The Transcriptional Coactivator PGC-1 Regulates the Expression and Activity of the Orphan Nuclear Receptor Estrogen-Related Receptor α (ERRα)*

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The estrogen-related receptor α (ERRα) is one of the first orphan nuclear receptors identified. Still, we know little about the mechanisms that regulate its expression and its activity. In this study, we show that the transcriptional coactivator PGC-1, which is implicated in the control of energy metabolism, regulates ERRα at two levels. First, PGC-1 induces the expression of ERRα. Consistent with this induction, levels of ERRα mRNA in vivo are highest in PGC-1 expressing tissues, such as heart, kidney, and muscle, and up-regulated in response to signals that induce PGC-1, such as exposure to cold. Second, PGC-1 interacts physically with ERRα and enables it to activate transcription. Strikingly, we find that PGC-1 converts ERRα from a factor with little or no transcriptional activity to a potent regulator of gene expression, suggesting that ERRα is not a constitutively active nuclear receptor but rather one that is regulated by protein ligands, such as PGC-1. Our findings suggest that the two proteins act in a common pathway to regulate processes relating to energy metabolism. In support of this hypothesis, adenovirus-mediated delivery of small interfering RNA for ERRα, or of PGC-1 mutants that interact selectively with different types of nuclear receptors, shows that PGC-1 can induce the fatty acid oxidation enzyme MCAD (medium-chain acyl-coenzyme A dehydrogenase) in an ERRα-dependent manner.

The nuclear receptor ERRα was identified in 1988 as a protein that shares significant sequence similarity to known steroid receptors, such as the estrogen receptor (1). ERRα and its relatives ERRβ and ERRγ form a small family of orphan nuclear receptors that are evolutionarily related to the estrogen receptors ERRα and ERRβ, and whose in vivo function is still unclear (Refs. 1 and 2 and reviewed in Ref. 3). The three ERRs recognize and bind similar DNA sequences, which include estrogen response elements (EREs) recognized by ERRs, as well as extended ERE half-sites that have been termed ERR response elements (4–7). Despite their high similarity to ligand-dependent receptors, ERRs seem to regulate transcription in the absence of known natural lipophilic agonist ligands. Searches for ligands have so far identified only synthetic antagonists. 4-Hydroxytamoxifen, which binds ERRβ and ERRγ but not ERRα, and diethylstilbestrol, which binds all three ERRs, inhibit the ability of ERRs to activate transcription (8, 9). In support of the pharmacological data, elucidation of the crystal structure of the ERR LBD suggests that the ERRs assume the conformation of ligand-activated nuclear receptors in the absence of ligand (10) and that agonist ligands may not be required. These findings raise the question of how the activity of these nuclear receptors is regulated.

One way to control orphan receptor activity is to express the receptors in a temporally and spatially restricted manner. ERRα is expressed widely; however, particularly high ERRα mRNA levels have been noted at sites of ossification during development, and in heart, kidney, brown fat, and muscle in adults (Refs. 5 and 11–16 and reviewed in Ref. 17). Thus, differential expression of ERRα may contribute to the regulation of ERRα-mediated transcription. The mechanisms and signals that regulate ERRα expression are not clear.

The activity of orphan nuclear receptors may also be regulated at the protein level via interactions with specific cofactors. ERRα has been reported variably as an activator, a repressor, or a DNA-binding factor with little activity, suggesting that cellular factors determine the ability of the ERRα protein to activate transcription (4–6, 11, 16, 18–21). Possible candidates for exerting such control are coactivators that interact with ERRα, such as members of the p160 family of coactivators. Overexpression of p160 coactivators can indeed enhance ERRα-mediated transcription at model reporters (18–20). However, ERRα shows weak transcriptional activity in cells that express endogenous p160 coactivators (5, 20), suggesting that additional cofactors may be important.

PGC-1 is a transcriptional coactivator of many nuclear receptors, as well as specific other transcription factors like the nuclear respiratory factor 1 (NRF-1) and members of the MEF2 (myocyte enhancer factor 2) family (22–28). PGC-1 is expressed in a tissue-selective manner, with the highest mRNA levels found in heart, kidney, brown fat, and muscle (22, 25, 29, 30). Moreover, PGC-1 expression is induced in a tissue-specific manner by signals that relay metabolic needs. Exposure to cold leads to the induction of PGC-1 in brown fat and muscle, starvation induces PGC-1 expression in heart and liver, and physical exercise increases its expression in muscle (22, 28,

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31–33). PGC-1 function has been implicated in the control of energy metabolism, as PGC-1 expression stimulates mitochondrial biogenesis and modulates mitochondrial functions and utilization of energy (Refs. 23, 24, and 31 and reviewed in Ref. 34). The nuclear receptors PPARγ, TRα, PPARα, HNF4, and GR, and the transcription factors NRF-1, MEF2C, and MEF2D, interact with, and may recruit, PGC-1 to the promoters of target genes that execute the metabolic effects of PGC-1. Additional transcription factors are likely to contribute to PGC-1 function.

In the study presented here, we show that PGC-1 regulates, first, the expression of ERRα mRNA and, second, the transcriptional activity of the ERRα protein. Our findings indicate that ERRα by itself is a poor activator of transcription and that PGC-1 fulfills a specific role as a coactivator required for ERRα function. The interactions of PGC-1 and ERRα suggest that the two proteins act in a common pathway.

EXPERIMENTAL PROCEDURES

Plasmids and Adenoviral Vectors—Expression plasmids for wild-type and mutant human PGC-1, and luciferase reporter plgk1, pAUC, and pαCRE/cRE2-Luc (referred to in this study as pERE-Luc), have been described previously (35, 36). pSG5-mERRα (starting at aa 91–408 in the vector pGBKT7 (Clontech). pAS2-ERRαLBD expresses the ERRα LBD fused to the Gal4 DBD and was generated by cloning the annealed primers CCT GGG ATG CTC TTT TTG GAA A (ERRα 907/927-s) and AGC TTT TTC TTT GGA A (ERRα 907/927-a) into pSUPER (37). Yeast expression vectors for Gal4-ERE-Luc (aa 1–408, wild-type or mutants), were generated by subcloning the PGC-1 cDNA fragments encoding aa 91–408 in the vector pGKT7 (Clontech). Plasmid pSISERα was generated by cloning the annealed primers GAT CCC GCA CCA TCC GAG CCT CAT TCA AGA GAT GAG A (ERRα) and GCGACACCAGAGCGTTCAC (exon 5) for mouse ERRα (product 201 bp). CGG GATGATGGCGGAGG (exon 1) and CGGCGCTTGGGCTGTTAGA (exon 2) for p21 (product 212 bp), GGAGGACGGCAGAACTG (exon 4) and GAGACCGAGAGGCTTCA (exon 5) for mouse ERα (product 130 bp); primers for mouse PGC-1 and actin have been described previously (36). In two proteins act in a common pathway.

RESULTS

PGC-1 Induces ERRα Expression—To identify genes that are induced by PGCoL-1 and that could execute the cellular processes activated by PGC-1, we compared the RNA profiles of SAOS2 cells infected with adenoviral vectors expressing PGC-1 with those of cells infected with control vectors expressing β-galactosidase or GFP. Analysis of the RNA profiles after hybridization to high density oligonucleotide arrays (data not shown) identified the orphan nuclear receptor ERRα as a gene that is induced strongly by PGC-1. Expression of PGC-1 led to the induction of ERRα at the RNA and protein level in SAOS2-GR(+) cells, as well as in HtTA-1, HepG2, and 293 cells (Fig. 1A and data not shown). Evaluation of protein levels by immunoblotting showed that the increase in the levels of ERRα protein followed closely the appearance of PGC-1 protein at different times after infection, suggesting that ERRα induction is an early event upon PGC-1 expression (Fig. 1B).

ERRα mRNA levels have been reported to be high in PGC-1 expressing tissues, such as kidney, heart, muscle, and brown adipose tissue (5, 13–16, 22, 25, 29, 30). Analysis of mRNA expression levels in tissues of adult mice shows that indeed ERRα levels correlate with PGC-1 mRNA levels (Fig. 1C). PGC-1 expression in some of these tissues is known to be induced in response to physiological signals, such as exposure to cold (22). Thus, to test the ability of PGC-1 to induce ERRα in vivo, we determined PGC-1 and ERRα mRNA levels in the brown fat and muscle of mice that were exposed to cold for 6 h. As seen in Fig. 1D, the increase in ERRα expression was accompanied by an increase in ERRα mRNA levels, suggesting that PGC-1 can also induce ERRα expression in vivo.

PGC-1 Strongly Induces ERRα-mediated Transcription—The finding that PGC-1 expression of ERRα suggests that PGC-1 enhances also the activity of ERRα-regulated promoters. To test this, we transfected 293 cells with a PGC-1 expression vector and a reporter that carries the luciferase under the control of the minimal ADH promoter with or without binding sites for ERRα (pERE-Luc and pαLuc, respectively). PGC-1 strongly enhanced expression from the pERE-
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Luc reporter, in a manner dependent on the presence of the binding sites for ERRα (Fig. 2A). Estradiol, tamoxifen, or hydroxytamoxifen did not affect the enhancement by PGC-1 (data not shown), suggesting that it was not mediated by receptors that are regulated by these ligands and can recognize the same DNA binding site (e.g., ERRα, ERRγ, ERRβ, or ERRγ). To confirm that endogenous, PGC-1-induced ERRα was mediating the effect of PGC-1 on the pERE-Luc reporter, we determined the effect of inhibiting the expression of ERRα. For this, cells were transfected with a vector expressing a small interfering (si) RNA specific for ERRα (pSiERRα) (37). Expression of the ERRα-specific siRNA led to a decrease in ERRα mRNA levels (Fig. 2B) and a decrease in the PGC-1-mediated induction of the luciferase reporter, demonstrating that endogenous ERRα was required for the PGC-1 effect (Fig. 2C). In the absence of PGC-1, pSiERRα decreased ERRα expression (Fig. 2B) but had no effect on the pERE-Luc reporter (Fig. 2C), suggesting that in this context ERRα was not transcriptionally active.

**PGC-1 Activates ERRα at the Protein Level**—PGC-1 interacts physically with many nuclear receptors and enhances their transcriptional activity (reviewed in Ref. 34). Thus, PGC-1 could also interact with ERRα. In this case, the increased ERRα-mediated transcription could be the combined result of PGC-1 inducing ERRα levels and enhancing ERRα activity. To address this, we first asked whether overexpression of ERRα would lead to the same phenotype as PGC-1 expression. If the only function of PGC-1 were to increase ERRα levels, we would expect that exogenous ERRα expression would mimic the PGC-1 effect. Surprisingly, overexpression of ERRα had very little effect on pERE-Luc (<2-fold), suggesting that ERRα alone was not sufficient for the transcriptional activation of this reporter (Fig. 3A). Coexpression of PGC-1 with ERRα led to an increase in luciferase expression that was stronger than that

![Image](https://example.com/image.png)

**FIG. 2.** PGC-1 induces ERRα-mediated transcription. A, 293 cells were transfected with a luciferase reporter driven by either just the minimal ADH promoter (pΔLuc) or 2 EREs upstream of the minimal ADH promoter (pERE-Luc) and either the control vector pcDNA3 or a PGC-1 expression vector. Data are the mean ± S.D. of luciferase activities from three experiments performed in duplicates. B, 293 cells were transfected with the empty vector pSUPER (37) or the vector expressing siRNA for ERRα (pSiERRα) and either pcDNA3 (+/vector) or the PGC-1 expression vector pcDNA3/HA-PCG-1 (+/PCG-1). Transfection efficiency was 40–50%. RNA was prepared 48 h later. ERRα mRNA levels were determined by quantitative RT-PCR and normalized to levels of 36B4. Data are the average of two experiments performed in duplicates. C, 293 cells were transfected with the pERE-Luc reporter, a control or PGC-1 expression vector as indicated, and either the control pSUPER or the siRNA expressing pSiERRα. Data represent the mean ± S.D. of luciferase activities from two experiments performed in duplicates.

seen with just endogenous ERRα, indicating that PGC-1 activated the exogenously introduced ERRα (Fig. 3A).

To determine the effect of PGC-1 on the activity of ERRα directly, we evaluated the consequence of PGC-1 expression on the activity of a Gal4 DBD-ERRα LBD chimera, using a Gal4-responsive luciferase reporter. In this context, endogenous ERRα does not interfere with the luciferase readout. As seen in Fig. 3B, Gal4-ERRα LBD by itself activated transcription modestly, ~2-fold, suggesting that the LBD of ERRα carries only a
tested the contribution of the L3 site to the PGC-1/ERR
previous studies, we had noted that the L3 site can mediate a
effect on the physical interaction of PGC-1 with ERR
Mutations in motif L1, alone or in combination with L2, had no
while the double L2A/L3A mutation abolished the interaction.

weak transcriptional activation function. Addition of PGC-1
converted the Gal4-ERRα LBD fusion to a strong activator of
transcription, indicating that PGC-1 enables the transcriptional
function of ERRα (Fig. 3B).

ERRα Interacts with PGC-1 via an Atypical L-rich Box—
PGC-1 harbors three Leu-rich motifs (L1, L2, and L3), one of
which (L2) bears the consensus LXXLL sequence present in
many proteins that interact with the LBD of nuclear receptors.
The L2 motif serves as the major binding site for many nuclear
receptors, and mutations in L2 disrupt the interactions of
PGC-1 with nuclear receptors tested so far (24, 26, 35). Surpris-
ingly, PGC-1 harboring a mutant L2 (L2A) was still capable
of interacting with ERRα in a yeast two-hybrid assay; in the
same context, the L2A mutant was severely compromised for
interaction with PPARγ, RXRα, and ERRγ (Fig. 4, A and B). In
previous studies, we had noted that the L3 site can mediate a
weak interaction with the glucocorticoid receptor (35). We thus
tested the contribution of the L3 site to the PGC-1/ERRα in-
teraction. As seen in Fig. 4, A and B, PGC-1 bearing a disruption
of just L3 (L3A) was also capable of interacting with ERRα,
while the double L2A/L3A mutation abolished the interaction.
Mutations in motif L1, alone or in combination with L2, had no
effect on the physical interaction of PGC-1 with ERRα (data not
shown). Thus, we concluded that motifs L2 and L3 can be used
equivalently for physical interactions between PGC-1 and
ERRα, while L2 is the preferred site for most other receptors
(Fig. 4, A and B).

Next, we determined the requirement of the physical inter-
action between PGC-1 and ERRα for the activation of the ERRα
LBD in mammalian cells, using the context of the Gal4-ERRα
LBD chimera. Single mutations in either L2 or L3 did not
compromise the PGC-1 effect (Fig. 4C), suggesting that inter-
action via either site is sufficient for activation of ERRα by
PGC-1. The double L2A/L3A mutation abolished the activation,
indicating that the physical interaction between the two pro-
teins is necessary for the effect of PGC-1 on the ERRα LBD
(Fig. 4C).

PGC-1 Can Induce the Expression of the Endogenous Gene
MCAD in an ERRα-dependent Manner—The ability of PGC-1
to induce ERRα expression and activity predicts that PGC-1
should also induce the expression of ERRα target genes. To test
this, we determined the effect of PGC-1 on the RNA levels of a
proposed ERRα target, the MCAD, an enzyme in fatty acid
oxidation (5, 13). As seen in Fig. 5, PGC-1 expression led to the
induction of MCAD in HtTA-1 and SAOS2-GR(+) cells. To
address whether the induction was mediated by ERRα, we
asked whether suppression of ERRα expression affected the
response of MCAD to PGC-1. Induction of HtTA-1 cells with
adenoviruses that express ERRα-specific siRNA led to a de-
crease in ERRα mRNA levels (Fig. 5A), and a reduced induction
are indeed used selectively by different nuclear receptors to recruit PGC-1 at their respective endogenous target genes.

**DISCUSSION**

Many members of the nuclear receptor superfamily are still orphan receptors, with no known physiological ligands. The mechanisms that regulate the activity of these receptors are not fully understood. The results presented here provide evidence that the transcriptional coactivator PGC-1 is a key regulator of the orphan nuclear receptor ERRα. PGC-1 acts at two levels. First, it induces ERRα expression, and second, it associates with ERRα and enables the transcriptional activation of ERRα target genes. PGC-1 expression is known to be regulated in a tissue-selective manner by physiological signals that relay metabolic needs (22, 28, 31–33). Accordingly, PGC-1 function has been implicated in the regulation of energy metabolism (Refs. 23, 24, and 31 and reviewed in Ref. 34). Our findings suggest that ERRα functions in PGC-1-regulated pathways, where it may contribute to the transcriptional activation of genes important for energy homeostasis.

The activity of several orphan nuclear receptors is restricted by expression of the receptors in specific tissues or at particular times (reviewed in Ref. 17). The mechanisms that control the selective expression of these receptors are often not clear. The observation that PGC-1 induces ERRα mRNA levels provides a molecular explanation for the high ERRα expression in heart, kidney, muscle, and brown fat, *i.e.* tissues that express PGC-1. Moreover, it suggests physiological signals that are likely to control ERRα expression, as shown here for exposure to cold in brown fat and muscle. In support of these findings, Ichida et al. have recently shown that fasting, which is known to induce PGC-1 expression in the liver (28, 33), also increases ERRα mRNA levels (40). The spatial and temporal correlation of PGC-1 and ERRα expression implies that ERRα induction is an early, and possibly direct, outcome of PGC-1 action. Future studies must address whether PGC-1 acts directly at the ERRα promoter. Additional regulatory mechanisms may restrict or enhance ERRα induction by PGC-1, in a tissue- or physiological state-dependent manner.

Interestingly, we find that in the absence of PGC-1, ERRα is a very weak activator of transcription. Coexpression of PGC-1 enables potent transcriptional activation by ERRα. These findings suggest that ERRα is not a constitutively active receptor and that transformation into an active form is favored by binding to protein ligands, such as PGC-1, rather than to small lipophilic ligands. Expression levels of PGC-1 may explain why ERRα has been reported as an efficient transcriptional activator in some cells (*e.g.* ROS 17/28) and a poor activator in others (4–6, 11, 16, 18–21). Many established cell lines express very low, if any, levels of PGC-1. Importantly, the ability of PGC-1 to activate ERRα at the protein level predicts that physiological signals that induce PGC-1 are likely to activate ERRα-mediated transcription, even in the absence of increased ERRα expression.

The activation of ERRα at the protein level requires the physical interaction of PGC-1 with ERRα. Surprisingly, this interaction differs from that of PGC-1 with other nuclear receptors. While PGC-1 recognizes most receptors tested until now (GR, ERRα, TRα, RXRα, RARα, PPARα, PPARγ, HNF4) via the canonical LXXLL motif L2, it can interact with ERRα equally well via the L2 or the L3 site. Similar to our findings, Huss et al. have recently shown that ERRα, as well as the related receptor ERRγ, bind the L3 site of PGC-1 (41), suggesting that the L3-mediated interaction is characteristic of the ERR subfamily of receptors. Interestingly, the differential utilization of the Leu-rich motifs can be used to dissect the receptors that mediate specific PGC-1 functions, as shown by the
fact that L2A mutations disrupt GR-dependent, but not ERR-dependent, effects of PGC-1. Thus, the L2 and L3 mutants of PGC-1 may provide useful tools for elucidating the types of receptors that recruit PGC-1 at distinct promoters.

The in vivo functions of ERR are not yet defined. Based on its ability to bind ERs and modulate some estrogen-responsive genes, ERR has been proposed to modulate ER signaling and possibly play a role in ER-dependent tumors (6, 20, 21). A function of ERRs in bone development is supported by the high levels of ERR at sites of ossification during embryogenesis, and the ability of ERR to promote osteoblast differentiation in vitro and to activate the promoter of the MCAD gene, suggest a role in the mitochondrial β-oxidation of fatty acids (24), and possibly other aspects of energy homeostasis. Interestingly, the close relationship of PGC-1 and ERR activity may reflect not only an involvement of ERRs in known PGC-1-regulated functions, but also of PGC-1 in processes where ERR roles have been suggested, such as bone development and homeostasis or breast cancer.

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