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Citation
Lin, Jiandie, Pere Puigserver, Jerry Donovan, Paul Tarr, and Bruce M. Spiegelman. 2002. "Peroxisome Proliferator-Activated Receptor γ Coactivator 1β (PGC-1β), A Novel PGC-1-Related Transcription Coactivator Associated with Host Cell Factor." Journal of Biological Chemistry 277 (3): 1645–48. doi:10.1074/jbc.C100631200.

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THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 277, No. 3, Issue of January 18, pp. 1645–1648, 2002
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Printed in U.S.A.

Accelerated Publication

Peroxisome Proliferator-activated Receptor γ Coactivator 1β (PGC-1β), A Novel PGC-1-related Transcription Coactivator Associated with Host Cell Factor*

Received for publication, November 1, 2001,
and in revised form, November 28, 2001
Published, JBC Papers in Press, November 30, 2001,
DOI 10.1074/jbc.C100631200

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Peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1) plays a critical role in regulating multiple aspects of energy metabolism, including adaptive thermogenesis, mitochondrial biogenesis, and fatty acid β-oxidation. Recently, this coactivator of nuclear receptors/transcription factors has been shown to control hepatic gluconeogenesis, an important component of the pathogenesis of both type-1 and type-2 diabetes. We described here the cloning of a novel *bona fide* homologue of PGC-1, PGC-1β (PGC-1 was renamed as PGC-1α), first identified through searches of new data base entries. Despite the fact that PGC-1α and -1β share similar tissue distributions with highest levels of expression in brown fat and heart, their mRNAs are differentially regulated in the brown adipose tissue upon cold exposure and during brown fat cell differentiation. Like PGC-1α, PGC-1β mRNA levels are increased significantly in the liver during fasting, suggesting a possible role for this factor in the regulation of hepatic gluconeogenesis and/or fatty acid oxidation. Consistent with this, PGC-1β was shown to physically interact and potently coactivate hepatic nuclear factor 4 and peroxisome proliferator-activated receptor α, nuclear receptors that are essential for hepatic adaptation to fasting. Finally, using sequence comparisons between PGC-1α and -1β, we have identified a conserved amino acid motif that serves as a docking site for host cell factor, a cellular protein implicated in cell cycle regulation and viral infection. HCF is shown to bind to both PGC-1α and -1β and augment their transcriptional activity.

The transcriptional function of many nuclear receptors (NRs)[1] is regulated by ligand-dependent recruitment of coactivators to the C-terminal ligand binding domain (1, 2). A number of coactivators, including the p160 family, p300/CBP and P/CAF, contain intrinsic histone acetyl transferase activity and regulate transcription by modulating histone acetylation (1). Other coactivators, consisting of heterogeneous proteins with little sequence homology, modulate transcription by acting as protein docking interfaces that recruit histone acetyl transferase-containing complexes or associate with basal transcription factors such as RNA polymerase II holoenzyme (3). The interaction between NRs and many coactivators requires a conserved L*XX*LL motif, which is believed to form hydrophobic contacts with the receptors (4, 5).

PGC-1 was initially identified as a PPARγ-interacting protein from a BAT library and was subsequently found to associate with an array of NRs and transcription factors (6–9). Importantly, PGC-1 has been shown to coordinately regulate the program of mitochondrial biogenesis and adaptive thermogenesis in BAT and skeletal muscle, mainly through the coactivation of PPARs and nuclear respiratory factor 1 (NRF1), a nuclear transcription factor that regulates the expression of many mitochondrial genes (6, 7). In transgenic mice, PGC-1 increases mitochondrial biogenesis and β-oxidation of fatty acids in the heart, likely through augmentation of PPARα and NRF1 transcriptional activity (10). Recently, PGC-1 expression was found to be elevated in fasted liver and several models of type-1 and type-2 diabetes; in addition, PGC-1 can directly control the activation of hepatic gluconeogenesis (11, 12). Despite playing an important role in coordinating multiple physiological processes, no close homologue for PGC-1 has been found. We described here the identification of a novel coactivator, which is closely related to PGC-1, that we have termed PGC-1β. Furthermore, we identified HCF, a cellular protein that is involved in herpes simplex virus (HSV) infection and cell cycle regulation (13, 14), as a novel binding partner that increases the transcriptional activity of both PGC-1α and -1β.

MATERIALS AND METHODS

Plasmid Construction—Full-length PGC-1β cDNA clone was obtained by ligating the 5′ end of PGC-1β cDNA generated by GENERACER (Invitrogen) to an expressed sequence tag cDNA clone (AA288169) that contains the 3′ end. GST-PGC-1β (N-350) was generated by inserting a PCR fragment coding for the N-terminal 350 amino acids in frame into pGEX-5X1 vector. Fusion constructs between GAL4-DBD and various regions of PGC-1β or HCF were generated by subcloning PCR-amplified cDNA fragments in frame into pCMX-GAL4 plasmid (6). N-terminal FLAG-tagged PGC-1β (amino acid 2–1014) was obtained by subcloning the cDNA insert into pCATCH FLAG plasmid (15). All PCR fragments were verified by sequencing.

Transient Transfection—BOSC cells and COS cells were maintained in Dulbecco's modified Eagle's medium plus 10% fetal bovine serum. The cells were transfected using FuGENE according to the manufacturer (Roche Molecular Biochemicals). Reporter constructs for HNF4α (3× gAF1 luc) and NRF1 (4× NRF1 luc) were described previously (7, 11). Luciferase assays were performed 48 h after transfection.

* This work was supported in part by National Institutes of Health Merit Award R37DK31405 (to B. M. S.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

‡ Supported by a postdoctoral fellowship from the American Heart Association.

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[1] The abbreviations used are: NR, nuclear receptor; PPAR, peroxisome proliferator-activated receptor; PGC-1, PPARγ coactivator-1; BAT, brown adipose tissue; HSV, herpes simplex virus; HCF, host cell factor; NRF, nuclear respiratory factor; RRM, RNA recognition motif; HBM, HCF binding motif; RAR, retinoic acid receptor; TR, thyroid receptor; GR, glucocorticoid receptor; HNF4, hepatic nuclear receptor 4; GST, glutathione *S*-transferase; DBD, DNA binding domain; PRC, PGC-1-related coactivator.

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RNA Expression Analysis—HIB1B cells were maintained and induced to differentiate as described (6). To induce UCP-1 expression, differentiated cells were treated with 10 μM forskolin for 6 h before RNA isolation. For cold exposure, C57/Bl6 mice were maintained at 4 °C for 6 h before sacrifice. RNA samples were analyzed by Northern hybridization using specific cDNA probes.

Protein Interaction Studies—Binding assays using GST fusion proteins were performed essentially as described (6). Ligands were included in some binding reactions as indicated. For coimmunoprecipitation assays, BOSC cells were transiently transfected with various combinations of plasmids and lysed after 36 h in a buffer containing 100 mM Tris (pH = 8.0), 250 mM NaCl, 1% Nonidet P-40, 1 mM EDTA, 1 mM $MgCl_2$, and protease inhibitors. The lysates were incubated with 10 μl of anti-FLAG-Sepharose beads (Sigma) for 1 h at room temperature. The beads were then washed four times with the lysis buffer and resuspended in SDS-PAGE buffer. The samples were then processed for immunoblotting analysis.

RESULTS

PGC-1 is not known to have any close homologues. Because a great amount of sequence data has recently been entered into the genomic and expressed sequence tag databases, we searched these databases for transcripts with similarities to the N terminus of PGC-1. In contrast to the C terminus, this domain is uniquely found in rodent and human PGC-1. A partial transcript in the Celera mouse genome database (mCT4723) was found to encode a novel protein sharing a high degree of sequence identity to PGC-1, which we designated PGC-1β (AF453324). To keep nomenclature consistent, we thus renamed PGC-1 as PGC-1α. Sequence analysis revealed that the 3.6-kb cDNA contains an open reading frame of 1014 amino acids that has similarity to PGC-1α across the entire molecule, including three L*XX*LL motifs at the N terminus and one RNA recognition motif (RRM) at the C terminus (Fig. 1*A*). Identity between PGC-1α and -1β is especially high in the N-terminal activation domain and the C-terminal RNA binding domain (40 and 48%, respectively; see Fig. 1*B*). Furthermore, sequence comparison of all PGC-1 family members, including PGC-1-related coactivator (PRC), revealed a novel conserved region containing a tetrapeptide motif (DHDY; amino acid 683–686) that has been previously identified in other proteins as a putative binding site for HCF, a protein involved in the regulation of cell cycle progression and the assembly of a multiprotein transcriptional complex during HSV infection (16, 17). The function of this motif will be analyzed below. PGC-1β also contains two glutamic/aspartic acid-rich acidic domains, but unlike PGC-1α and PRC, it lacks most of the arginine/serine-rich domain, a region that has been implicated in the regulation of RNA processing (18). Human PGC-1β is predicted to share over 70% amino acid sequence identity with mouse PGC-1β and is localized to 5q33. Murine PGC-1β is localized to chromosome 18. BLAST searches also revealed that the PGC-1 family of proteins is also well conserved in species such as chicken, zebrafish, and *Xenopus*, suggesting that PGC-1 may play important roles common to all of these species, perhaps linked to mitochondrial function and/or the regulation of other cellular and developmental processes.

PGC-1β mRNA is expressed in a highly tissue-selective manner as shown by Northern hybridization (Fig. 1*C*). PGC-1β mRNA is most abundantly present in brown adipose tissue and heart, both notable for containing very high concentrations of mitochondria. These results strongly suggest that like PGC-1α, PGC-1β may play an important role in mitochondrial function, respiration, and/or thermogenesis. Two predominant species of PGC-1β mRNA (5 and 9 kb) were detected; this may result from the usage of two alternative polyadenylation signals present in the 3′ end of the PGC-1β gene. Moderate levels of PGC-1β mRNA are also observed in skeletal muscle, liver, and white adipose tissue.

A

MAGNDCGALL DEELSSFFLN YLSDTQGGDS GEEQLCADLP ELDLSQLDAS 50
DFDSATCFGE LQWCPETSET EPSQYSPDDS ELFQIDSENE ALLAALTKTL 100
DDIPEDDVGL AAFPELDEGD TPSCTPASPA PLSAPPSPTL ERLLSPASDV 150
DELSLLQKLL LATSSPTASS DALKDGATWS QTSLSSRSQR PCVKVDGTQD 200
KKTPTLRAQS RPCTELHKHL TSVLPCPRVK ACSPTPHPSP RLLSKEEEEE 250
VGEDCPSPWP TPASPQDSLA QDTASPDSAQ PPEEDVRAMV QLIRYMHTYC 300
LPQRKLPQRA PEPIPQACSS LSRQVQPRSR HPPKAFWTEF SILRELLAQD 350
ILCDVSKPYR LAIPVYASLT PQSRPRPPKD SQASPAHSAM AEEVRITASP 400
KSTGPRPSLR PLRLEVKRDV NKPTRQKREE DEEEEEEEEE EEEEKEEEEE 450
EWGRKRPGRG LPWTKLGRKM DSSVCPVRRS RRLNPELGPW LTFTDEPLGA 500
LPSMCLDTET HNLEEDLGSL TDSSQGRQLP QGSQIPALES PCESGCGDTD 550
EDPSCPQPTS RDSSRCLMLA LSQSDSLGKK SFEESLTVEL CGTAGLTPPT 600
TPPYKPMEED PFKPDTKLSP GQDTAPSLPS PEALPLTATP GASHKLPKRH 650
PERSELLSHL QHATTQPVSQ AGQKRPFSCS FGDHDYCQVL RPEAALQRKV 700
LRSWEPIGVH LEDLAQQGAP LPTETKAPRR EANQNCDPTH KDSMQLRDHE 750
IRASLTKHFG LLETALEGED LASCKSPEYD TVFEDSSSSS GESSFLLEEE 800
EEEEGGEED DEGEDSGVSP PCSDHCPYQS PPSKASRQLC SRSRSSSGSS 850
SCSSWSPATR KNFRRESRGP CSDGTPSVRH ARKRREKAIG EGR**VVYIRNL** 900
SSDMSSRELK KRFEVFGEIV ECQVLTRSKR GQKHGFITFR CSEHAALSVR 950
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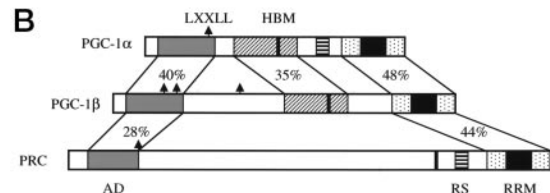

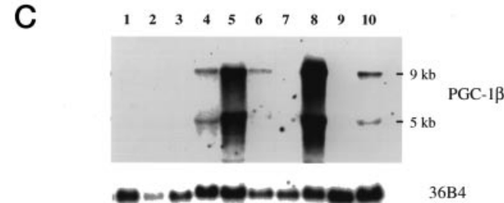

FIG. 1. **Amino acid sequence, gene structure, and tissue distribution of PGC-1β mRNA.** *A*, amino acid sequence of PGC-1β. Three L*XX*LL motifs are *underlined*. RRM is shown in *bold*, and the HBM is *boxed*. *B*, protein sequence alignment of PGC-1α, PGC-1β, and PRC, with the degree of sequence identity to PGC-1β shown. Conserved domains/motifs are indicated *above* and *below* the diagram, including activation domain (*AD*), L*XX*LL and HBM motifs, the arginine/serine-rich domain, and RRM. *C*, Northern blot analysis of RNA from various tissues using PGC-1β cDNA as a probe. *1*, adrenal gland; *2*, brain; *3*, kidney; *4*, liver; *5*, heart; *6*, muscle; *7*, lung; *8*, BAT; *9*, spleen; *10*, white adipose tissue. Hybridization to 36B4 is shown as a control for RNA loading.

PGC-1α was initially identified as a transcription coactivator that controls mitochondrial biogenesis and adaptive thermogenesis in skeletal muscle and brown fat. In contrast to the cold-inducible expression of PGC-1α, the expression of PGC-1β in BAT is not increased in response to cold exposure (Fig. 2*A*). Given its abundant expression in the brown fat, it is possible that PGC-1β is an important factor in the determination and/or differentiation of brown adipocytes. To test whether the expression of PGC-1β is regulated during brown fat differentiation, the mouse brown fat cell line HIB1B was induced to undergo differentiation and examined for the PGC-1β expression (19). Compared with undifferentiated cells, the expression of PGC-1β is elevated on days 3 and 5 of differentiation, parallel with a concomitant decrease in the PGC-1α expression (Fig. 2*B*). Upon treatments with forskolin, an activator of adenylyl cyclase, PGC-1α level is rapidly induced along with the key uncoupling protein of brown fat, UCP-1. In contrast, PGC-1β expression is slightly decreased. These results indicate that PGC-1α and -1β are likely to perform distinct roles in brown fat differentiation and the regulation of other brown fat functions such as adaptive thermogenesis.

PGC-1α expression is highly induced in the liver during fasting and has been shown to play a direct role in the activation of hepatic gluconeogenesis in primary hepatocyte culture

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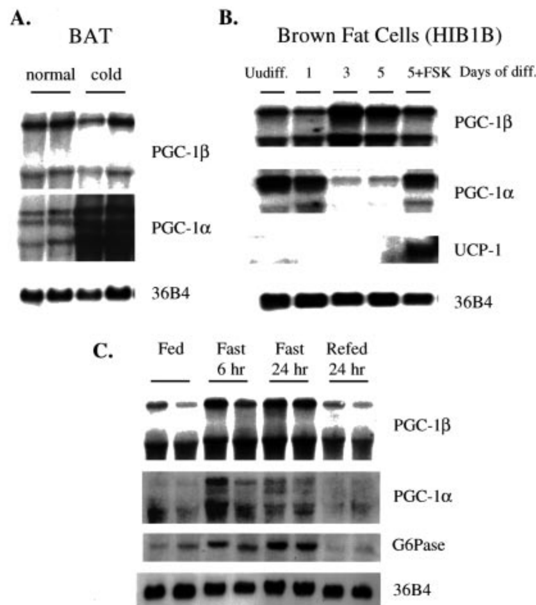

FIG. 2. **Highly regulated expression of PGC-1β.** *A*, Northern blot analysis of BAT RNA from mice exposed to 25 °C (*normal*) or 4 °C (*cold*) for 6 h. *B*, Northern blot analysis of brown fat cell RNA during differentiation (*diff.*) and forskolin treatment. HIB1B cells were induced to undergo differentiation for various periods of time. Cells differentiated for 5 days were treated with 10 μM forskolin (*FSK*) for 6 h. *C*, Northern blot analysis of liver RNA isolated from fasted/refed mice. Note significant induction of PGC-1β mRNA expression during fasting along with the gluconeogenic enzyme glucose-6-phosphatase (*G6Pase*).

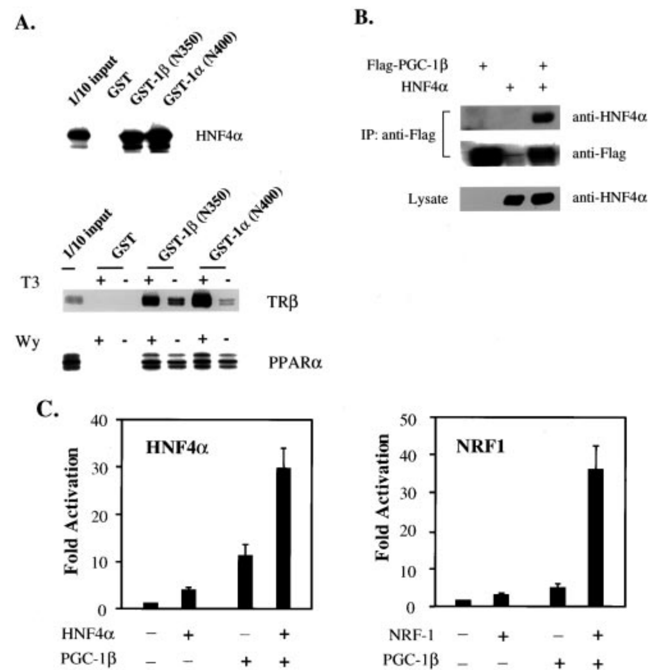

FIG. 3. **Physical interaction between PGC-1β and nuclear receptors.** *A*, a purified fusion protein between the N-terminal 350 amino acids of PGC-1β and GST was incubated with *in vitro*-translated HNF4α, TRβ, or PPARα and examined for interaction as described. *B*, BOSC cells were transfected with expression constructs as indicated. Total cell lysate or immunoprecipitated (*IP*) complex was examined by immunoblotting analysis. *C*, coactivation of nuclear receptors by PGC-1β. COS cells were cotransfected with vectors expressing HNF4α or NRF1 along with reporter plasmids (3× gAF1 luc for HNF4α and 4× NRF1 luc for NRF1), alone or in the presence of PGC-1β. *Error bars* indicate S.E. of three independent experiments made in duplicate.

and rats (11, 12). Elevated expression of PGC-1α has also been shown in models of both type-1 and type-2 diabetes (11). As shown in Fig. 2*C*, the expression of PGC-1β is significantly increased in the liver during fasting, a pattern that is strikingly similar to the regulation of PGC-1α expression. These results suggest that PGC-1β might be part of the regulatory pathways that activate the hepatic adaptation during fasting, such as the elevation of gluconeogenesis, β-oxidation of fatty acids, and ketogenesis.

PPARα and HNF4α are important transcription regulators implicated in hepatic fatty acid oxidation and gluconeogenesis during periods of food deprivation (20). We therefore asked whether PGC-1β would physically interact with and coactivate these transcription factors. The N terminus of PGC-1β (1–350), which contains three putative nuclear receptor binding motifs (L*XX*LL), is able to "pull down" *in vitro*-translated HNF4α with similar efficiency as PGC-1α (Fig. 3*A*). Furthermore, the full-length PGC-1β is readily coimmunoprecipitated with HNF4α when coexpressed in BOSC cells, indicating *in vivo* association of these two proteins (Fig. 3*B*). In contrast to PPARα and -γ, the recruitment of PGC-1β by RARα and TRβ is highly dependent on their respective ligands (Fig. 3*A* and data not shown). Consistent with a potential role in regulating hepatic gluconeogenesis, PGC-1β potently enhances the transcriptional activity of GR and HNF4α on reporter constructs containing multimerized cognate binding sites (Fig. 3*C*). Coactivation of GR by PGC-1β is strictly dependent on the presence of glucocorticoid, indicating ligand-dependent recruitment of the coactivator to the receptor; the latter is also observed for TRβ and RARα (data not shown). Although PGC-1β alone has minimal effect on the reporter plasmids for GR and RARα, it significantly coactivates HNF4α reporter construct; this is probably because of the presence of endogenous nuclear receptors that may bind to the responsive elements. In addition to coactivating NRs, PGC-1β is also a potent regulator of the transcriptional activity of NRF1, a central transcription factor in the control of mitochondrial biogenesis (Fig. 3*C*). Ligand-dependent binding and coactivation of several receptors by PGC-1β demonstrate that PGC-1β regulates the transcriptional activity of multiple NRs, likely through direct physical association with these factors. Significantly, these include factors known to be important in mitochondrial biogenesis, fatty acid oxidation, and gluconeogenesis.

Sequence alignment of all PGC-1 family members revealed several conserved patches of amino acids that may be important for their function. One such region contains a tetrapeptide motif, DHDY, that is a putative HCF binding motif (HBM; (D/E)H*X*Y). Proteins containing this motif have been shown to associate with HCF, including HSV viral protein VP16 and a basic leucine-zipper protein, LZIP (16). HCF does not bind DNA by itself; however, it can be recruited by DNA-binding transcription factors such as Oct-1 and functions as a scaffold for the assembly of transactivation complexes (21). Although HCF has been found in complex with Oct-1 and VP16, the cellular targets for this factor remain unclear. It is therefore possible that PGC-1α and -1β may mediate the recruitment of HCF-containing protein complexes to the NR binding sites, thereby modulating NR-regulated transcription. To test whether PGC-1α and -1β are physically associated with HCF *in vivo*, FLAG-tagged HCF was cotransfected with GAL-PGC-1α or -1β and analyzed by immunoprecipitation followed by Western blot. As shown in Fig. 4*A*, HCF strongly interacts with both PGC-1α and PGC-1β, thus identifying a novel interaction partner for PGC-1-related coactivators. Recruitment of HCF to PGC-1β increases the transcriptional activity of PGC-1β 3-fold in a cotransfection assay (Fig. 4*B*). On the other hand, PGC-1β can be recruited by the N-terminal 380 amino acids of HCF, a domain that has been shown to interact with HBM-containing

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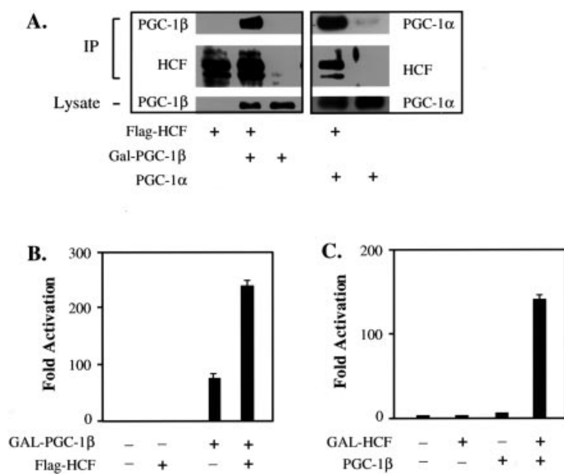

FIG. 4. **Interaction and activation of PGC-1 by HCF.** *A*, BOSC cells were transiently transfected with expression constructs as indicated. Total cell lysate was immunoprecipitated with anti-FLAG antibodies (*IP*) and examined by immunoblotting analysis for the presence of PGC-1β (anti-GAL4 DBD), PGC-1α (anti-PGC-1α), and HCF (anti-FLAG). Note both PGC-1α and -1β are present in the immunocomplex containing HCF. *B*, BOSC cells were transiently transfected with expression constructs as indicated along with 5XUAS luciferase reporter plasmid. *C*, the N-terminal 380 amino acids of HCF were fused to GAL4-DBD. The resulting construct was transiently transfected into BOSC cells alone or in the presence of FLAG-PGC-1β with 5XUAS luciferase plasmid. Luciferase activity was expressed as -fold activation over vector alone. *Error bars* indicate S.E. of three independent experiments made in duplicate.

proteins, and potently increases the transcriptional activity of HCF fused to the GAL4 DBD (Fig. 4*C*). Coactivation of HCF was also observed for PGC-1α (data not shown). These results demonstrate that HCF can function in complex with PGC-1α/1β to activate transcription from target genes.

DISCUSSION

We described here the identification of a transcription coactivator that is closely related to PGC-1α. PGC-1β has sequence homology to PGC-1α across the molecule, but it is clearly the product of a distinct gene. PGC-1β physically interacts with a number of NRs both *in vitro* and *in vivo* and potently augments their transcriptional activity. Expression of PGC-1β is elevated in the liver during fasting, suggesting PGC-1β, like PGC-1α, may play an important role in the activation of metabolic programs underlying hepatic adaptation during fasting. Consistent with this, PGC-1β was found to coactivate HNF4α, GR, and PPARα, transcription factors that coordinate the activation of gluconeogenesis and fatty acid oxidation in the liver. PGC-1β mRNA is abundant in both BAT and heart, tissues that contain dense mitochondria and high levels of substrate oxidation. Given that PGC-1β is a potent coactivator for NRF1, it is highly likely that PGC-1β regulates mitochondrial function and respiration. In contrast to the cold-inducible expression of PGC-1α, the expression of PGC-1β mRNA is not altered by exposure of animals to cold temperature or treatment of brown adipocyte culture with forskolin. On the other hand, PGC-1β mRNA is elevated during brown fat differentiation, suggesting that PGC-1α and -1β perform distinct functions during brown fat determination/differentiation and adaptive thermogenesis.

The availability of this new sequence information allows us to identify conserved motifs among PGC-1 family members that may be important for their function. We reported here that all known coactivators in the PGC-1 family, including PGC-1α, -1β, and PRC, contain a functional docking site for HCF. The association between HCF and PGC-1β enhances the transcriptional activity of PGC-1β, suggesting that the assembly of PGC-1·HCF complexes may be important in the coactivation of NRs by PGC-1. HCF is a critical component of a transactivation complex formed along with HSV VP16 and octamer-binding protein Oct-1; this complex is important for immediate early gene expression during viral infection (14, 22). The activity of HCF is also required for cell cycle progression (14). It is therefore possible that PGC-1, in complex with HCF and DNA-binding transcription factors such as NRs, plays an as yet unidentified role in gene expression during viral infection and cell proliferation, perhaps related to mitochondrial-linked energy metabolism. This must be addressed in future studies.

Acknowledgments—We thank Dr. Elisabetta Muller for critically reading the manuscript. We also thank Dr. Anthony Hollenberg for providing TR reporter constructs, Dr. Daryl Granner for the GR and HNF4α plasmids, Dr. Richard Scarpulla for NRF1 construct, and Drs. Thomas Kristie and Winship Herr for the HCF plasmids.

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J. Biol. Chem. 2002, 277:1645-1648.
doi: 10.1074/jbc.C100631200 originally published online November 30, 2001

Access the most updated version of this article at doi: 10.1074/jbc.C100631200

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