Transcription Dysregulation of the PGC-1α Pathway in Huntington's Disease Pathogenesis: From Metabolic Derangement to Neurodegeneration

Albert R. La Spada, MD, PhD

Departments of Cellular and Molecular Medicine,
Neurosciences, and Pediatrics
Division of Biological Sciences, the Institute for Genomic Medicine
Sanford Consortium for Regenerative Medicine
University of California, San Diego
La Jolla, California

SfN Society for Neuroscience

NOTES

Clinical Description and Molecular Genetics of Huntington's Disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by motor and cognitive impairment (Nance, 1997). The motor abnormality stems from dysfunction of the involuntary movement control region of the midbrain known as the striatum, and is manifested as a hallmark feature of uncontrollable dance-like movements ("chorea"). In HD, significant degeneration and atrophy occur in the striatum and cerebral cortex, while cerebellar, thalamic, and spinal cord neuron populations are spared (Ross et al., 1997). Neuroanatomical studies have revealed that GABAergic medium spiny neurons (MSNs) in the striatum are selectively vulnerable in HD, while medium aspiny and large cholinergic striatal neurons are preserved (Ferrante et al., 1985; Graveland et al., 1985). HD is relentlessly progressive, and after pronounced cognitive decline, patients succumb to the disease usually 15 to 25 years after disease onset. In 1993, a CAG triplet repeat expansion mutation in the coding region of the *huntingtin (htt)* gene was identified as the cause of HD (MacDonald et al., 1993). As observed for other polyglutamine (polyQ) repeat diseases, polyQ-htt tracts that exceed a certain length threshold (~37 repeats) adopt a novel pathogenic conformation, yielding conformers that are resistant to normal protein turnover, culminating in cell toxicity and neurodegeneration (La Spada and Taylor, 2010).

PGC-1α links Transcription Interference With Mitochondrial Abnormalities in HD

Neurons in the brain have enormous demands for continued mitochondrial production of high-energy phosphate-bonded compounds. In 1993, Beal and colleagues reported that chronic administration of a mitochondrial toxin, 3-nitropropionic acid, resulted in a selective loss of medium spiny neurons in the striatum (Beal et al., 1993). This provocative finding, which was corroborated by numerous studies in HD cell culture models, mice, and human patients (Lin and Beal, 2006), suggested that mitochondrial dysfunction may underlie HD pathogenesis and account for cell-type specificity in this disorder. At the same time, the necessity of nuclear localization of htt for HD disease pathogenesis highlighted nuclear pathology as a key step in the neurotoxicity cascade (Saudou et al., 1998). An extensive body of literature then emerged, suggesting that N-terminal fragments of mutant htt protein interfere with gene transcription in HD (Riley and Orr, 2006).

HD Transgenic Mice Display Profound Thermoregulatory Defects

Because neurological deficits in HD are gradually progressive, considerable emphasis has been placed on identifying objective and reproducible measures of disease onset and progression (i.e., "biomarkers") to improve the predictive value of therapeutic trials. We therefore chose to evaluate several metabolic parameters, including body temperature, in a commonly used model of HD, the *N171-82Q* transgenic mouse (Schilling et al., 1999). When we monitored body temperature, we found that HD mice developed progressive hypothermia compared with their wild-type (WT) counterparts (Figs. *1A, B*). As motor symptoms and weight loss progressed, some HD *N171-82Q* mice displayed profoundly deranged thermoregulation, with body temperatures dropping to 27°C or less. HD mice with temperatures below 30°C were not within hours or minutes of death, as they remained mobile and alive for at least another 48 h, often considerably longer. In light of this striking hypothermia phenotype, we reasoned that HD *N171-82Q* mice might not be capable of maintaining body temperature in the face of a 4°C cold challenge—a process known as "adaptive thermogenesis" (Lowell and Spiegelman, 2000).

After obtaining HD *N171-18Q* transgenic mice to control for htt protein overexpression, we established three cohorts of mice: HD 82Q, HD 18Q, and WT. Individual mice were placed at 4°C for up to 9 h, and body temperatures were recorded at 1-h intervals. Although control mice were able to maintain normal thermoregulation, HD transgenic mice displayed significant reductions in body temperature during the cold challenge, even when presymptomatic for baseline hypothermia (Figs. 1*C, D*). In rodents, brown adipose tissue (BAT) is the principal tissue that mediates adaptive thermogenesis, and is distinguished from white fat by its high degree of vascularization and mitochondrial density (Wang et al., 2005). Hematoxylin and eosin staining of BAT from HD mice revealed marked abnormalities, including reductions in cell density and nuclei number (Figs. 1*E, F*). Indeed, the BAT of HD mice appeared like white fat in histology sections, suggesting that the thermogenesis defect likely involves abnormalities in BAT composition and function. Importantly, reverse transcriptase PCR (RT-PCR) analysis indicated that the mutant *htt* transgene is expressed in BAT (Weydt et al., 2006).

NOTES

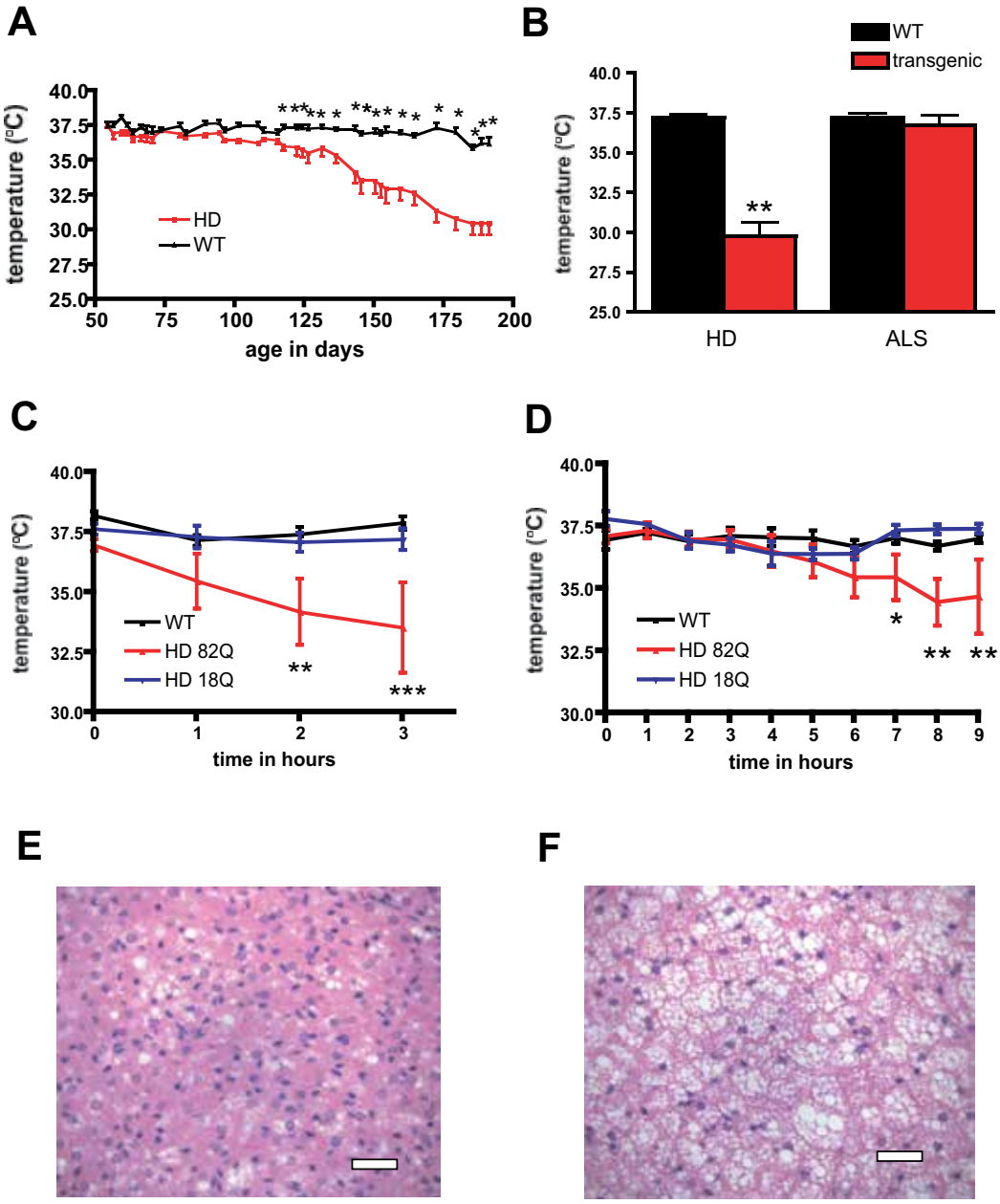


Figure 1. HD mice display a temperature regulation defect and abnormal BAT. ***A***, Body temperature in HD N171-82Q male mice (red line) and nontransgenic controls (WT, black line). By 120 d, HD mice display a marked reduction in body temperature (p = 0.027), and this reduction progresses with time. By 150 d, the difference in body temperature is extreme (HD: ~33°C; WT: ~37°C; p = 0.003). ***B***, End-stage HD mice exhibit profound hypothermia (n = 6; $p < 0.001$ by t test), while end-stage SOD1 G93A ALS (amyotrophic lateral sclerosis) mice do not (n = 5; p = 0.45 by t test). ***C***, HD transgenic mice display an adaptive thermogenesis defect. Twenty-week-old mice were placed at 4°C, and body temperatures were recorded. By 1 h, HD 82Q mice displayed a significant reduction in body temperature (**$p < 0.01$) that worsened with time (***$p < 0.001$). ***D***, Younger HD mice displayed a thermoregulatory defect by 7 h into the cold challenge (*$p < 0.05$) that progressively worsened (**$p < 0.01$). ***E–F***, Twenty-week-old HD mice and WT controls were euthanized, and infrascapular BAT samples were stained. While WT BAT appears normal (***E***), BAT from HD 82Q mice is markedly abnormal (***F***), showing decreased cellular content (note fewer nuclei) and marked accumulation of large lipid droplets. Scale bar, 20 μm. Modified with permission from Weydt et al. (2006), their Fig. 1.

NOTES

The PGC-1α–UCP-1 Circuit Is Disrupted in the BAT of HD Transgenic Mice

In mammals, after cold is sensed by the hypothalamus, an increase in sympathetic tone in the periphery ensues. In rodents, BAT is the target of this increased sympathetic output. PPAR-gamma coactivator-1-alpha (PGC-1α) is a transcription coactivator whose expression in BAT is dramatically upregulated in response to β-adrenergic stimulation (Puigserver et al., 1998). The principal effector of adaptive thermogenesis in BAT is uncoupling protein 1 (UCP-1), whose expression is restricted to mitochondria of BAT (Puigserver and Spiegelman, 2003). To determine whether PGC-1α transactivation of UCP-1 is normal in HD mice, we dissected infrascapular BAT after cold challenge, isolated total RNA, and measured *PGC-1α* and *UCP-1* transcripts. We observed marked upregulation of *PGC-1α* in the BAT of cold-challenged control and HD mice (Fig. 2*A*). This result indicates that hypothalamic sensing of temperature change, elevation of sympathetic tone, and β-adrenergic stimulation of *PGC-1α* in BAT are intact. Detection of *c-fos* upregulation in the ventromedial hypothalamic nucleus of cold-challenged HD mice confirmed hypothalamus activation in response to cold (Weydt et al., 2006). Despite preservation of hypothalamus-mediated β-adrenergic stimulation of *PGC-1α* in BAT, cold-challenged HD mice failed to upregulate *UCP-1* messenger RNA (mRNA) (Fig. 2*B*). In addition, cold-challenged levels of UCP-1 protein were decreased in the BAT of HD mice (Fig. 2*C*). These results suggest that interference with PGC-1α coactivation of UCP-1 in BAT accounts for the adaptive thermogenesis defect in HD.

To further investigate this hypothesis, 3T3-L1 preadipocyte cells were transfected with UCP-1 promoter–reporter constructs along with mutant or normal htt in the presence or absence of PGC-1α. While baseline transactivation levels were similar, polyQ-htt repressed stimulation of UCP-1 promoter activity; importantly, mutant htt repression of *UCP-1* transcription could be overcome by coexpression of PGC-1α (Fig. 2*D*). Because preadipocyte cells are not committed to BAT differentiation, we established primary brown adipocyte cultures from HD *N171-82Q* and control mice. Upon norepinephrine (NE) stimulation, primary brown adipocytes from HD mice and nontransgenic controls displayed comparable *PGC-1α* induction (Weydt et al., 2006); however, *UCP-1* induction was significantly blunted in adipocytes expressing polyQ-expanded htt (Fig. 2*E*). Failure of *UCP-1* induction was confirmed at the protein level (Weydt et al., 2006).

Evidence for PGC-1α Transcription Interference in Mouse Striatum

To determine whether PGC-1α function was compromised in the striatum of HD *N171-82Q* transgenic mice, we isolated striatal RNAs and measured the expression level of PGC-1α target genes whose protein products mediate oxidative metabolism in mitochondria (Mootha et al., 2003; Leone et al., 2005). In 20-week-old HD mice, there was a significant reduction in the expression of such mitochondrial genes (Fig. 3*A*). These findings support a role for PGC-1α transcription interference in the degeneration of the striatum in HD.

Human HD Patients Display PGC-1α Transcription Interference in the Striatum

PGC-1α transcription abnormalities in the brain and periphery of the *N171-82Q* HD model led us to ask: Do HD patients display PGC-1α transcription interference in the striatum? To address this question, we analyzed caudate nucleus microarray expression data obtained from a large cohort of human HD patients and matched controls (Hodges et al., 2006). We selected 26 genes known to rely on PGC-1α coactivator function for their expression (Mootha et al., 2003; Leone et al., 2005), and using the gcrma application from the Bioconductor open-source software program (www.bioconductor.org) (Bolstad et al., 2003; Gentleman et al., 2004), we noted significant reductions in 24 of these 26 PGC-1α target genes (Fig. 3*B*) (Weydt et al., 2006). The presence of significant expression reductions in 35 of 46 probes (corresponding to the 26 PGC-1α target genes) from the Affymetrix GeneChip Human Genome U133 Array Set (HG-U133A/B, consisting of 45,000 probes) (Affymetrix, Santa Clara, CA) is highly unlikely to occur by chance ($p < 0.0001$; χ^2). Thus, these results strongly support PGC-1α transcription interference in the striatum of presymptomatic and early-stage HD patients.

To validate these findings, we obtained striatal RNAs from a subset of these cases and performed real-time RT-PCR analysis. We confirmed significant reductions in mitochondrial PGC-1α target genes in the human HD sample set (Fig. 3C). To control for the validation analysis, we included the glial

NOTES

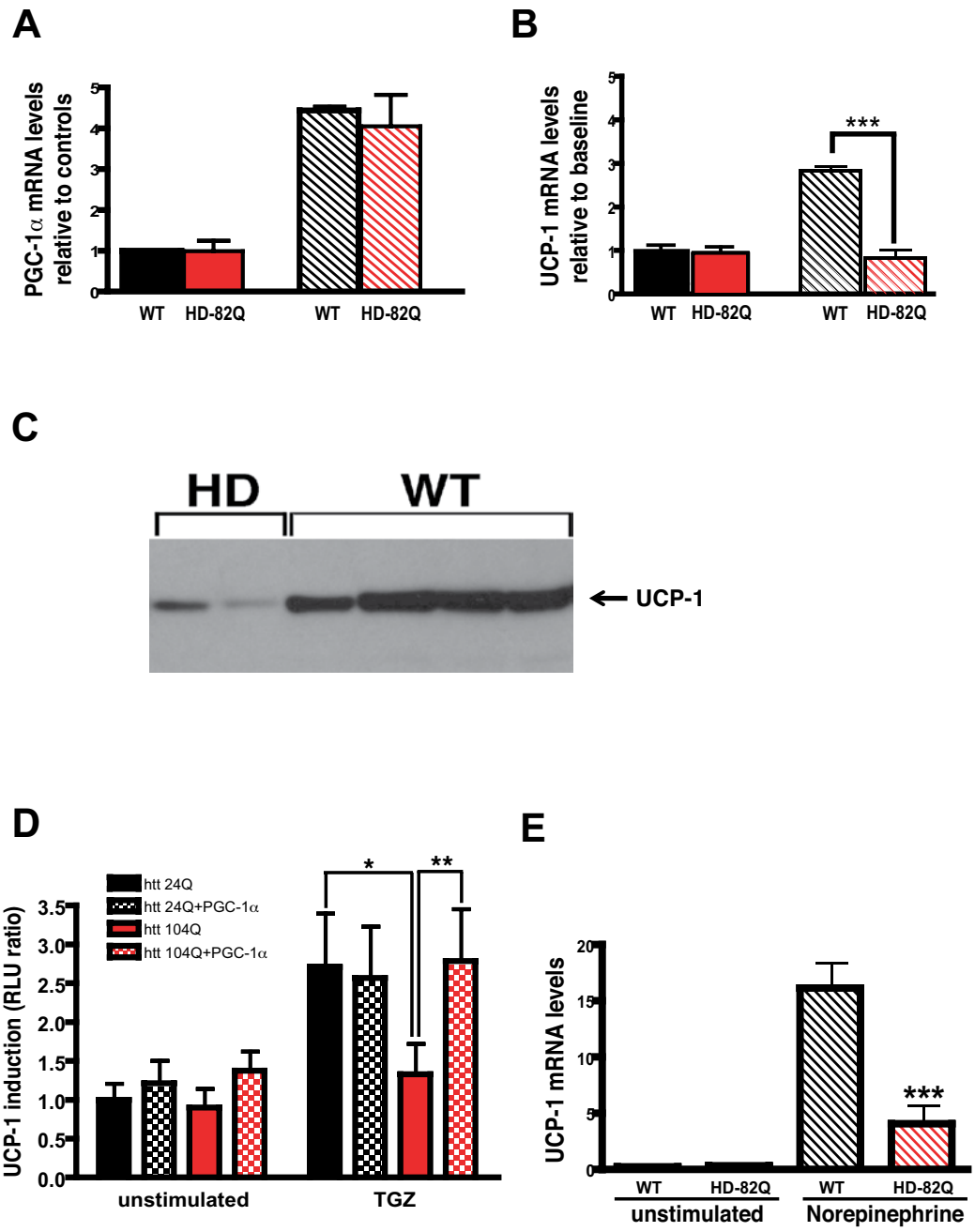


Figure 2. HD mice display PGC-1α transcription interference and BAT abnormality. ***A***, HD mice induce PGC-1α upon cold challenge. Here we see quantitative PCR analysis of BAT RNAs, from HD 82Q (red) and WT mice (black) housed at room temperature (solid bars) or in the cold for 3 h (striped bars). Upregulation of PGC-1α is similar ($p = 0.77$; *t* test). ***B***, HD mice fail to induce UCP-1 RNA during cold challenge. WT mice increase UCP-1 by approximately threefold, but HD 82Q mice display no induction (***$p < 0.001$). ***C***, HD transgenic mice fail to upregulate UCP-1 protein expression during cold challenge. Western blot analysis of brown fat UCP-1 protein levels in cold-challenged HD N171-82Q mice (HD) and nontransgenic littermate controls (WT) indicates upregulation of UCP-1 in WT mice at the end of the 3-h cold challenge compared with HD mice. Staining of SDS-PAGE gels prior to transfer confirmed equivalent loading of brown fat protein samples (not shown). ***D***, polyQ-Htt transcription interference of PGC-1α. 3T3-L1 preadipocytes were cotransfected with PPARγ, retinoid X receptor–alpha (RXRα), UCP-1 promoter reporter, Renilla luciferase–cytomegalovirus (pRL-CMV), exon1/2 htt 24Q or 104Q, and PGC-1α. Htt 104Q suppresses the UCP-1 promoter reporter in cells treated with troglitazone (TGZ) (*$p = 0.011$). Transfection of PGC-1α rescues htt 104Q repression (**$p < 0.005$). ***E***, HD brown adipocytes do not respond to NE. NE yields upregulation of UCP-1 in WT adipocytes, but UCP-1 induction is blunted in adipocytes expressing htt 82Q (***$p < 0.001$ by t test). RLU, Relative luciferase units. Modified with permission from Weydt et al. (2006), their Figs. 2*A*–*D*.

NOTES

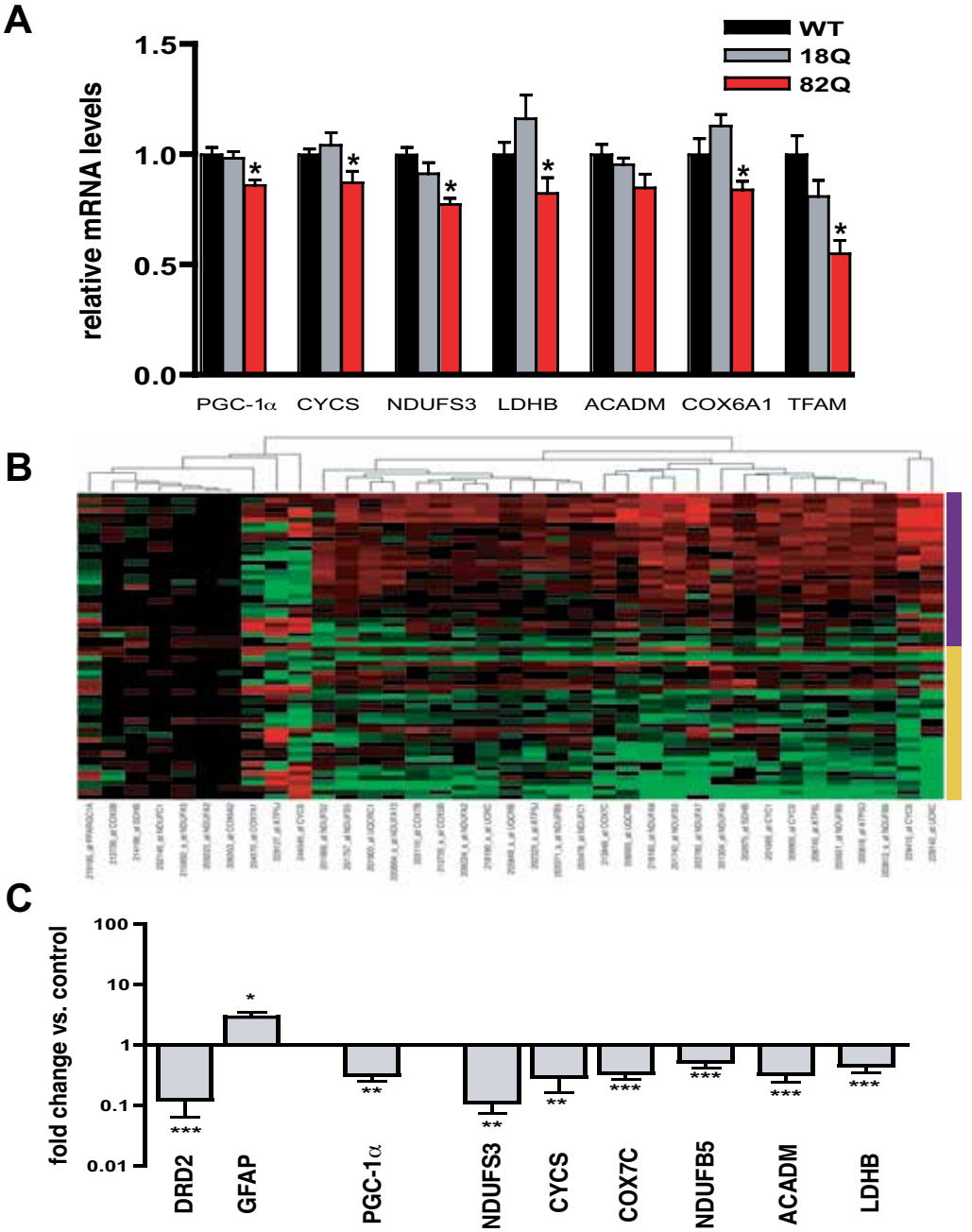


Figure 3. PGC-1α transcription interference in HD striatum. ***A***, RT-PCR analysis of striatal RNAs from sets (n = 5/group) of 20-week-old HD 82Q mice (red), 18Q mice (gray), and WT mice (black) indicates that RNA levels for PGC-1α and six of its mitochondrial target genes are reduced in HD brain. (All HD 82Q: *$p < 0.05$, except p = 0.17 for ACADM). ***B***, Microarray expression analysis of PGC-1α–regulated genes in human caudate. Here we see a heat map comparing the caudate nucleus expression of 26 PGC-1α target genes for 32 Grade 0–2 HD patients (gold bar) and 32 controls (purple bar). Most PGC-1α target genes are downregulated in HD patients. ***C***, Confirmation of microarray data. We obtained striatal RNA samples for HD patients and controls and measured RNA expression levels for six PGC-1α targets, PGC-1α, and two control genes (*GFAP* and *DRD2*). We thus confirmed significant reductions in the expression of PGC-1α targets and detected reduced PGC-1α in human HD striatum from early-grade patients. Statistical comparisons were performed using the t test (*$p < 0.05$; **$p < 0.005$; ***$p < 0.0005$). Modified with permission from Weydt et al. (2006), their Fig. 4.

NOTES

fibrillary acidic protein *(GFAP)* and dopamine D2 receptor *(DRD2)* genes in this experiment, as GFAP is known to be significantly upregulated and DRD2 is known to be significantly downregulated in expression studies of HD caudate (Luthi-Carter et al., 2000; Hodges et al., 2006).

PGC-1α Impairment Links Transcription Interference With HD Mitochondrial Dysfunction

Based on our findings (Weydt et al., 2006) and the work of another group published independently (Cui et al., 2006), a new model for HD pathogenesis has emerged (McGill and Beal, 2006; Ross and Thompson, 2006; Greenamyre, 2007). According to this model, mitochondrial dysfunction in HD is postulated to result directly from PGC-1α transcription interference.

Induction of PGC-1α Expression Rescues Neurological Phenotypes in HD Transgenic Mice

To determine whether increased expression of PGC-1α can ameliorate HD, we developed a system to induce PGC-1α expression in transgenic mice by obtaining a tet-responsive element (TRE)–PGC-1α transgenic line (Russell et al., 2004). We also derived a line of *Rosa26-rtTA* mice (Belteki et al., 2005) and crossed *Rosa26-rtTA* males with *TRE-PGC-1α* females to generate *Rosa26-rtTA–TRE-PGC-1α* bigenic mice. When *Rosa26-rtTA–TRE-PGC-1α* bigenic mice receive doxycycline (Dox), the rtTA becomes activated and should promote the expression of *PGC-1α*.

To validate our induction system, we derived *Rosa26-rtTA–TRE-PGC-1α* bigenic mice. These mice were fed Dox for 6 weeks beginning at weaning, and we then observed marked induction of *PGC-1α* (Tsunemi et al., 2012). To test whether restoring PGC-1α function can ameliorate neurological disease in HD, we crossed HD *N171-82Q* mice with inducible PGC-1α bigenic mice, utilizing a breeding scheme that yielded three different cohorts: triple transgenic mice, HD mice (no *rtTA* or *PGC-1α* transgenes), and non-HD controls. We subjected the cohorts to behavioral testing, and noted that expression of PGC-1α at levels consistent with prior induction significantly improved forepaw grip strength, gait, and performance on the ledge test in HD mice (Tsunemi et al., 2012). PGC-1α expression also enabled HD triple transgenic mice to perform comparably with control mice on the rotarod.

PGC-1α Prevents Huntingtin Protein Aggregation and Rescues HD Neurodegeneration

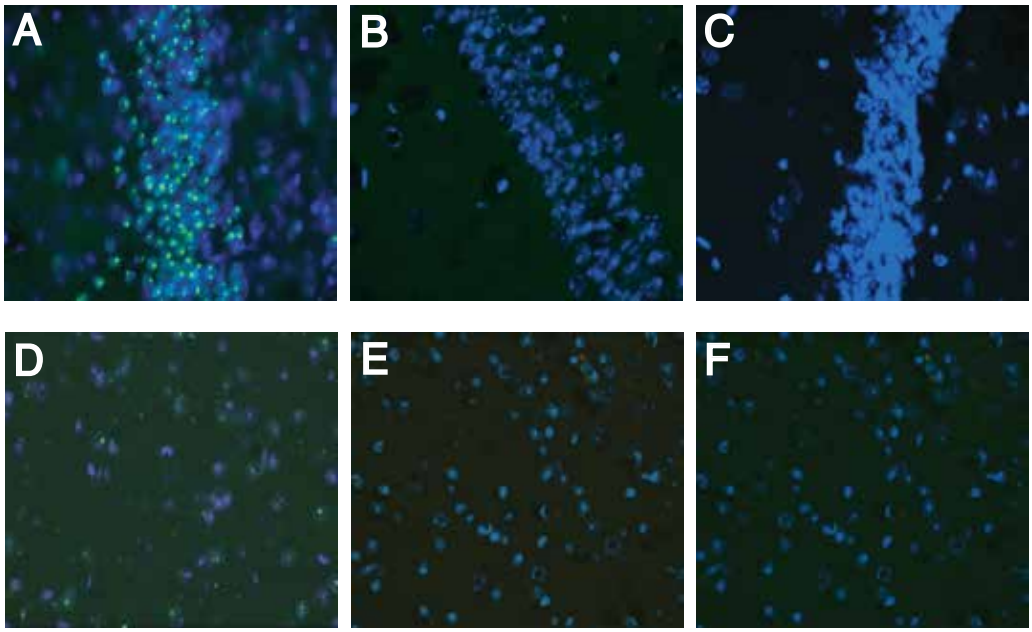
The formation of protein aggregates, visible at the light microscope level, is an established pathological hallmark of HD. Although aggregates are not the toxic species, their production requires misfolded htt; hence, their elimination correlates with marked reductions in pathogenic htt protein (Rubinsztein, 2006). When we examined the brains of 18-week-old HD mice induced to express PGC-1α, we observed a dramatic reduction in htt protein aggregation in hippocampus and cortex (Figs. 4*A–F*). Quantification of neurons containing htt protein aggregates confirmed this observation and demonstrated that induction of PGC-1α in triple transgenic mice is required for this outcome (Fig. 4G). We also noted a significant reduction in htt protein aggregation in the striatum, though there were fewer cells with aggregates there.

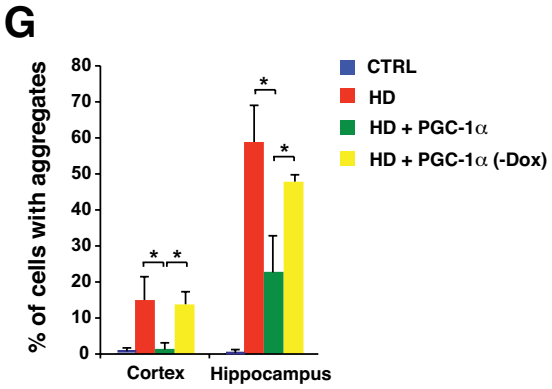
Filter trap assay is a widely used method for measuring SDS-insoluble misfolded proteins (Muchowski et al., 2002), and a variety of antibodies are available for detecting different amyloidogenic species, including 1C2 (polyQ tracts), A11 (prefibrillar oligomers), and OC (fibrils) (Kayed et al., 2007). Using these antibodies, we performed filter trap assays on protein lysates isolated from the striatum of HD, triple transgenic, and control mice, and noted obvious reductions in SDS-insoluble htt, oligomeric htt, and fibrillar htt in HD mice induced to express PGC-1α (Fig. 4H). Observed reductions in insoluble htt species could not be attributed to an effect of PGC-1α on HD transgene expression because quantitative RT-PCR analysis had revealed similar levels of *htt* transgene mRNA in HD transgenic mice expressing PGC-1α and in HD mice lacking both transgenes (Tsunemi et al., 2012). To determine whether improved behavior and reduced htt aggregation in HD triple transgenic mice were accompanied by an amelioration of neurodegeneration, we completed a stereological assessment of the striatum, and found that induction of PGC-1α significantly increased striatal volume and neuron number (Tsunemi et al., 2012).

PPARδ Is a Potent Regulator of Mitochondrial and Metabolic Function

The peroxisome proliferator–activated receptors (PPARs) are a family of nuclear, ligand-activated receptors that transcriptionally regulate important metabolic and physiological functions. Three PPARs

NOTES





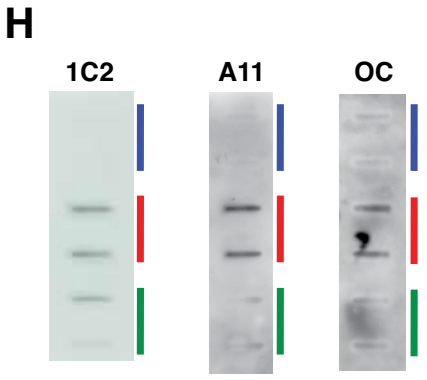


Figure 4. PGC-1α expression prevents htt aggregate formation. ***A–F***, Sections from the frontal cortex (***A–C***) and hippocampus CA3 region (***D–F***) of 18-week-old HD mice (***A, D***), non-HD littermate controls (***B, E***), and HD mice induced to express PGC-1α (***C, F***). Anti-htt antibody EM48 (green); DAPI (blue). ***G***, Quantification of htt aggregate formation in 18-week-old HD mice (*$p < 0.05$). ***H***, Filter trap assays were performed using different antibodies that detect alternative misfolded species of htt protein. 1C2 (polyQ tracts), A11 (oligomers), and OC (fibrils) each reveal a reduction in SDS-insoluble htt protein for 18-week-old HD transgenic mice expressing PGC-1α (green), compared with HD mice lacking the PGC-1α transgene (red). Non-HD controls do not exhibit appreciable levels of SDS-insoluble, oligomeric, or fibrillar htt protein (blue). Error bars indicate SD. Modified with permission from Tsunemi et al. (2012), their Figs. 2*A–H*.

NOTES

have been identified thus far: PPARα, PPARδ, and PPARγ (Berger and Moller, 2002). PPARα is expressed primarily in the liver, heart, and muscle and plays a key role in regulating fatty-acid breakdown. PPARγ regulates adipogenesis and thermoregulation in mammals, and is thus highly expressed in adipose tissue. PPARδ is widely expressed and regulates fatty-acid catabolism. Whereas all three PPARs interact with PGC-1α to promote oxidative metabolism and metabolic activity, overexpression of constitutively active PPARδ in skeletal muscle in transgenic mice dramatically favors a shift in muscle fibers to an oxidative metabolic status, thereby vastly improving exercise performance, even in untrained mice (Wang et al., 2004). A greatly enhanced oxidative metabolic shift can also be achieved in the skeletal muscle of WT mice treated with the PPARδ agonist GW501516, when combined with exercise (Narkar et al., 2008).

PPARδ CNS Expression and Neural Function: Is PPARδ Involved in HD?

While the role of PPARδ in CNS is yet to be explored, quantitative Western blot analysis indicates that PPARδ protein is expressed more highly in brain than in muscle, by at least twofold (Girroir et al., 2008). As PPARδ exhibits the highest expression of all three PPARs in the brain, one group has reported that PPARδ agonist treatment can ameliorate ischemic brain injury and reduce MPTP-induced striatal dopamine depletion in rodents (Iwashita et al., 2007). Interestingly, PPARα and PPARγ agonists have been shown to be therapeutically beneficial in the MPTP rodent model of Parkinson's disease (Dehmer et al., 2004; Kreisler et al., 2007). However, because PPARδ can be partially activated by these agonists, neuroprotection in these studies may actually result from PPARδ activation. In any event, there is good reason to believe that PPARδ could be involved in normal neural function and disease and to expect that PPARδ dysfunction could be contributing to HD pathogenesis.

Acknowledgments

This paper was adapted from Weydt et al., 2006, Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1alpha in Huntington's disease neurodegeneration, Cell Metab 4:349–362; and Tsunemi et al., 2012, PGC-1alpha rescues Huntington's disease proteotoxicity by preventing oxidative stress and promoting TFEB function, Sci Transl Med 4:142ra197.

References

Beal MF, Brouillet E, Jenkins BG, Ferrante RJ, Kowall NW, Miller JM, Storey E, Srivastava R, Rosen BR, Hyman BT (1993) Neurochemical and histologic characterization of striatal excitotoxic lesions produced by the mitochondrial toxin 3-nitropropionic acid. J Neurosci 13:4181–4192.

Belteki G, Haigh J, Kabacs N, Haigh K, Sison K, Costantini F, Whitsett J, Quaggin SE, Nagy A (2005) Conditional and inducible transgene expression in mice through the combinatorial use of Cre-mediated recombination and tetracycline induction. Nucleic Acids Res 33:e51.

Berger J, Moller DE (2002) The mechanisms of action of PPARs. Annu Rev Med 53:409–435.

Bolstad BM, Irizarry RA, Astrand M, Speed TP (2003) A comparison of normalization methods for high density oligonucleotide array data based on variance and bias. Bioinformatics 19:185–193.

Cui L, Jeong H, Borovecki F, Parkhurst CN, Tanese N, Krainc D (2006) Transcriptional repression of PGC-1alpha by mutant *huntingtin* leads to mitochondrial dysfunction and neurodegeneration. Cell 127:59–69.

Dehmer T, Heneka MT, Sastre M, Dichgans J, Schulz JB (2004) Protection by pioglitazone in the MPTP model of Parkinson's disease correlates with I kappa B alpha induction and block of NF kappa B and iNOS activation. J Neurochem 88:494–501.

Ferrante RJ, Kowall NW, Beal MF, Richardson EP, Jr Bird ED, Martin JB (1985) Selective sparing of a class of striatal neurons in Huntington's disease. Science 230:561–563.

Gentleman RC, Carey VJ, Bates DM, Bolstad B, Dettling M, Dudoit S, Ellis B, Gautier L, Ge Y, Gentry J, Hornik K, Hothorn T, Huber W, Iacus S, Irizarry R, Leisch F, Li C, Maechler M, Rossini AJ, Sawitzki G, et al. (2004) Bioconductor: open software development for computational biology and bioinformatics. Genome Biol 5:R80.

Girroir EE, Hollingshead HE, He P, Zhu B, Perdew GH, Peters JM (2008) Quantitative expression patterns of peroxisome proliferator-activated receptor-beta/delta (PPARbeta/delta) protein in mice. Biochem Biophys Res Commun 371:456–461.

Graveland GA, Williams RS, DiFiglia M (1985) Evidence for degenerative and regenerative changes in neostriatal spiny neurons in Huntington's disease. Science 227:770–773.

NOTES

Greenamyre JT (2007) Huntington's disease—making connections. N Engl J Med 356:518–520.

Hodges A, Strand AD, Aragaki AK, Kuhn A, Sengstag T, Hughes G, Elliston LA, Hartog C, Goldstein DR, Thu D, Hollingsworth ZR, Collin F, Synek B, Holmans PA, Young AB, Wexler NS, Delorenzi M, Kooperberg C, Augood SJ, Faull RL, et al. (2006) Regional and cellular gene expression changes in human Huntington's disease brain. Hum Mol Genet 15:965–977.

Iwashita A, Muramatsu Y, Yamazaki T, Muramoto M, Kita Y, Yamazaki S, Mihara K, Moriguchi A, Matsuoka N (2007) Neuroprotective efficacy of the peroxisome proliferator–activated receptor delta-selective agonists *in vitro* and *in vivo*. J Pharmacol Exp Ther 320:1087–1096.

Kayed R, Head E, Sarsoza F, Saing T, Cotman CW, Necula M, Margol L, Wu J, Breydo L, Thompson JL, Rasool S, Gurlo T, Butler P, Glabe CG (2007) Fibril specific, conformation dependent antibodies recognize a generic epitope common to amyloid fibrils and fibrillar oligomers that is absent in prefibrillar oligomers. Mol Neurodegener 2:18.

Kreisler A, Gele P, Wiart JF, Lhermitte M, Destee A, Bordet R (2007) Lipid-lowering drugs in the *MPTP* mouse model of Parkinson's disease: fenofibrate has a neuroprotective effect, whereas bezafibrate and HMG-CoA reductase inhibitors do not. Brain Res 1135:77–84.

La Spada AR, Taylor JP (2010) Repeat expansion disease: progress and puzzles in disease pathogenesis. Nat Rev Genet 11:247–258.

Leone TC, Lehman JJ, Finck BN, Schaeffer PJ, Wende AR, Boudina S, Courtois M, Wozniak DF, Sambandam N, Bernal-Mizrachi C, Chen Z, Holloszy JO, Medeiros DM, Schmidt RE, Saffitz JE, Abel ED, Semenkovich CF, Kelly DP (2005) PGC-1alpha deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis. PLoS Biol 3:e101.

Lin MT, Beal MF (2006) Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 443:787–795.

Lowell BB, Spiegelman BM (2000) Towards a molecular understanding of adaptive thermogenesis. Nature 404:652–660.

Luthi-Carter R, Strand A, Peters NL, Solano SM, Hollingsworth ZR, Menon AS, Frey AS, Spektor BS, Penney EB, Schilling G, Ross CA, Borchelt DR, Tapscott SJ, Young AB, Cha JH, Olson JM (2000) Decreased expression of striatal signaling genes in a mouse model of Huntington's disease. Hum Mol Genet 9:1259–1271.

MacDonald ME, Ambrose CM, Duyao MP, Myers RH, Lin C, Srinidhi L, Barnes G, Taylor SA, James M, Groot N, MacFarlane H, Jenkins B, Anderson MA, Wexler NS, Gusella JF, Bates GP, Baxendale S, Hummerich H, Kirby S, North M, et al. (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72:971–983.

McGill JK, Beal MF (2006) PGC-1alpha, a new therapeutic target in Huntington's disease? Cell 127:465–468.

Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstråle M, Laurila E, Houstis N, Daly MJ, Patterson N, Mesirov JP, Golub TR, Tamayo P, Spiegelman B, Lander ES, Hirschhorn JN, Altshuler D, et al. (2003) PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. Nat Genet 34:267–273.

Muchowski PJ, Ning K, D'Souza-Schorey C, Fields S (2002) Requirement of an intact microtubule cytoskeleton for aggregation and inclusion body formation by a mutant huntingtin fragment. Proc Natl Acad Sci USA 99:727–732.

Nance MA (1997) Clinical aspects of CAG repeat diseases. Brain Pathol 7:881–900.

Narkar VA, Downes M, Yu RT, Embler E, Wang YX, Banayo E, Mihaylova MM, Nelson MC, Zou Y, Juguilon H, Kang H, Shaw RJ, Evans RM (2008) AMPK and PPARdelta agonists are exercise mimetics. Cell 134:405–415.

Puigserver P, Spiegelman BM (2003) Peroxisome proliferator–activated receptor-gamma coactivator 1 alpha (PGC-1 alpha): transcriptional coactivator and metabolic regulator. Endocr Rev 24:78–90.

Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM (1998) A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. Cell 92:829–839.

Riley BE, Orr HT (2006) Polyglutamine neurodegenerative diseases and regulation of transcription: assembling the puzzle. Genes Dev 20:2183–2192.

NOTES

Ross CA, Thompson LM (2006) Transcription meets metabolism in neurodegeneration. Nat Med 12:1239–1241.

Ross CA, Becher MW, Colomer V, Engelender S, Wood JD, Sharp AH (1997) Huntington's disease and dentatorubral-pallidoluysian atrophy: proteins, pathogenesis and pathology. Brain Pathol 7:1003–1016.

Rubinsztein DC (2006) The roles of intracellular protein-degradation pathways in neurodegeneration. Nature 443:780–786.

Russell LK, Mansfield CM, Lehman JJ, Kovacs A, Courtois M, Saffitz JE, Medeiros DM, Valencik ML, McDonald JA, Kelly DP (2004) Cardiac-specific induction of the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1alpha promotes mitochondrial biogenesis and reversible cardiomyopathy in a developmental stage-dependent manner. Circ Res 94:525–533.

Saudou F, Finkbeiner S, Devys D, Greenberg ME (1998) Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. Cell 95:55–66.

Schilling G, Becher MW, Sharp AH, Jinnah HA, Duan K, Kotzuk JA, Slunt HH, Ratovitski T, Cooper JK, Jenkins NA, Copeland NG, Price DL, Ross CA, Borchelt DR (1999) Intranuclear inclusions and neuritic aggregates in transgenic mice expressing a mutant N-terminal fragment of huntingtin. Hum Mol Genet 8:397–407.

Tsunemi T, Ashe TD, Morrison BE, Soriano KR, Au J, Roque RA, Lazarowski ER, Damian VA, Masliah E, La Spada AR (2012) PGC-1alpha rescues Huntington's disease proteotoxicity by preventing oxidative stress and promoting TFEB function. Sci Transl Med 4:142ra197.

Wang L, Liu J, Saha P, Huang J, Chan L, Spiegelman B, Moore DD (2005) The orphan nuclear receptor SHP regulates PGC-1alpha expression and energy production in brown adipocytes. Cell Metab 2:227–238.

Wang YX, Zhang CL, Yu RT, Cho HK, Nelson MC, Bayuga-Ocampo CR, Ham J, Kang H, Evans RM (2004) Regulation of muscle fiber type and running endurance by PPARdelta. PLoS Biol 2:e294.

Weydt P, Pineda VV, Torrence AE, Libby RT, Satterfield TF, Lazarowski ER, Gilbert ML, Morton GJ, Bammler TK, Strand AD, Cui L, Beyer RP, Easley CN, Smith AC, Krainc D, Luquet S, Sweet IR, Schwartz MW, La Spada AR (2006) Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1alpha in Huntington's disease neurodegeneration. Cell Metab 4:349–362.