# Activation of PPARγ Coactivator–1 Through Transcription Factor Docking

Pere Puigserver,[1] Guillaume Adelmant,[1] Zhidan Wu,[1] Melina Fan,[1] Jianming Xu,[2] Bert O'Malley,[2] Bruce M. Spiegelman[1]*

Transcriptional coactivators have been viewed as constitutively active components, using transcription factors mainly to localize their functions. Here, it is shown that PPARγ coactivator–1 (PGC-1) promotes transcription through the assembly of a complex that includes the histone acetyltransferases steroid receptor coactivator–1 (SRC-1) and CREB binding protein (CBP)/p300. PGC-1 has a low inherent transcriptional activity when it is not bound to a transcription factor. The docking of PGC-1 to peroxisome proliferator-activated receptor γ (PPARγ) stimulates an apparent conformational change in PGC-1 that permits binding of SRC-1 and CBP/p300, resulting in a large increase in transcriptional activity. Thus, transcription factor docking switches on the activity of a coactivator protein.

Transcription factors exert their effects through docking of coactivator or corepressor proteins. Coactivators belong to two broad classes. In the first class, proteins like the SRC and CBP/p300 families contain histone acetyltransferase (HAT) activity that modifies chromatin structure (*1*). The second class, those in the vitamin D receptor–interacting proteins, thyroid receptor–associated proteins, and activator-recruited cofactor complexes, may mediate a direct connection between particular DNA binding proteins and RNA polymerase II (*2–4*). This model portrays the DNA binding transcription factor in a largely passive role, localizing the coactivator complex to genes that are marked for activation. Conversely, the coactivator complex has been thought to be constitutively active, requiring only proper positioning in the genome to initiate transcription. We have investigated the mechanism of transcriptional function and the role of transcription factor docking to coactivators. PGC-1 is a coactivator of nuclear respiratory factor–1 (NRF-1), PPARγ, and other nuclear receptors and is induced by exposure to cold temperatures. When expressed in cells, PGC-1 activates thermogenic gene expression, inducing uncoupling proteins, and stimulates mitochondrial biogenesis (*5*, *6*). We show that full-length PGC-1, despite these activities, is a relatively inactive molecule that requires docking to PPARγ or NRF-1 in order to undergo a conformational change and affect transcriptional activity.

[1]Dana-Farber Cancer Institute and Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA. [2]Department of Cell Biology, Baylor College of Medicine, Houston, TX 77040, USA.

*To whom correspondence should be addressed. E-mail: bruce_spiegelman@dfci.harvard.edu

Because PGC-1 has no HAT domains, we examined whether PGC-1 interacts with other HAT coactivators such as SRC-1, CBP/p300, and p300/CBP-associated factor (p/CAF). We fused full-length PGC-1 to the DNA binding domain (DBD) of yeast GAL4. Transcriptional output was measured with a reporter construct driven by GAL4 binding sites. As shown previously, PGC-1 had some transcriptional activity when fused to the GAL4 DBD (GAL4–PGC-1) (*5*) (Fig. 1A). However, this activity increased at least 10-fold when it was coexpressed with SRC-1, p300, or CBP, whereas p/CAF had no detectable effect (*7*). This suggests that this transcriptional enhancement could reflect a functional interaction with PGC-1. We tested for a physical interaction by performing coimmunoprecipitation experiments. When SRC-1 or CBP was coexpressed with PGC-1 in cells, immunoprecipitation of SRC-1 or CBP brought down GAL4–PGC-1 (Fig. 1B). Immunoprecipitated PGC-1 has a small amount of HAT activity (Fig. 1C); however, when SRC-1 and CBP were coexpressed either alone or in combination, a large increase in HAT activity was observed. Thus, PGC-1 can exist in transfected cells in a complex with SRC-1 and CBP/p300, and this complex has HAT activity. However, most of this activity derives from the CBP and SRC-1 components.

We mapped the domains of SRC-1 and p300 responsible for interactions with PGC-1 by producing fusion proteins with glutathione S-transferase (GST). PGC-1 interacted with a domain of SRC-1, encompassing amino acids 782 to 1139 (Fig. 1D). An interaction was also observed between amino acids 1805 and 2441 of p300 and PGC-1. The region of SRC-1 that bound PGC-1 overlaps the region known to interact with p300 and p/CAF. Likewise, the region of p300 interacting with PGC-1 overlaps the region known to interact with p/CAF, SRC-1, and the viral oncoprotein E1A (*8*, *9*).

To provide an independent test of whether SRC-1 was required for the transcriptional activity of PGC-1, we transfected fibroblasts derived from mice that lack SRC-1 (*10*). In wild-type cells, GAL4–PGC-1 activated transcription of the reporter that was three times as efficient as that in mutant (knockout) cells (Fig. 2A). This loss of efficiency was regained when SRC-1 was replenished. Expression of CBP could overcome this deficiency of SRC-1, but overexpression of p/CAF could not. Thus, SRC-1 is required for the full transcriptional activity of PGC-1, although some residual activity is present even in the absence of SRC-1. Although it is not completely specific for CBP/p300, the viral oncoprotein E1A is an inhibitor of these coactivators by suppressing HAT activity (*11*) and competing for coactivator binding (*12*). E1A inhibits the transcriptional activity of PGC-1, with or without coexpression of additional CBP (Fig. 2B).

Deletion analysis revealed that transcriptional activation was localized to amino acids 1 to 170 of PGC-1 (Fig. 3A). Full-length PGC-1 is much less active than constructs that delete amino acids 170 to 350. This putative negative regulatory domain of PGC-1 amino acids 170 to 350 overlaps with the domain of PGC-1 that is involved in docking PPARγ and NRF-1 (*5*, *6*). To investigate whether transcription factor docking might be an activating event for PGC-1, we cotransfected GAL4–PGC-1 with various alleles of PPARγ and NRF-1 (Fig. 3B). Transcriptional activation was increased equivalently with wild-type PPARγ or with several alleles lacking or defective in the following transcriptional activation domains: a point mutation in the AF-2 activation domain (AF-2m) [$Glu^{499} \rightarrow Gln^{499}$ (E499Q)], deletion of both activation domains (ΔAF1-AF2m) or a fragment of PPARγ that contains only amino acids 128 to 229 (DNA binding/hinge region). This fragment of PPARγ is known to be involved in mediating the docking of this receptor to PGC-1 (*5*). We confirmed that this fragment of PPARγ does not interact with CBP/p300 or SRC-1, using proteins prepared in vitro (*13*). Likewise, NRF-1 wild type and a dominant negative of NRF-1 [deletion lacking amino acids 305 to 503 and is transcriptionally inactive (*6*)] also increased the transcriptional activity of PGC-1 (Fig. 3B). PPARγ and the transcriptionally inactive PPARγ fragment (amino acids 128 to 229) also activated GAL4-p/CAF, a coactivator that otherwise has very low intrinsic transcriptional activity in this assay (Fig. 3B). This suggests that the function of transcription factor docking as an activating event can be generalized to different coactivators.

Because transcription factor binding stimulates the activity of PGC-1, we examined whether there is a similar alteration in the binding of SRC-1 and CBP/p300 to PGC-1. Notably, the 1 to 400 amino acid portion of PGC-1, containing the transcription factor docking domain, is reduced in binding of SRC-1 and p300, in relation to the 1 to 180 amino acid portion of PGC-1 that lacks this domain (Fig. 4A). This binding of SRC-1 and p300 to the 1 to 400 amino acid fragment of PGC-1 is strongly stimulated by the 128 to 229 amino acid fragment of PPARγ. In contrast, this piece of PPARγ had no effect on the binding of SRC-1 and p300 to the 1 to 180 amino acid domain of PGC-1. A green fluorescent protein (GFP) control polypeptide had no effect on any of these binding events. We also investigated whether the binding of SRC-1 and p300 to PGC-1 could be stimulated by coexpression of PPARγ or NRF-1 in cells. Coexpression of either transcription factor with PGC-1 increased the amount of SRC-1 and p300 that coimmunoprecipitated with PGC-1 (Fig. 4B). Expression levels of SRC-1 and p300 were similar for each sample (*14*). These data illustrate that the docking of PPARγ or NRF-1 to PGC-1 augments the transcriptional activity of this coactivator by increasing the binding to SRC-1 and p300.

These data also suggest that the docking of PPARγ to PGC-1 induces a conformational change that reveals a cryptic binding capacity. To explore this further, we incubated in vitro translated PGC-1 with limiting concentrations of trypsin, in the presence or absence of the PGC-1 docking domain of PPARγ. The lowest amounts of trypsin used (1 μg) caused a cleavage of PGC-1 in the presence of PPARγ but not in the absence of PPARγ at any trypsin concentration used (Fig. 4C). Because PGC-1 was detected through an $NH_2$-terminal immunotag, this induced cleavage site could be localized to amino acids 180 to 220. This is considerably distant from the PPARγ binding site located at amino acids 338 to 403 (*5*). Hence, transcription factor docking causes an activating conformational change in PGC-1.

On the basis of these results, it is necessary to modify the view that transcription factors function in gene activation primarily to recognize cognate DNA sequences and localize coactivator machines. Three independent lines of evidence show that transcription factor binding activates PGC-1. First, the transcriptional activity of GAL4–PGC-1 is enhanced by coexpression with NRF-1 and PPARγ or the fragment of PPARγ that mediates docking. Second, this same fragment of PPARγ enhances SRC-1 and p300 binding to PGC-1 in vitro and in vivo. Last, protease digestion reveals a new site of cleavage, dis-

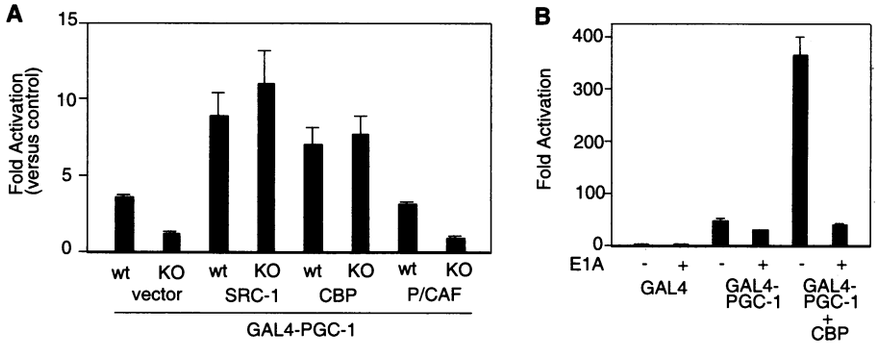


**Fig. 2.** Transcriptional activity of PGC-1 is dependent on SRC-1 and CBP/p300. (**A**) PGC-1–dependent transcriptional activity is reduced in cells lacking SRC-1. Fibroblasts were obtained from wild-type (wt) mice or from those lacking SRC-1 [knockout (KO)] (*10*) and were transiently transfected with 5XUAS reporter, GAL4–PGC-1 plasmid with (+) or without (–) vector (empty plasmid), SRC-1, CBP, and p/CAF. Luciferase assays were performed 48 hours after transfection. (**B**) E1A viral oncoprotein inhibits PGC-1–dependent transcriptional activity. Transfection experiments were performed as in (A) except for the E1A 12*S* expression plasmid. Error bars in (A) and (B) indicate SEM of four independent experiments made in duplicate.

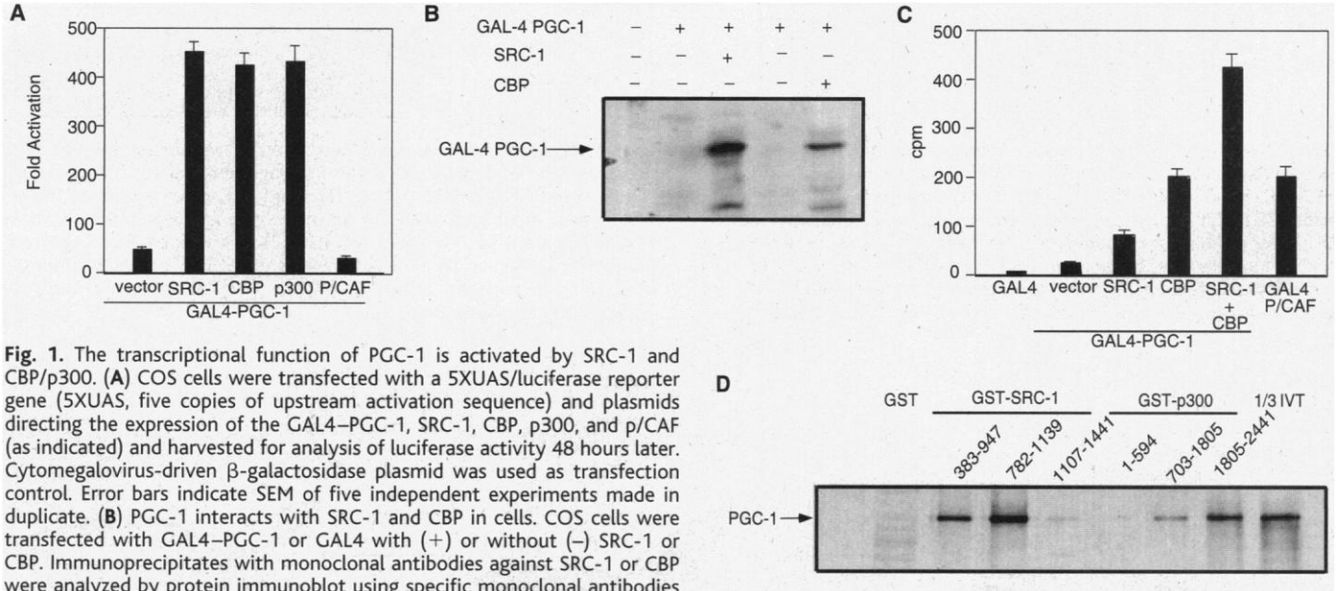


**Fig. 1.** The transcriptional function of PGC-1 is activated by SRC-1 and CBP/p300. (**A**) COS cells were transfected with a 5XUAS/luciferase reporter gene (5XUAS, five copies of upstream activation sequence) and plasmids directing the expression of the GAL4–PGC-1, SRC-1, CBP, p300, and p/CAF (as indicated) and harvested for analysis of luciferase activity 48 hours later. Cytomegalovirus-driven β-galactosidase plasmid was used as transfection control. Error bars indicate SEM of five independent experiments made in duplicate. (**B**) PGC-1 interacts with SRC-1 and CBP in cells. COS cells were transfected with GAL4–PGC-1 or GAL4 with (+) or without (–) SRC-1 or CBP. Immunoprecipitates with monoclonal antibodies against SRC-1 or CBP were analyzed by protein immunoblot using specific monoclonal antibodies to GAL4 DBD (*16*). (**C**) PGC-1 is associated with SRC-1– and CBP-dependent HAT activity. COS cells were transfected with plasmids directing the expression of GAL4–PGC-1 or GAL4 and SRC-1 or CBP. After 48 hours, whole-cell extracts were immunoprecipitated with a polyclonal antibody to GAL4 DBD. HAT activity was measured in the immunoprecipitates with a liquid HAT assay (*17*); cpm, counts per minute. Error bars indicate SEM of two independent experiments made in duplicate. (**D**) PGC-1 physically interacts in vitro with SRC-1 and p300. GST–SRC-1 and GST-p300 fragments were incubated with full-length [$^{35}$S]PGC-1 produced by translation in vitro. After extensively washing the glutathione agarose beads, the specifically bound [$^{35}$S]PGC-1 was eluted and resolved by SDS-PAGE and detected by autoradiography (*18*). IVT, in vitro translation.

tal to the PPARγ binding site, when this transcription factor docks. It is likely that three distinct states of PGC-1 exist (Fig. 5), in what we term a "spring-trap" model. When PGC-1 is not docked on a transcription factor, it has low transcriptional activity and minimal ability to assemble a complex involving SRC-1 and CBP/p300. Upon docking to an appropriate target, it undergoes a conformational change that is permissive for cofactor binding and thus sets the trap. This state of PGC-1 then captures SRC-1, CBP/p300, and perhaps other components, stimulating gene expression. Undocked but active PGC-1 could theoretically bind SRC-1 and p300 and thus interfere with their functions on various DNA-bound targets. It is also noteworthy that p/CAF shows a similar activation through docking of PPARγ, suggesting that the stimulatory role of transcription factor binding to coactivator is likely to be a more general effect.

These data also represent an example of positive regulation of coactivator transcriptional activity. The E1A viral oncoprotein negatively regulates CBP/p300 (*11, 12*), whereas recent data suggest that calcium flux is an activating signal for the stimulatory transcriptional activity of CBP (*15*). It seems likely that coactivators and corepressors will

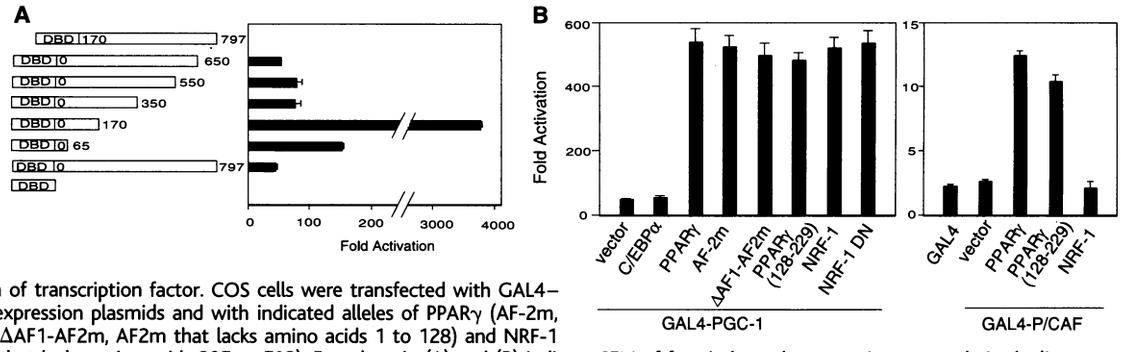


**Fig. 3.** PPARγ and NRF-1 augments the transcriptional activity of PGC-1. (**A**) Mapping of the activation domain of PGC-1 (*19*). Transient transfection experiments were performed as in Fig. 1A. (**B**) Stimulation of PGC-1– and p/CAF-dependent transcriptional activity by expression of transcription factor. COS cells were transfected with GAL4–PGC-1 or GAL4-p/CAF expression plasmids and with indicated alleles of PPARγ (AF-2m, point mutation E499Q; ΔAF1-AF2m, AF2m that lacks amino acids 1 to 128) and NRF-1 (DN, deletion of NRF-1 that lacks amino acids 305 to 503). Error bars in (A) and (B) indicate SEM of four independent experiments made in duplicate.

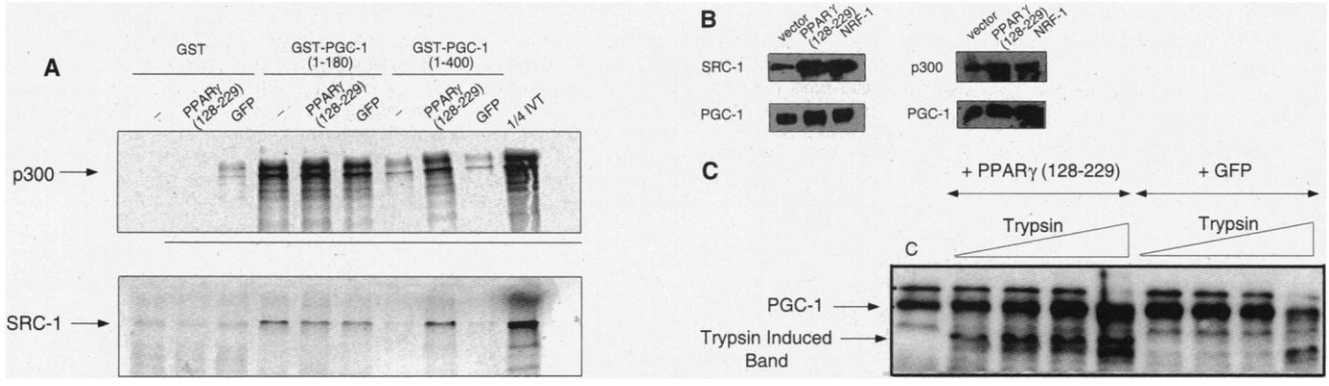


**Fig. 4.** Docking of PPARγ to PGC-1 increases the binding of p300 and SRC-1. (**A**) GST–PGC-1 fragments (2 to 5 μg) were incubated with [$^{35}$S]SRC-1 and [$^{35}$S]p300. Ten micrograms of His-tagged PPARγ (amino acids 129 to 228) or His-tagged GFP were added to the indicated samples (*20*). Dashes indicate no addition of His-tagged proteins. (**B**) PPARγ and NRF-1 increase the binding of PGC-1 to SRC-1 and p300 in cells. Immunoprecipitates performed from transient transfected cells with an antibody to flag (to precipitate transfected flag–PGC-1 protein) were analyzed by protein immunoblot with specific monoclonal antibodies against SRC-1 and p300. (**C**) A PPARγ fragment induces a conformation change in the PGC-1 $NH_2$-terminus. In vitro translated flag–PGC-1 was incubated with different amount of trypsin and with a PPARγ fragment (amino acids 128 to 229) or a GFP control. Digested bands were resolved by SDS-PAGE and analyzed by protein immunoblot analysis with an antibody to flag (*21*). C indicates control, without any trypsin added.

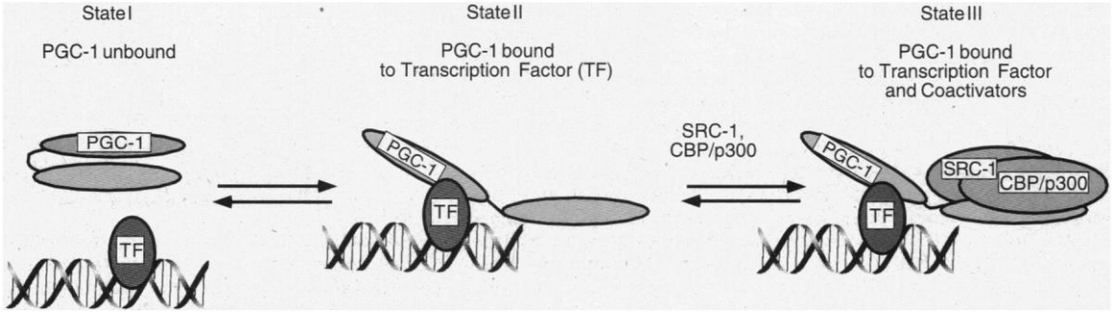


**Fig. 5.** Three-state model of PGC-1 activation. PGC-1 occurs in multiple states with different transcriptional activity. In a low-activity state (state I), PGC-1 is unbound to any transcription factor (TF). PGC-1 docking to a transcription factor causes a conformational change that results in a state permissive for cofactor binding (state II). This is in equilibrium with state III, where SRC-1, CBP/p300, and perhaps other proteins bind and activate transcription at this locus.

have multiple modes of regulation, including temporal control of expression (like PGC-1) and regulation of inherent activity through transactivation factor docking and signal transduction systems.

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16. Whole-cell extracts were prepared by lysing the cells in a buffer containing 100 mM tris (pH 8.5), 250 mM NaCl, 1% NP-40, 1 mM EDTA, protease inhibitors (Boehringer Mannheim), and 0.1 mM phenylmethylsulfonyl fluoride. Whole-cell lysates were incubated with monoclonal antibodies against SRC-1 or CBP/p300 for 2 hours at 4°C, followed by an overnight incubation with protein A/G Sepharose beads. Immunoprecipitates were extensively washed with the lysis buffer, resolved by SDS–polyacrylamide gel electrophoresis (SDS-PAGE) and protein immunoblot with specific antibodies against GAL4 DBD monoclonal antibodies.
17. Whole-cell lysates were incubated with polyclonal antibodies against GAL4 DBD for 2 hours at 4°C, followed by an overnight incubation with protein A/G Sepharose beads. Immunoprecipitates were washed three times with the lysis buffer and used for HAT assays in solution with histones as substrates [J. E. Brownell and C. D. Allis, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 6364 (1995)].
18. GST–SRC-1 constructs were made as described [T. E. Spencer *et al.*, *Nature* **389**, 194 (1997)]. GST-p300 constructs were made as described in (*8*). GST pull-down assays were performed as described in (*5*).
19. GAL4–PGC-1 deletions were performed by ligating PGC-1 polymerase chain reaction (PCR) fragments into Sal I–Eco RV cloning sites of pCMX expression vector. Expression levels for these different deletions in transfected cells were similar. GAL4-p/CAF was performed by ligating p/CAF PCR full-length fragment into Eco RI and Eco RV.
20. GST–PGC-1 fragments were generated by cloning the PCR fragments of PGC-1 into PGEX vectors. We made GST proteins in *Escherichia coli*, using manufacturer's instructions (Pharmacia). His-tagged PPARγ (amino acids 128 to 229) and His-tagged GFP were made by cloning PCR products into a PET30 vector. We expressed His-tagged proteins in *E. coli* and purified them under nondenaturing conditions, using manufacturer's protocol (Qiagen). Proteins were renatured by dialyzing against the binding buffer [20 mM Hepes (pH 7.7), 75 mM KCl, 0.1 mM EDTA, 2.5 mM $MgCl_2$, 0.05% NP-40, 2 mM dithiothreitol, and 10% glycerol] and kept at −80°C until further use. In vitro binding assays were performed as described in (*5*), with the same amount of GST fusion proteins (analyzed by Coomassie staining).
21. Flag-tagged PGC-1 [in vitro translated with the TnT kit (Promega)], 0.1 μg of His-tagged purified proteins, and different amounts of trypsin (from 1 to 5 μg) were mixed with a buffer (50 mM $NH_4HCO_3$) in a total volume of 30 μl and incubated at 25°C for 10 min. The reaction was stopped by adding SDS-PAGE sample buffer. Digested fragments were analyzed by immunoblotting with a monoclonal antibody to flag (Sigma).


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# Evidence for Autoregulation of Cystathionine γ-Synthase mRNA Stability in *Arabidopsis*


**Yukako Chiba,[1] Mari Ishikawa,[1] Fumiko Kijima,[1]* R. Huw Tyson,[2] Jungsup Kim,[3] Ayako Yamamoto,[1]† Eiji Nambara,[1] Thomas Leustek,[3] Roger M. Wallsgrove,[2] Satoshi Naito[1]‡**



**Control of messenger RNA (mRNA) stability serves as an important mechanism for regulating gene expression. Analysis of *Arabidopsis* mutants that overaccumulate soluble methionine (Met) revealed that the gene for cystathionine γ-synthase (CGS), the key enzyme in Met biosynthesis, is regulated at the level of mRNA stability. Transfection experiments with wild-type and mutant forms of the CGS gene suggest that an amino acid sequence encoded by the first exon of CGS acts in cis to destabilize its own mRNA in a process that is activated by Met or one of its metabolites.**


Genetic studies of metabolic pathways in bacteria and yeast have revealed important regulatory mechanisms. For example, studies of amino acid biosynthesis operons in bacteria led to an understanding of mRNA attenuation (*1*), and the histidine biosynthesis pathway of yeast led to an understanding of the complex interplay between general and pathway-specific controls (*2*). With the exception of tryptophan biosynthesis in *Arabidopsis* (*3*), genetic methods have not been extensively used to analyze amino acid biosynthesis in plants. To study the molecular mechanisms for regulation of methionine biosynthesis in plants, we used *Arabidopsis* mutants, termed *mto1*, that overaccumulate soluble Met (*4*).

Met, a sulfur-containing amino acid, functions not only as a protein component but also as a precursor of *S*-adenosylmethionine, the primary methyl donor in many transmethylation reactions and, in plants, a precursor of the phytohormone ethylene (*5*). Met is an essential dietary amino acid for mammals. Studies with the aquatic plant *Lemna* have shown that the cellular concentration of soluble Met remains unchanged over a 3000-fold range in sulfur availability (*6*), indicating that Met biosynthesis is tightly regulated in plants. Cystathionine γ-synthase (CGS) catalyzes the first committed step in Met biosynthesis, and it has been suggested to be a key regulatory site of the pathway (*5*). Indeed, CGS activity in *Lemna* and barley is regulated positively and negatively in response to the availability of Met (*7*).

Analyses of CGS expression in *mto1-1* mutant plants revealed that the steady-state levels of CGS mRNA, protein, and enzyme activity are three- to fivefold higher than in wild-type plants (Fig. 1, A to C). Application of Met to wild-type plants reduced the amount of mRNA for CGS, whereas no such effect was observed in the *mto1-1* mutant (Fig. 1D). This suggests that wild-type plants down-regulate the level of CGS mRNA in response to exogenous Met, and this regulation is impaired in the *mto1* mutant.

A liquid callus culture system (*8*) was used for further studies. As with whole plants, the steady-state level of CGS mRNA was reduced by feeding calli from wild-type plants with Met


[1]Division of Applied Bioscience, Graduate School of Agriculture, Hokkaido University, Sapporo 060-8589, Japan. [2]Biochemistry and Physiology Department, IACR-Rothamsted, Harpenden, Hartfordshire AL5 2JQ, United Kingdom. [3]Biotechnology Center for Agriculture and the Environment, Rutgers University, New Brunswick, NJ 08901–8520, USA.

*Present address: Fukujuen CHA Research Center, Kyoto 619-0223, Japan.

†Present address: Laboratory of Molecular Phylogenetics, Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo 113-0032, Japan.

‡To whom correspondence should be addressed. E-mail: naito@abs.agr.hokudai.ac.jp

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