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PGC-1α at the intersection of bioenergetics regulation and neuron function: From Huntington's disease to Parkinson's disease and beyond

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Abstract

Neurons are specialized cells with unique features, including a constant high demand for energy. Mitochondria satisfy this constant demand, and are emerging as a central target for dysfunction in neurodegenerative disorders, such as Huntington's disease (HD) and Parkinson's disease. PPARγ co-activator-1α (PGC-1α) is a transcription co-activator for nuclear receptors such as the PPARs, and thereby coordinates a number of gene expression programs to promote mitochondrial biogenesis and oxidative phosphorylation. Studies of PGC-1α knock-out mice have yielded important insights into the role of PGC-1α in normal nervous system function and potentially neurological disease. HD is caused by a polyglutamine repeat expansion in the huntingtin protein, and decades of work have established mitochondrial dysfunction as a key feature of HD pathogenesis. However, after the discovery of the HD gene, numerous reports produced strong evidence for altered transcription in HD. In 2006, a series of studies revealed that PGC-1α transcription interference contributes to HD neurodegeneration, linking the nuclear transcriptionopathy with the mitochondrial dysfunction. Subsequent work has strengthened this view, and further extended the role of PGC-1α within the CNS. Within the last year, studies of Parkinson's disease, another involuntary movement disorder long associated with mitochondrial dysfunction, have shown that PGC-1α dysregulation is contributing to its pathogenesis. As PGC-1α is likely also important for aging, a process with considerable relevance to neuron function, translational studies aimed at developing therapies based upon the PGC-1α pathway as a high priority target are underway.

Introduction

The CAG - polyglutamine (polyQ) repeat diseases comprise one category of neurodegenerative disorders. These diseases share a common mutational basis - all polyQ repeat diseases are caused by the abnormal elongation of CAG trinucleotide repeats, which are translated into polyQ tracts in the different disease proteins. Since the initial discovery of the first CAG - polyglutamine repeat disease in 1991 (La Spada *et al.*, 1991), at least 22 repeat expansion disorders have been identified (La Spada and Taylor, 2010). In the course

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of exploring the mechanistic basis of neurodegeneration in polyQ repeat diseases, numerous theories of pathogenesis have been proposed, including: transcription dysregulation (Bithell *et al.*, 2009; Quintanilla and Johnson, 2009), mitochondrial dysfunction (Quintanilla and Johnson, 2009), apoptosis activation (Offen *et al.*, 2000), autophagy dysfunction (Rubinsztein, 2006), increased oxidative stress (Browne and Beal, 2006), excess excitatory activity (Okamoto *et al.*, 2009), and reduced neurotrophic factor expression (Zuccato and Cattaneo, 2009). A series of studies on the transcription factor PPARγ co-activator-1α (PGC-1α) and its role in the CNS now indicate that PGC-1α dysfunction may underlie a number of apparently disparate cellular and molecular pathologies, thereby potentially resolving the confusion over how so many different pathways could all be involved in CAG - polyglutamine neurodegeneration. In this review, we will focus on recent advances in our understanding of the role of PGC-1α in neurodegeneration, highlighting evidence for PGC-1α impairment in Huntington's disease and Parkinson's disease.

Mitochondria perform a variety of different functions

Mitochondria are membrane-enclosed organelles present in all eukaryotic cells. Mitochondria perform numerous functions including energy production, scavenging excess reactive oxygen species (ROS), and heat generation. Mitochondria produce ATP through a biochemical process known as "oxidative phosphorylation". As neurons constantly have a high demand for energy, dysfunction of mitochondria in the nervous system always has serious consequences. A common by-product of chemical reactions in oxidative phosphorylation involving molecular oxygen is the generation of large amounts of ROS. To counter this so-called "oxidative stress", eukaryotic cells have evolved a set of proteins and pathways aimed at eliminating ROS (Lin and Beal, 2006), and among their defenses against oxidative stress are detoxifying enzymes, such as superoxide dismutase 2 (SOD2), which localizes to the mitochondrion itself to quench oxidative species. Numerous studies have shown that oxidative stress due to mitochondrial dysfunction will have a deleterious effect on neurons. For example, SOD2 null mice develop neurological defects and display dramatic spongiform degeneration in the cortex and brainstem (Melov *et al.*, 1998).

In addition to performing bioenergetics functions, mitochondria carry out a number of other important tasks. For example, mitochondria can generate heat in brown adipose tissue (Puigserver *et al.*, 1998). Normally, protons transferred from the mitochondrial matrix into the intermembrane space to create the chemiosmotic gradient produced during oxidative phosphorylation are used to drive ATP production. However, protons can re-enter the mitochondrial matrix without driving the ATP synthase, and instead short-circuit oxidative phosphorylation by passing through intramembrane proteins called uncoupling proteins (UCPs). Induction of UCP1 in brown adipose tissue in parallel with mitochondrial biogenesis is a common strategy among homeothermic mammals to maintain core body temperature (Puigserver and Spiegelman, 2003). Another important task of mitochondria is to regulate calcium homeostasis by serving as a storage site for calcium ions - a process that is especially important in myocytes and neurons where calcium flux is directly tied to muscle contraction and action potential generation (Lin and Beal, 2006). Finally, and perhaps most importantly, mitochondria orchestrate a number of biochemical processes and molecular pathways that control apoptosis (i.e. programmed cell death) (Mattson, 2000). Depolarization of the outer mitochondrial membrane is a key step in this process, resulting in the release of key apoptotic mediators from the inter-membrane space. Clearly, mitochondria are charged with the regulation of numerous essential pathways, but to what extent these different processes are interconnected or even integrated remains unclear. Recent work now indicates that a likely candidate for integrating a number of these pathways is the transcription regulatory protein PGC-1α.

The PPARs belong to the nuclear receptor family of transcription factors

Nuclear receptors (NRs) are members of a large superfamily of ligand-regulated (and orphan) DNA-binding transcription factors that perform a broad range of physiological activities, primarily by transducing steroid, retinoid, thyroid, and lipophilic endocrine hormone signals into specific patterns of gene expression (Lonard *et al.*, 2007). NRs regulate gene expression through their ability to bind to specific sequences in the promoters of their target genes. This transcription is carried out by RNA polymerase II. Transcriptional co-regulators (i.e. co-activators & co-repressors) are protein factors that are directly recruited by NRs to modulate NR-regulated gene expression without binding to DNA. While there are 48 known NRs in humans, there are nearly 300 transcriptional co-regulators that control the transcriptional activity of NRs, indicating that carefully coordinated regulation of NR activity is crucial to execute complex physiological functions.

The fact that mutations occurring within more than 100 co-regulators are sufficient to produce specific human diseases further indicates that co-regulators are very important (Lonard *et al.*, 2007). Peroxisome proliferator-activated receptors (PPARs) are one family of NRs. PPARα regulates the expression of genes involved in fatty acid β-oxidation and is a major regulator of energy homeostasis (van Raalte *et al.*, 2004). PPARβ/δ is widely expressed, and also is a key regulator of metabolic pathways, promoting fatty acid oxidation, oxidative phosphorylation, and muscle fiber type switching (Wang *et al.*, 2004). PPARγ is essential for the development of adipose tissue, and controls a variety of metabolic processes in the liver and periphery (Lowell, 1999).

The discovery of PGC-1α

Brown adipose tissue (BAT) is characterized by relatively small lipid droplets among a high number of densely packed mitochondria, indicating that it is a highly active metabolic tissue capable of enormous oxidative phosphorylation pathway activity. White adipose tissue (WAT), however, typically contains a single huge lipid droplet and is mainly used for fat storage. BAT uses lipids as a fuel for body temperature regulation (adaptive thermogenesis) upon exposure to cold. As noted above, mitochondrial UCPs are proteins that reside in the inner mitochondrial membrane, and enable BAT cells to generate heat by promoting a futile cycle at the inner mitochondrial membrane to permit adaptive thermogenesis. Although PPARγ is expressed in both WAT and BAT, transactivation studies found that PPARγ activates UCPs only in BAT (Puigserver *et al.*, 1998). This suggested the existence of a PPARγ cofactor that was assigned a specific role in BAT. To identify this putative co-factor, investigators screened a mouse BAT cDNA library, and using the yeast two-hybrid system, discovered a novel protein that they named PGC-1α (Puigserver *et al.*, 1998). Subsequent studies demonstrated that exposure to cold results in the dramatic up-regulation of PGC-1α expression in rodent BAT and muscle (Wu *et al.*, 1999). PGC-1α over-expression in cultured cells was then found to induce UCP1, as well as a number of enzymes in the oxidative phosphorylation pathway. These studies also showed that PGC-1α can stimulate mitochondrial biogenesis and respiration in oxidative tissues, such as muscle cells, by induction of UCP2 and nuclear respiratory factors (NRFs) (Wu *et al.*, 1999).

PGC-1α is a highly versatile co-activator

PGC-1α is a member of a family of transcriptional co-activators that includes PGC-1β and the PGC-related co-activator (PRC) (Andersson and Scarpulla, 2001; Esterbauer *et al.*, 1999; Lin *et al.*, 2002a). All of these proteins share homology in their N-terminal and C-terminal regions. Analysis of tissue expression patterns revealed that PGC-1α and PGC-1β are highly expressed in BAT, heart, skeletal muscle, kidney, and brain - all highly oxidative tissues (Esterbauer *et al.*, 1999; Lin *et al.*, 2002a). PGC-1α enhances mitochondrial biogenesis,

fatty acid oxidation, and oxidative metabolism, and PGC-1α controls the expression of key gluconeogenesis pathway enzymes in the liver (Yoon *et al.*, 2001). PGC-1α is preferentially expressed in muscle enriched for type I myocytes, and can convert type II myocytes to type I fibers (Lin *et al.*, 2002b). All of the PPARs primarily utilize transcription factors from the PGC-1 family to co-activate the expression of their respective target genes (Lin *et al.*, 2005). As a co-activator, PGC-1α also interacts with a variety of other transcription factors, including nuclear respiratory factors 1 and 2 (i.e. NRF-1 and NRF-2) and nuclear hormone receptors, such as the estrogen-related receptor a (ERRα) and thyroid receptor, to initiate a diverse set of metabolic programs in different tissues (Lin *et al.*, 2005). NRF-1, NRF-2, and ERRα are principally responsible for regulating the expression of many nuclear-encoded mitochondrial genes, including cytochrome c (Cyt C), the components of complexes I-V, and mitochondrial transcription factor A (Tfam) (Kelly and Scarpulla, 2004). PGC-1α can perform different tasks in different cell types by interacting with different transcription factors in a cell-specific fashion. For example, PGC-1α interacts with MEF2c in skeletal muscle, while engaging with HNF4α and FOXO1 in the liver. PGC-1α expression and activity are tightly regulated. PGC-1α levels are elevated by a number of external stimuli: cold in BAT, exercise and decreased ATP levels in skeletal muscle, and fasting in the liver. A number of different signaling pathways are involved in PGC-1α regulation. PGC-1α has an important role in regulating the metabolism and consequently the survival of GABAergic neurons in the developing brain (Cowell *et al.*, 2007). PGC-1α remains highly expressed in the adult brain; however, the range of its activities and functions in the adult brain are yet to be fully elucidated.

Insights into PGC-1α function from studies of knock-out mice

To determine the role of PGC-1α in metabolism and thermoregulation, the Spiegelman lab generated PGC-1α knock-out mice (Lin *et al.*, 2004). Although these workers anticipated that PGC-1α knock-out mice would display a predisposition to obesity, they instead noted that the mice were lean. The explanation for their enigmatic leanness turned out to be a phenotype of pronounced hyperactivity. Further analysis of PGC-1α knock-out mice revealed neurological abnormalities, including myoclonus, dystonia, exaggerated startle responses, and clasping (which is a stereotypical finding in all polyQ and HD mouse models). Neuropathology examination yielded evidence of degeneration in cortex, thalamus, basal ganglia, and hippocampus, with the most pronounced degeneration in the striatum. Indeed, a striking spongiform pattern of change was observed predominantly in striatum. This lesion was accompanied by massive gliosis and significant neuronal loss.

Interestingly, real-time RT-PCR analysis of hyperactive PGC-1α knock-out mice documented significant reductions in the expression of mitochondrial genes. In addition to their phenotype of hyperactivity and striatal neurodegeneration, the PGC-1α knock-out mice displayed reduced thermogenic capacity due to a failure of induction of UCPl gene expression. In 2005, the Kelly lab independently generated another PGC-1α knock-out line, and also noted degeneration of the basal ganglia in PGC-1α null mice (Leone *et al.*, 2005). To further characterize the role of PGC-1α in different tissues, conditional knock-out of PGC-1α using various Cre recombinase driver lines has been pursued. To evaluate the role of PGC-1α in the forebrain, *PGC-1α*$^{flox/flox}$ mice were crossed with calcium / calmodulin-dependent protein kinase IIα (CaMKIIα)-Cre transgenic mice, and the resultant PGC-1α $^{flox/flox}$; CaMKIIα-Cre mice were found to display neurodegeneration in the striatum, as well as resistance to diet-induced obesity (Ma *et al.*, 2010), which was attributed to reduced hypothalamic expression of agouti-related protein and neuropeptide Y upon fasting. These findings suggest that impaired PGC-1α function in neurons alters energy balance and increases energy expenditure.

Clinical and pathological description of HD

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by motor and cognitive impairment, accompanied by a variable degree of personality change and psychiatric illness (Nance, 1997). The motor abnormality stems from dysfunction of the involuntary movement control region of the basal ganglia known as the striatum, and is manifested as a hallmark feature of uncontrollable dance-like movements ("chorea"). The disorder is relentlessly progressive, and after pronounced cognitive decline, patients succumb to the disease usually 10 to 30 years after disease onset. Neuropathology studies of HD have established a five point grading system (grade 0 to 4) to track the progression of the disorder in affected patients (Vonsattel *et al.*, 1985). This work has indicated that the caudate and putamen in the striatum are principally involved in classic HD, with 95% of caudate nucleus neurons lost in grade 4 HD patients. Even grade 0 HD patients display caudate pathology with as many as 1/3 of caudate neurons already depleted. Further neuroanatomical studies revealed that GABAergic medium spiny (type II) neurons in the striatum are selectively vulnerable in HD, as medium aspiny and large cholinergic striatal neurons are preserved (Ferrante *et al.*, 1985; Graveland *et al.*, 1985). In classic HD (as opposed to juvenile-onset HD (Ross *et al.*, 1997)), significant cerebral cortex degeneration and atrophy occurs, while cerebellar, thalamic and spinal cord neuron populations are spared. In addition to neurological abnormalities, HD patients may suffer from a wide range of other physiological problems. Among them, weight loss - or an inability to gain weight - appears an especially prominent finding that can actually precede the neurological manifestations, and can occasionally compromise quality of life (Aziz *et al.*, 2008a).

HD is caused by a CAG / polyglutamine repeat expansion mutation

HD displays the genetic feature of anticipation, defined as earlier disease onset and more rapid disease progression in successive generations of a pedigree segregating the disease gene. This feature served as an important clue for discovery of the causal mutation, as a trinucleotide repeat expansion encoding an elongated glutamine tract in the huntingtin (htt) protein was determined to be responsible for HD in 1993 (Huntington's *et al.*, 1993). HD is thus one of nine inherited neurodegenerative disorders all caused by CAG trinucleotide repeats that expand to produce disease by encoding elongated polyglutamine (polyQ) tracts in their respective protein products (Zoghbi and Orr, 2000). Included in this CAG/ polyglutamine repeat disease class are spinal and bulbar muscular atrophy (SBMA), dentatorubral-pallidoluysian atrophy (DRPLA), and six forms of spinocerebellar ataxia (SCA1, 2, 3, 6, 7 and 17). Based on work done on all of these disorders, investigators have learned that once glutamine tracts exceed the mid-30's, the polyglutamine tract adopts a novel conformation that is pathogenic. An anti-polyQ antibody (1C2) can specifically detect this structural transformation, as it will only bind to disease length polyQ tracts from patients with the different diseases (Trottier *et al.*, 1995). Once in this conformation, it is unclear how the polyQ tract expansions mediate the patterns of neuronal cell loss seen in each disease, as most of the polyQ disease gene products show overlapping patterns of expression within the CNS, but narrowly restricted pathology.

Models of HD polyglutamine neurotoxicity

To understand the molecular basis of htt polyQ neurotoxicity, investigators have generated numerous in vitro and in vivo models. The literature describing all this work is exhaustive, but several reviews summarizing many of these studies are available (Crook and Housman, 2011; La Spada *et al.*, 2011; Ross and Tabrizi, 2011). Out of this work, certain key themes have emerged as important features of polyQ neurotoxicity in general and HD disease

pathogenesis in particular. One key finding is that after polyQ-expanded proteins misfold, they tend to become sequestered into large "aggregates" or "inclusions" - structures that are clearly visible at the light microscope level (Paulson, 1999). The discovery of such inclusions has linked the polyQ diseases with virtually all neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and the prion diseases. The presence of misfolded, accumulating mutant proteins in these diseases is now recognized as an important common theme in the field (Lunkes and Mandel, 1997; Williams and Paulson, 2008). However, work done on HD and other polyQ diseases suggests that aggregates may not be toxic *per se*, but rather signify the presence of misfolded proteins whose toxic action is playing out in the soluble phase and/or at the level of oligomers or protofibril structures ("microaggregates") (Poirier *et al.*, 2002; Wacker *et al.*, 2004).

Another crucial aspect of polyQ neurotoxicity is the role of proteolytic cleavage in disease pathogenesis. Studies of HD suggest that proteolytic cleavage of the htt protein is a key step in the neurotoxicity pathway. The htt gene encodes an enormous protein of 3,144 amino acids with the glutamine tract beginning at codon #18; analysis of aggregates from HD patients and in vitro models indicated that glutamine- and amino-terminal epitopes are present in nuclear, cytosolic, and axonal aggregates (DiFiglia, 2002). In a landmark study, one group used a 1.6 kb fragment of the huntingtin gene containing only the first 2% of the huntingtin coding region to derive lines of transgenic mice ("R/6") that showed a neurological phenotype that included features of HD (Mangiarini *et al.*, 1996). This study demonstrated that only an extremely tiny amino-terminal portion of the htt protein (including the polyQ tract) was necessary to yield a HD-like illness in mice. Careful analysis of the so-called R/6 HD transgenic mice yielded the discovery of inclusions of material aggregating within the nuclei of neurons (Davies *et al.*, 1997). These neuronal intranuclear inclusions (or NIs as they are now abbreviated) were also recognized in human HD, SBMA, DRPLA, SCA1, SCA3, and SCA7 patients (Ross, 1997). The accumulation of polyQ disease proteins (or peptide fragments thereof) in nuclei raised the question of whether nuclear entry might be a required step for disease pathogenesis. Exclusion of mutant htt peptide from the nucleus in a primary striatal neuron HD model prevented cell death (Saudou *et al.*, 1998), suggesting that nuclear entry is indeed required for polyQ neurotoxicity in HD. A compelling in vivo study of SCA1 in the *Pcp2* B05 transgenic mouse model revealed that mutation of the ataxin-1 nuclear localization signal (NLS) prevented ataxin-1 polyQ neurotoxicity (Klement *et al.*, 1998). In SBMA, ligand-mediated nuclear translocation appears associated with androgen receptor (AR) neurotoxicity as both SBMA patients and mouse models show gender-specific neurotoxicity (Sopher *et al.*, 2004), and castration of male SBMA transgenic mice can rescue AR polyQ neurotoxicity in muscle cells and neurons (Katsuno *et al.*, 2002).

Role of transcription dysregulation in HD disease pathogenesis

The necessity of nuclear localization for HD disease pathogenesis highlighted nuclear pathology as a likely early step in the neurotoxicity cascade. As glutamine tracts and glutamine-rich regions often occur in transcription factors and permit functional protein-protein interactions to occur in the formation of transcription activation complexes in species as diverse as yeast, fruit flies, chicken, and humans (Gerber *et al.*, 1994), a hypothesis of "transcription interference" or "transcription dysregulation" was formulated. According to this hypothesis, polyQ-expanded disease proteins (or peptides) accumulating in the nucleus inappropriately interact with transcription factors and regulators to disrupt normal transcriptional functions (La Spada and Taylor, 2003). Studies of htt have implicated a number of important transcription factors and co-activators. One of the most studied and strongly implicated transcription factors is CREB-binding protein (CBP), a transcriptional

co-activator involved in the regulation of multiple genes through its intrinsic histone acetylation activity (that remodels chromatin to allow the transcription machinery to access target genes). A number of studies have reported htt interference of CBP-mediated transcription in a polyQ length-dependent fashion (McCampbell *et al.*, 2000; Nucifora *et al.*, 2001; Steffan *et al.*, 2000; Sugars *et al.*, 2004). Furthermore, drugs that block histone deacetylation (HDAC inhibitors), and thereby favor the outcome of CBP action (i.e. histone acetylation), have been found to be therapeutically beneficial in Drosophila and mouse models of HD (Hockly *et al.*, 2003; Steffan *et al.*, 2001). Spl, a ubiquitously expressed DNA binding factor that recruits the TFIID complex, and TAFII130, a factor that mediates transcription activation complex assembly, have also been identified as targets of mutant htt protein (Dunah *et al.*, 2002). Interaction of polyQ-expanded htt with CBP, Spl, and TAFII130 has been shown to occur in the nucleus and to involve the amino-terminal region of htt. Htt also interacts with RAP-30, and polyQ-expanded htt can interfere with Spl-dependentand TFII-F-dependenttransactivation (Dunah *et al.*, 2002; Zhai *et al.*, 2005). Roles for CREB-CBP and Spl gene targets in maintenance of normal neuronal function are suggested by other studies (Mantamadiotis *et al.*, 2002; Ryu *et al.*, 2003), supporting the conclusion that interference with CBP and Spl action could have deleterious effects upon neuronal health and survival. Loss of BDNF expression via a different mechanism, failure of cytosolic sequestration of a repressor protein (REST) by full-length htt due to polyQ expansion, may also contribute to HD pathogenesis (Zuccato *et al.*, 2003).

Abnormal energy homeostasis in neurodegenerative disease

A peripheral energy deficit in HD patients is evidenced by the observation that the ATP/ADP ratio in HD patient-derived lymphoblastoid cell lines is significantly decreased (Seong *et al.*, 2005). This ratio inversely decreases with the length of the CAG repeat tract in HD. A decreased ATP/ADP ratio is also observed in *ST-Hdh* cells, which are striatal-like cell lines derived from Hdh^{Q111} knock-in mice (Gines *et al.*, 2003). Skeletal muscle shows energetic disturbances in HD patients similar to those evident in HD striatal-like neurons. Muscle ATP production at rest, during recovery from exercise, and at maximum activity output are all reduced in HD patients (Lodi *et al.*, 2000). Impaired muscle ATP production is even observed in asymptomatic mutation carriers (Saft *et al.*, 2005). R6/2 HD mice develop cardiac dysfunction by 8 weeks of age, and this progresses to severe heart failure by 12 weeks of age (Mihm *et al.*, 2007). These results indicate that ubiquitous expression of mutant htt protein causes mitochondrial dysfunction in cells with high-energy demand, contributing to weight loss. While an inability to gain weight is particularly apparent in HD patients, it turns out that weight loss is actually a common feature of many neurodegenerative disorders (Aziz *et al.*, 2008b), having been described in Parkinson's disease (Kashihara, 2006), Alzheimer's disease (Tamura *et al.*, 2007) and amyotrophic lateral sclerosis (Vaisman *et al.*, 2009). The mechanism behind this is controversial and may differ among the various diseases. Since HD patients display an involuntary movement disorder, described as 'chorea' to denote its rhythmic quality, many clinicians assumed that the choreiform movement disorder could explain the increased energy consumption, thereby accounting for the weight loss. However, HD patients present with weight loss prior to the onset of chorea (Farrer and Meaney, 1985). Another formal possibility is difficulty swallowing food, such that HD patients do not achieve adequate caloric intake; however, metabolic studies have clearly established that HD patients lose weight despite taking in ample calories (Aziz *et al.*, 2008a). Instead, recent studies of human HD patients (Aziz *et al.*, 2008a) and mouse models (Weydt*et al.*, 2006) indicate that the inability to maintain body weight in HD is due to elevated energy expenditure. While the exact basis of the increased energy expenditure in HD is still unclear, considerable evidence has accumulated in support of mitochondrial dysfunction as the principal cause.

Evidence for mitochondrial abnormalities and defective energy metabolism in HD

Neurons in the brain have enormous demands for continued production of high-energy phosphate-bonded compounds such as ATP. In 1993, Beal et al. 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 suggested that mitochondrial dysfunction may underlie HD pathogenesis and perhaps account for cell-type specificity in this disorder. Follow-up studies performed upon HD patient material documented significant reductions in the enzymatic activities of complexes II, III, and IV of the mitochondrial oxidative phosphorylation pathway in caudate and putamen (Browne *et al.*, 1997; Gu *et al.*, 1996), while not detecting such alterations in HD cerebella or fibroblasts (Tabrizi *et al.*, 1999). Additional work noted striatal-specific decreases in aconitase activity, a likely target of Ca++-dependent, free radical producing intramitochondrial enzymes (Tabrizi *et al.*, 1999). PET scan analysis of HD patients strongly supports the hypothesis of defective energy metabolism, as diminished rates of cerebral glucose metabolism are apparent in certain regions of the cortex and throughout the striatum (Stoessl *et al.*, 1986). Magnetic resonance spectroscopy corroborates such findings, revealing elevated lactate levels in striata of HD patients (Harms *et al.*, 1997).

As mitochondrial energy production and metabolic pathways supply energy for ion exchange pumps whose function is to maintain an electrochemical gradient across the mitochondrial membrane, defective energy metabolism could translate into an enhanced susceptibility of HD mitochondria to undergo depolarization. A number of studies have evaluated this, and have found that mitochondria from HD patients are exquisitely sensitive to depolarizing stresses. In one study, treatment of HD lymphoblasts with complex IV inhibitors resulted in mitochondrial depolarization and apoptotic cell death involving caspase activation (Sawa *et al.*, 1999). In another study, electrical measurements of HD lymphoblast mitochondria yielded lower than normal membrane potentials and depolarization in response to modest Ca++ loads (Panov *et al.*, 2002). As mitochondrial membrane depolarization results in caspase activation, and pathogenic cleavage of htt protein appears to be mediated in part by caspases, mitochondrial dysfunction may represent an early step in the HD neurotoxicity cascade.

PGC-1α transcription interference contributes to HD pathogenesis

The discovery of neurological abnormalities and pronounced neuropathology in PGC-1α knock-out mice strongly suggested that PGC-1α plays a critical role in the brain. In 2006, we, and others, reported strong evidence implicating PGC-1α dysfunction in HD neurodegeneration (Cui *et al.*, 2006; Weydt *et al.*, 2006). In a commonly used model of HD, the N171-82Q transgenic mouse (Schilling *et al.*, 1999), we found that HD mice developed progressive hypothermia, beginning at 15 – 17 weeks of age (Weydt *et al.*, 2006). HD transgenic mice also displayed significant reductions in body temperature during cold challenge, even while presymptomatic for baseline hypothermia. While PGC-1α induction in N171-82Q HD mice upon cold exposure was intact, we noted that UCP-1 mRNA up-regulation was severely blunted, suggesting that PGC-1α transcriptional activity is impaired in BAT from N171-82Q HD mice. PGC-1α transcriptional activity was altered in the striatum, as well (Cui *et al.*, 2006). When we examined microarray data from human striatum, we found that the vast majority of PGC-1α target genes are coordinately down-regulated in striatal RNAs from asymptomatic and presymptomatic HD patients (Weydt *et al.*, 2006). Furthermore, PGC-1α expression was reduced in medium spiny neurons from HD patients, and PGC-1α transcriptional activity was markedly decreased in HD striatal-like cells, in medium spiny neurons from a knock-in HD mouse model, and in postmortem

human striatum (Cui *et al.*, 2006). Restoring PGC-1α expression by lentiviral injection, however, prevented striatal atrophy in HD mice.

Since these original reports in 2006, a number of other groups have independently shown that impaired PGC-1α function is a likely contributor to HD pathology, demonstrating reduced PGC-1α target gene expression in muscle from HD transgenic mice, and linking sequence variants at the PGC-1α gene locus with differences in HD disease severity (Chaturvedi *et al.*, 2009; Weydt *et al.*, 2009). All of these studies, taken together, suggest that PGC-1α transcription disturbance is a central feature of HD pathogenesis. By delineating a role for PGC-1α transcription interference in HD pathogenesis, this line of investigation has yielded a model wherein HD nuclear transcriptionopathy and mitochondrial dysfunction, viewed for more than a decade as occurring independently in parallel (Greenamyre, 2007), are now understood as linked with mitochondrial dysfunction resulting in part from PGC-1α dysfunction (Figure 1).

Very recent work has now extended the specter of PGC-1α transcription interference from the neuronal lineage to a non-neural cell type in HD by documenting a role for PGC-1α in myehnation (Xiang *et al.*, 2011). Apparently, PGC-1α is present in oligodendrocytes, where it promotes the expression of genes required for proper myehnation (Figure 1), including myelin basic protein (MBP). Upon electron microscopy analysis, HD transgenic mice were found to exhibit deficient myehnation, and this was accompanied by decreased expression of MBP, suggesting that defective PGC-1α function may result in abnormal myelination in HD. As PGC-1α knock-out mice exhibit white matter abnormalities in the striatum together with significant reductions in the expression of myelin-associated oligodendrocyte basic protein (MOBP) (Lin *et al.*, 2004), glial abnormalities resulting from PGC-1α impairment could very well be contributing to neurodegenerative disorders. Indeed, a role for PGC-1α in Schwann cell differentiation has also been demonstrated (Cowell *et al.*, 2008).

Parkinson's disease: Another neurodegenerative disorder characterized by mitochondrial dysfunction

Parkinson's disease (PD) is a disorder characterized by motor symptoms including at least two of the following: tremor, bradykinesia, muscular rigidity, and postural instability (Lang and Lozano, 1998). These motor problems, known as "parkinsonism", reflect an ongoing process of loss of dopamine-producing neurons from the pars compacta of the substantia nigra (SN). Although many disease processes can include parkinsonism as a feature, classic PD is defined by the presence of a characteristic intracellular cytoplasmic inclusion known as the "Lewy body". Lewy bodies (LBs) are particularly prominent in the substantia nigra of PD patients, but also occur in neurons of the brainstem, hypothalamus, hippocampus, and sometimes cortex. Loss of dopaminergic neurons in the SN pars compacta is the crucial neuropathlogical feature of PD, however, and accounts for the clinical signs and symptoms in this disorder. The notion that mitochondrial dysfunction contributes to disease pathogenesis in PD is supported by an extensive literature that has documented mitochondrial oxidative phosphorylation pathway dysfunction in PD patients and mammalian cell lines (Moore et al., 2005; Schapira et al., 1989; Swerdlow et al., 1996). As complex I inhibitors such as MPTP, rotenone, and paraquat can produce a parkinsonian syndrome in rodents and human, mitochondrial dysfunction has emerged as a likely factor in causing PD (Beal, 2005). Furthermore, recessive mutations in PINK1, parkin, and DJ-1 are sufficient to cause PD in human patients, and all of these genes produce proteins believed to function in mitochondrial physiology (Chu, 2010). For a more in-depth review of PD pathogenic mechanisms and pathobiology, the reader is referred to a number of recent review articles on this topic (Martin *et al.*, 2011; Schnabel, 2010; Vives-Bauza and Przedborski, 2011).

Evidence for PGC-1α impairment in Parkinson's disease

Recent studies now suggest that PGC-1α impairment is also involved in PD pathogenesis (Shin *et al.*, 2011; Zheng *et al.*, 2010). From a meta-analysis of 17 independent microarray studies performed on PD, including post-mortem PD SN, post-mortem PD with LBs, and SN dopaminergic neurons isolated by laser capture microdissection, strong evidence for PGC-1α transcription interference emerged, as gene set enrichment analysis documented coordinate down-regulation of 425 PGC-1α regulated genes in PD samples (Zheng *et al.*, 2010). These findings indicate that defects in mitochondrial electron transport, glucose utilization, and glucose sensing occur early in PD pathogenesis. Furthermore, activation of PGC-1α could rescue dopaminergic neuron loss induced by mutant α-synuclein or the pesticide rotenone in primary neuron models. Another study has also found evidence for a link between PD caused by recessive mutations in parkin and altered PGC-1α activation (Shin *et al.*, 2011). In this work, PARIS (ZNF746) was identified as a substrate of the E3 ubiquitin ligase parkin, and shown to be a KRAB zinc finger protein that represses the expression of PGC-1α and its target gene, NRF-1 (Figure 1). Conditional knock-out of parkin in adult mice yielded progressive loss of dopaminergic neurons in a PARIS-dependent manner, and this was reversed by either parkin or PGC-1α co-expression (Shin *et al.*) These results suggest that PGC-1α is involved not only in HD, but also in PD.

PGC-1α and aging

Neurodegenerative disorders typically occur in individuals who are middle-aged or elderly, suggesting a connection between the aging process and diminished function of pathways critical for neuron survival. Resveratrol (3,5,4'-trihydroxystilbene) can extend lifespan, but this lifespan extension depends upon Sir2, a conserved NAD-dependent deacetylase proposed to mediate the beneficial effects of caloric restriction (Baur *et al.*, 2006). Resveratrol can also activate AMP-protein kinase (AMPK) and PGC-1α. As enhanced SIRT1 activity by resveratrol deacetylates PGC-1α, resulting in the induction of genes required for oxidative phosphorylation and mitochondrial biogenesis (Cui *et al.*, 2006; Lagouge *et al.*, 2006), PGC-1α has been implicated in the aging process. PGC-1α's role in controlling aging may also extend to influencing telomeres, the structures at the ends of linear chromosomes that have long been recognized as critical for the maintenance of chromosomal integrity (Maser and DePinho, 2002). As a cell divides, telomeres become shorter because conventional DNA polymerases cannot synthesize chromosomal ends completely. A recent study suggests that telomere shortening activates p53, which in turn binds and represses the transcription of PGC-1α and PGC-1β, resulting in impaired mitochondrial biogenesis and function, decreased gluconeogenesis, and increased reactive oxygen species (Sahin *et al.*, 2011). These results suggest that, during the aging process, PGC-1α is targeted by the sirtuin pathway and/or the telomere-p53 pathway.

Is PGC-1α a viable target for therapy development?

Direct evidence for the therapeutic potential of PGC-1α has come from gene expression studies in cell culture and animal models (Chaturvedi *et al.*, 2009; Cui *et al.*, 2006; St-Pierre *et al.*, 2006; Weydt *et al.*, 2006). Stable over-expression of PGC-1α in ST-Hdh-Q111 striatal-like cells, which are more sensitive to 3-NP, enhanced the mitochondrial membrane potential despite 3-NP treatment (Weydt*et al.*, 2006). Similarly, in ST-Hdh-Q111 striatal-like cells and in primary striatal neurons, adenoviral delivery or transfection of PGC-1α reduced mitochondrial toxicity (Cui *et al.*, 2006). Furthermore, lentiviral delivery of PGC-1α to the striatum of R6/2 HD mice completely prevented striatal atrophy and a decrease in neuronal volume at the site of PGC-1α injection (Cui *et al.*, 2006). In another independent study, adenovirus delivery and over-expression of PGC-1α enhanced survival

in mouse striatal progenitor neurons subjected to oxidative stress (St-Pierre *et al.*, 2006). The same adenoviral construct was also effective against the catabolic stressor and creatine analog, β-guanidinopropionic acid (GPA), in the muscle cells of the NLS-N171-82Q HD mouse model (Chaturvedi *et al.*, 2009). Finally, crossing PGC-1α null mice with a knock-in full-length HD model actually exacerbated the striatal lesions, indicating that endogenous expression of PGC-1α is neuroprotective in a late-onset mouse model of HD (Cui *et al.*, 2006).

Is it possible to activate PGC-1α in the CNS? One way to boost PGC-1α expression and function is by viral delivery, as noted above (Cui *et al.*, 2006). Another option is to modulate the upstream regulators of PGC-1α activation, such as SIRTl or AMPK. SIRTl can induce PGC-1α by deacetylating PGC-1α at specific lysine residues (Rodgers *et al.*, 2005), resulting in increased expression of PGC-1α target genes. There are several compounds, including the well-known compound resveratrol that can potently activate SIRTl (Milne *et al.*, 2007). A number of studies indicate that resveratrol may be neuroprotective (Foti Cuzzola *et al.*, 2011; Pasinetti *et al.*, 2011); however, whether this is PGC-1α-dependent remains to be determined. Evaluation of additional SIRTl activator compounds in neurodegenerative disorders and the role of PGC-1α induction in any observed therapeutic response is thus likely to be worthwhile. Another potential approach is to activate a PGC-1α target nuclear receptor. For example, when R6/2 HD transgenic mice are treated with the PPARγ agonist rosiglitazone, they demonstrate improvements in transcriptional abnormalities and mitochondrial dysfunction in the CNS (Chiang *et al.*, 2010; Chiang *et al.*, 2011; Quintanilla *et al.*, 2008). Thus, a variety of putative targets exist for small compound modulation of PGC-1α function. For these reasons, we predict that PGC-1α is a promising therapeutic pathway for HD and related neurodegenerative disorders, including especially PD.

Conclusions

A consistent theme in research on HD and related polyQ neurodegenerative disorders has been that insights gained from the study of these relatively rare disorders are often relevant to more common neurodegenerative diseases. The story of PGC-1α reinforces this view, as initial work implicating PGC-1α transcription interference in HD preceded the emerging data demonstrating a role for PGC-1α in PD by more than four years. Another importantaspect of the PGC-1α studies, linking it to HD and neurological disease, has been the realization that bioenergetics pathways are critically important in the CNS. This work has reignited interest in the role of metabolic processes in neurological disease, and suggests that a deeper understanding of mitochondrial biology and correspondingly mitochondrial dysfunction will be necessary, if we are to arrive at meaningful therapies to treat neurodegenerative disorders. As it has been 20 years since the discovery of the first repeat CAG - polyQ repeat expansion mutation (La Spada *et al.*, 1991), an important objective for the next decade of research on HD and related disorders is to develop interventions that will prevent or slow the progression of these diseases. A full understanding of how PGC-1α dysfunction yields neuronal compromise in HD and PD could be an important first step in unlocking novel targets and pathways amenable to directed therapy development.

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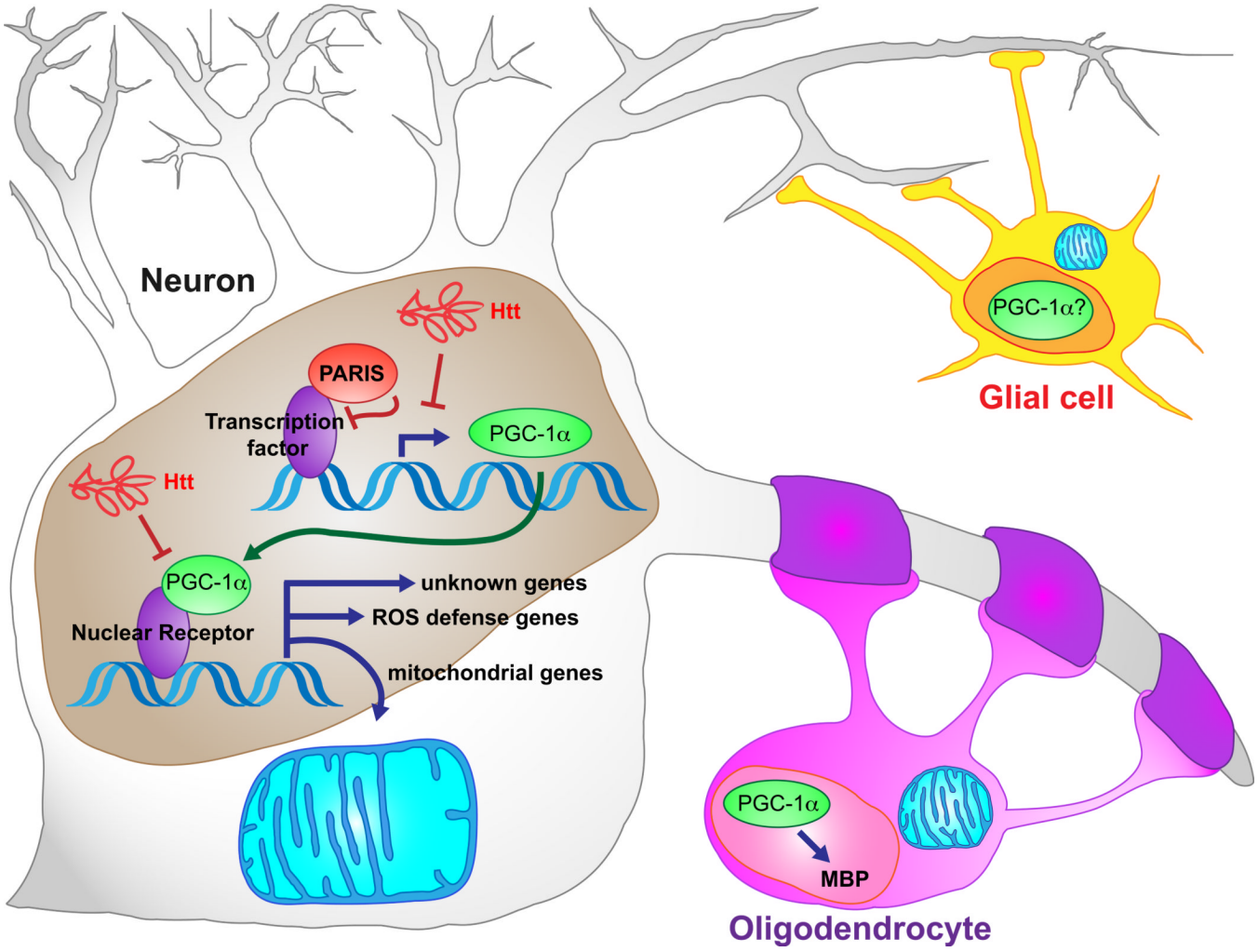

Figure 1. PGC-1α performs diverse functions in the CNS, and some of these functions are impaired in neurodegenerative disease

PGC-1α is a nuclear transcription co-activator, and is responsible for co-activating the expression of a large number of target genes, many of which produce proteins that function in the mitochondria and prevent the accumulation of reactive oxygen species (ROS). PGC-1α transcription dysregulation is a feature of Huntington's disease, as the mutant Htt protein inhibits PGC-1α activity at the promoters of its target genes, thereby yielding decreased mitochondrial biogenesis, mitochondrial function, and presumably ROS scavenging. In Parkinson's disease, PGC-1α function is similarly impaired. One possible mechanism by which PGC-1α transcription interference occurs in Parkinson's disease involves the protein PARIS, which inhibits PGC-1α co-activator function. PGC-1α may also function in other cell types in the CNS, including especially oligodendrocytes - where PGC-1α has been shown to regulate the expression of myelin basic protein (MBP) - and possibly other cells of the glial lineage.