functions with other classes of DNA-binding transcription factors such as nuclear respiratory factor 1 (NRF-1) (Knutti and Kralli 2001; Puigserver and Spiegelman 2003). PGC-1 α harbors leucine-rich motifs (LXXLL) that bind to the hormone-activated NRs. The N-terminal region contains a strong autonomous activation domain, which binds to other coactivators such as SRC-1 and CBP and is required for coactivator function (Puigserver et al. 1999). The C-terminal region of PGC-1 α contains an RNA recognition motif (RRM) and an RS domain (rich in Arg and Ser residues), both of which are characteristic of proteins involved in splicing, such as hnRNP and SR proteins. Indeed, PGC-1 α not only functions as a transcriptional coactivator, but can also influence splicing patterns of specific transcripts (Monsalve et al. 2000). Deletions within the C-terminal domain disrupt the ability of PGC-1 α to associate with RNA polymerase II, RNA-processing factors, and the Mediator complex, and to induce target genes, suggesting that this region contains both transcriptional coactivator and

splicing regulator functions (Monsalve et al. 2000; Wallberg et al. 2003).

PGC-1 α mRNA is predominantly expressed in heart, brown adipose tissue, kidney, skeletal muscle, and liver, and its expression is induced in response to stimuli known to regulate metabolic activity. For example, PGC-1 α expression is induced in brown adipose tissue and skeletal muscle by exposure to cold (Puigserver et al. 1998; Boss et al. 1999), in muscle in response to physical exercise, and in the liver and heart in response to short-term fasting (Knutti and Kralli 2001; Puigserver and Spiegelman 2003; Kelly and Scarpulla 2004). In accordance with the nature of the stimuli that induce its expression, PGC-1 α regulates a broad range of metabolic processes, including mitochondrial biogenesis, respiration, and gluconeogenesis, and thus enables physiologic adaptation to the energy needs imposed by the stimuli. These effects of PGC-1 α are mediated by several DNA-binding transcription factors. Mitochondrial biogenesis and the stimulation of oxidative phosphorylation in particular require the cooperation of PGC-1 α with the nuclear respiratory factors NRF-1 and NRF-2 and with estrogen-related receptor α (ERR α), an orphan nuclear receptor (Wu et al. 1999; Mootha et al. 2004; Schreiber et al. 2004).

As the major protein arginine methyltransferase (PRMT) in mammalian cells (Tang et al. 2000), PRMT1 methylates many RNA-binding proteins (Lee et al. 2005), as well as histone H4 (Chen et al. 1999; Strahl et al. 2001). Arginine methylation has been implicated in the regulation of many cellular processes, including signal transduction, subcellular localization of proteins, protein-protein interactions, and transcriptional regulation (Lee et al. 2005). Indeed, PRMT1 serves as a coactivator for NRs (Koh et al. 2001) and other DNA-binding tran-

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ral vectors, to test their ability to stimulate expression of the endogenous *ERRα* and cytochrome *c* (*cyt c*) genes, which are targets of PGC-1α and important for mitochondrial biogenesis (Schreiber et al. 2003, 2004; Mootha et al. 2004). A viral vector expressing green fluorescent protein (GFP) was used as a control. Although equivalent expression of mutant and wild-type proteins was observed (Fig. 7A, inset), the PGC-1α R3K mutant was substantially less efficient than the wild-type protein at inducing the expression of *ERRα* and *cyt c* mRNA (Fig. 7A), suggesting that arginine methylation is important for PGC-1α function at endogenous target genes in their native chromatin state.

To determine the role of endogenous PRMT1 in PGC-1α-dependent transcriptional programs, we next used the siRNA#1 to reduce endogenous *PRMT1* mRNA levels in SAOS2 cells (Fig. 7B). The siRNA-treated or untreated SAOS2 cells were subsequently infected with adenoviral vectors encoding GFP or PGC-1α. PGC-1α expression led

to increases in the levels of the endogenous *cyt c* and *ERRα* mRNAs; however, this induction by PGC-1α was partially inhibited in the cells treated with siRNA against PRMT1, compared with the cells that were not exposed to the siRNA (Fig. 7B). The effects of PGC-1α and the siRNA against PRMT1 were gene-specific, since the data shown are normalized against the expression of glyceraldehyde phosphate dehydrogenase (*GAPDH*) mRNA. Thus, endogenous levels of PRMT1 contribute to the ability of PGC-1α to induce the expression of target genes that are important for mitochondrial biogenesis.

Discussion

As an important controller of energy homeostasis, PGC-1α expression is highly regulated at the transcription level, in a tissue-specific manner and in response to several physiologic signals (Knutti and Kralli 2001; Puigserver and Spiegelman 2003; Kelly and Scarpulla 2004). In addition, the important roles of PGC-1α in metabolic regulation also appear to be modulated by a variety of post-translational modifications and interactions with other proteins. The docking of PPARγ to PGC-1α induces an apparent conformational change that allows binding of the collaborating coactivators SRC-1 and CBP/p300 to the N-terminal activation domain of PGC-1α (Puigserver et al. 1999). Moreover, there is evidence that a repressor protein competes with NRs for binding to PGC-1α, and this competition appears to be regulated by phosphorylation of the PGC-1α suppression domain by MAPK p38, which inhibits binding of the repressor protein (Knutti et al. 2001; Puigserver et al. 2001; Fan et al. 2004). Our data add arginine methylation to the list of post-translational regulatory mechanisms that govern PGC-1α activity and, in addition, implicate PRMT1 as an important component cooperating with PGC-1α in metabolic processes such as mitochondrial biogenesis. Although reductions in the level of PRMT1 caused relatively modest but significant decreases in the coactivator function of PGC-1α (Figs. 6, 7), it is noteworthy that the decreases in PGC-1α levels and the activity of PGC-1α-dependent pathways that have been correlated to insulin resistance in humans are very modest—35% decrease in PGC-1α expression and ~20% decrease in expression of genes encoding oxidative phosphorylation components such as *cyt c* (Mootha et al. 2003; Patti et al. 2003). These findings are indicative of the fact that small changes in pathways important for energy metabolism can have potent consequences over time, and suggest that modest effects on PGC-1α activity can be crucial for human health. Understanding the signals and mechanisms that enable PRMT1 to modify PGC-1α and modulate its activity may lead to ways to enhance PGC-1α activity and intervene in such diseases.

Our evidence indicates that methylation by PRMT1 of two or three of the Arg residues in an RERQR sequence, found within the C-terminal Glu-rich E region of PGC-1α (Fig. 3), plays a critical role in the coactivator function of PGC-1α and its ability to function synergistically with PRMT1 (Figs. 5–7). Detecting methylation of specific

Figure 7. Role of Arg methylation in induction of endogenous genes important for the biogenesis and function of mitochondria. (A) SAOS2 cells in six-well plates were infected with adenoviruses expressing GFP, PGC-1α wild type, or PGC-1α R3K mutant (multiplicity of infection = 40) and harvested 24 h later. mRNA levels for the *ERRα* and *cyt c* genes were determined by quantitative PCR and normalized to the level of *GAPDH* mRNA. (B) SAOS2 cells in six-well plates were transfected with siRNA#1 against PRMT1 (100 pmol/well) two times, separated by 72 h. Four hours after the second siRNA transfection, cells were infected with adenovirus expressing GFP or PGC-1α and harvested 24 h later. mRNA levels for the indicated genes were determined by quantitative PCR and normalized to the *GAPDH* mRNA level. The mean and range of variation shown are from duplicate transfections in a single experiment that is representative of five independent experiments, each with duplicate transfected cell cultures. In all five experiments, the multiplicity of infection was 10–40, and the reduction in PRMT1 mRNA levels caused by siRNA was at least 50%. A paired, two-tailed *t*-test performed on the values from the five experiments indicated that the siRNA against PRMT1 caused significant decreases in the PGC-1α-induced levels of *Cyt c* mRNA ($p = 0.014$) and *ERRα* mRNA ($p = 0.008$). For the five experiments, the mean decrease and 95% confidence interval was $35 \pm 15\%$ for *Cyt c* mRNA, $26 \pm 5\%$ for *ERRα* mRNA, and $75 \pm 9\%$ for *PRMT1* mRNA.

proteins in vivo is still a developing art, as witnessed by a variety of recent methodological papers (Boisvert et al. 2003; Rappsilber et al. 2003). We have been unable to demonstrate methylation of the PGC-1 α E region in vivo by mass spectrometry, labeling of cells with methyl-labeled methionine, or antibodies with supposedly general specificity toward proteins containing methyl-arginine. Our experience suggests that success with these approaches depends on the specific protein. Methylation of PGC-1 α by PRMT1 may be regulated, and may occur in vivo only, for example, when they are both recruited into a transcription complex and PGC-1 α adopts the appropriate conformation. In support of this idea, the conformation of PGC-1 α is regulated by protein-protein interactions (Puigserver et al. 1999).

In spite of our lack of direct evidence for in vivo methylation, our data provide strong indirect evidence that methylation of PGC-1 α by PRMT1 does occur in vivo and plays an important role in facilitating PGC-1 α coactivator function: (1) PGC-1 α and its E region are good substrates for PRMT1 but not CARM1. (2) PRMT1, but not CARM1, acts synergistically with PGC-1 α as a coactivator, and this synergy depends on the methyltransferase activity of PRMT1 and the E region of PGC-1 α . (3) The Arg residues that are methylated by PRMT1 are important for the synergy between PGC-1 α and PRMT1 and for the ability of PGC-1 α to stimulate expression of transiently transfected and endogenous target genes. (4) Endogenous PRMT1 is important for the coactivator function of PGC-1 α in the induction of transiently transfected and endogenous target genes.

While PRMT1 and its methyltransferase activity clearly affect the coactivator function of PGC-1 α , considerable PGC-1 α coactivator activity remains when PRMT1 levels are severely reduced (Figs. 6, 7B), when the Arg methylation sites in the E region are mutated (Figs. 5, 7A), or even when the entire C-terminal region (RS, E, and RRM domains) is deleted (Fig. 4). Thus PGC-1 α coactivator function has two components, one independent of PRMT1 and one dependent on PRMT1. The strong N-terminal activation domain appears to be important for both of these activities (Fig. 2), but the specific downstream mechanisms that mediate these two components of PGC-1 α activity remain to be defined.

Arginine methylation of PGC-1 α occurs in the E region, which contains a subnuclear localization signal (Monsalve et al. 2000), and thus could modulate the subnuclear distribution of PGC-1 α , as has been shown for the methylation of some RNA-binding proteins (Lee et al. 2005). If so, such an effect would be subtle, because no differences in the nuclear distribution of wild-type or R3K PGC-1 α protein, in the presence or absence of overexpressed PRMT1, were evident by immunofluorescence (data not shown). A PGC-1 α mutant lacking the C-terminal region exhibited reduced coactivator function (Fig. 4) and was deficient in binding to RNA polymerase II and some SR-type splicing factors (Monsalve et al. 2000), suggesting that this region is important for both transcriptional activation and regulation of mRNA splicing by PGC-1 α . The positive effect of PRMT1-mediated meth-

ylation suggests that methylation may cause an activating conformational change in PGC-1 α , enhance binding of positively acting proteins such as TRAP220 (Wallberg et al. 2003), and/or inhibit binding of repressor proteins. Further studies will be required to elucidate the downstream effects of PGC-1 α methylation and how it contributes to enhanced transcriptional activation.

Materials and methods

Plasmids

The following plasmids were previously described: pcDNA3-HA-PGC-1 α , encoding full-length human PGC-1 α , PGC-1 α .L2A, PGC-1 α .L2/3A (PGC-1 α bearing point mutations within the Leu-rich or LXXLL motifs, as indicated), and PGC-1 α .91C (PGC-1 α lacking the N-terminal activation domain) (Knutti et al. 2000); pSG5.HA-PRMT1, encoding HA epitope-tagged PRMT1 (Koh et al. 2001); GST-PRMT1, encoding a GST-PRMT1 fusion protein (Lin et al. 1996); pSG5.HA-CARM1, encoding HA-CARM1; pGEX4T1.CARM1, encoding GST-CARM1 (Chen et al. 1999); pHE0, encoding human estrogen receptor α (Green et al. 1988); and the luciferase reporter plasmid for ER, MMTV(ERE)-LUC (Umesono and Evans 1989).

Construction of plasmids encoding fragments of PGC-1 α fused to GST: PCR-amplified cDNA fragments encoding PGC-1 α fragments that include amino acids 1–306, 306–532, 532–640, and 640–798, were inserted into the BamHI and XhoI sites of pGEX4T1; pGEX4T3-RS, encoding PGC-1 α (566–632); pGEX4T3-E, encoding PGC-1 α (632–676); and pGEX4T3-RRM, encoding PGC-1 α (676–755), were constructed by inserting the appropriate cDNA fragments, amplified from pcDNA3-HA-PGC-1 α as a template and with primers containing BamHI and SalI sites, into the BamHI and SalI sites of pGEX4T3. The following mutations were generated with the Quickchange site-directed mutagenesis kit (Stratagene), using the corresponding wild-type plasmids as templates: pSG5.HA-PRMT1(E153Q); pGEX4T3-E(R4K), containing R644K, R647K, R651K, and R652K mutations; pGEX4T3-E(R3K), containing R665K, R667K, and R669K mutations; pcDNA3-HA-PGC-1 α (R3K), pcDNA3-HA-PGC-1 α . Δ C (Δ 566–755), pcDNA3-HA-PGC-1 α . Δ RS (Δ 566–632), pcDNA3-HA-PGC-1 α . Δ E (Δ 632–676), and pcDNA3-HA-PGC-1 α . Δ RRM (Δ 676–755). To construct the luciferase reporter pERR α -Luc, the ERR α -responsive sequences of the *ESRRA* promoter (nucleotides –537 to –829, relative to the transcription initiation site) were amplified by PCR and subcloned upstream of the minimal alcohol dehydrogenase promoter of pLuc (Iñiguez-Lluhi et al. 1997).

Cell culture and transfection

CV-1 and COS7 cells were transiently transfected in 12-well dishes as described previously (Ma et al. 1999). Where indicated, medium contained 20 nM estradiol during the last 30 h of growth. Luciferase activity results shown (mean and range of variation of two transfected wells) are from a single experiment, representative of three to five independent experiments. pSG5.HA and pcDNA3.1 empty vectors were added to all transfections to balance total DNA. Luciferase activity was determined with the Promega Luciferase Assay Kit according to the manufacturer's protocols. Because some coactivators enhance the activities of so-called constitutive promoters, constitutive reporter plasmids were not used routinely to normalize the lu-

ciferase activities but were used strategically to monitor transfection efficiency.

Adenovirus infections and RNA analysis

SAOS2 cells were infected with adenoviral vectors expressing GFP and PGC-1 α as described previously (Schreiber et al. 2003). Adenoviruses expressing PGC-1 α R3K were constructed by using the insert of pcDNA3-HA-PGC-1 α R3K. Total RNA was isolated using the TRIzol reagent (Invitrogen), cDNA was synthesized with the SuperScript Choice system (Invitrogen), and specific transcripts were quantified by quantitative real-time PCR using the SYBR Green PCR system (Applied Biosystems) and the Chromophore detection system (MJ Research) (Fig. 7A) or the Stratagene Mx3000P System (Fig. 7B). Gene-specific primers were used for human *ERR α* (Schreiber et al. 2003), human *cyt c* (Schreiber et al. 2004), and human *GAPDH* (5'-GAAGGTGAAGGTCGGAGTC-3' and 5'-GAAGATGGTGA TGGGATTTC-3'). *ERR α* and *cyt c* mRNA levels were normalized to *GAPDH* mRNA levels and estimated using standard curves (Fig. 7A; Schreiber et al. 2004) or the $\Delta\Delta C_t$ method cited in ABI User Bulletin #2 (Fig. 7B).

Methylation assays

Methylation assays (Chen et al. 1999) were performed with 1 μ g each of GST-fused enzyme and substrate.

RNA interference and immunoblots

The following siRNA oligonucleotides for human *PRMT1* were designed using the Target Finder program (Ambion), and chemically synthesized by the USC Norris Comprehensive Cancer Center Microchemical Core: siRNA#1 sense, 5'-AGAUUACU ACUUUGACUCCdTdT-3'; siRNA#1 antisense, 5'-GGAGU CAAAGUAGUAAUCUdTdT-3'; siRNA#2 sense, 5'-CUUUAU GUUUUUUAUUGGUUdTdT-3'; siRNA#2 antisense, 5'-AAC CAUAUAAAAACAUAAGdTdT-3'. Annealed siRNAs were transfected with Lipofectamine 2000 (Invitrogen) into COS7 cells in 24-well plates 48 h before DNA transfection. Luciferase assays were performed 48 h after DNA transfection. Parallel cell extracts were prepared in SDS sample buffer, separated by 12% SDS-PAGE, and transferred onto PVDF membrane. Immunoblots used antibodies against PRMT1 (Upstate Biotechnology) and, after stripping, β -actin (Santa Cruz). SAOS2 cells in six-well plates were transfected with siRNA#1 against *PRMT1* (100 pmol/well). After 72 h, cells were transfected again with siRNA#1 against *PRMT1* (100 pmol/well), medium was changed after 4 h, and then cells were infected with adenovirus expressing GFP or PGC-1 α and harvested 24 h later. mRNA levels for the indicated genes were determined by quantitative PCR and normalized to the *GAPDH* mRNA level.

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