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Review Article

Mitochondrial Dysfunction in Neurodegenerative Diseases and Cancer

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Mitochondria are important integrators of cellular function and therefore affect the homeostatic balance of the cell. Besides their important role in producing adenosine triphosphate through oxidative phosphorylation, mitochondria are involved in the control of cytosolic calcium concentration, metabolism of key cellular intermediates, and Fe/S cluster biogenesis and contributed to programmed cell death. Mitochondria are also one of the major cellular producers of reactive oxygen species (ROS). Several human pathologies, including neurodegenerative diseases and cancer, are associated with mitochondrial dysfunction and increased ROS damage. This article reviews how dysfunctional mitochondria contribute to Alzheimer's disease, Parkinson's disease, Huntington's disease, and several human cancers. Environ. Mol. Mutagen. 51:391–405, 2010.

Key words: mitochondria; neurodegenerative disease; cancer; ROS

INTRODUCTION

Mitochondria use metabolic intermediates generated during the tricarboxilic acid (TCA) cycle to generate adenosine triphosphate (ATP) during oxidative phosphorylation. These organelles also serve as a host of other important functions within the cell, such as homeostatic control of cytosolic calcium and iron concentration [Feissner et al., 2009], Fe/S cluster, and heme biogenesis [Lill and Muhlenhoff, 2005; Rouault and Tong, 2005; Hausmann et al., 2008] and also contribute to programmed cell death [Green and Reed, 1998; Garrido and Kroemer, 2004]. Mitochondria also contain their own genome, which must be replicated and maintained by nuclear encoded proteins, and thus the function of this organelle is fully integrated with the biology of the cell. Loss of mitochondrial function is associated with an increase in the generation of reactive oxygen intermediates and a number of human diseases [Van Houten et al., 2006]. After a brief overview of mitochondrial function and a description of mitochondrial deoxyribonucleic acid (mtDNA), this article discusses the role of mitochondrial dysfunction in neurodegenerative diseases [DiMauro and Schon, 2008; Schapira, 2008; Lee et al., 2009] and cancer [McBride et al., 2006; DeBerardinis, 2008; Frezza and Gottlieb, 2009] and shows that some gene products are important for both human pathologies.

MITOCHONDRIAL DNA

Human mitochondria contain a 16,569-bp circular DNA that encodes 37 genes. Thirteen of these genes encode for

Abbreviations: ABAD, Aβ-binding alcohol dehydrogenase; AD, Alzheimer's disease; Akt, acute transforming retrovirus thymoma; Aβ, amyloid-β; APP, amyloid precursor protein; ASCT2, sodium-dependent neutral amino acid transporter type 2; ATP, adenosine triphosphate; CypD, cyclophilin D; DNA, deoxyribonucleic acid; ES, embryonic stem; ETC, electron transport chain; FAD, flavin adenine dinucleotide; FDG, [^{18}F] 2-fluoro-2-D-glucose; FH, fumarate hydratase; Fis1, mitochondrial fission 1 protein; GLUT 1, glucose transporter 1; GPx, glutathione peroxidase; H_2O_2, hydrogen peroxide; HD, Huntington's disease; HIF-1, hypoxia-inducible transcription factor; HK, hexokinase; IDH1, isocitrate dehydrogenase 1; LDH-A, lactate dehydrogenase A; LRRK2, leucine-rich repeat kinase 2; Mfn1, mitofusin-1; Mfn2, mitofusin-2; MPTP, 1-methyl-4-phenyl-1,2,3,6-*tetra*-hydropyridine; mPTP, mitochondrial permeability pore; mtDNA, mitochondrial DNA; NADH, nicotinamide adenine dinucleotide; NFT, neurofibrillary tangles; 3-NPA; 3-nitropropionic acid; OPA1, optic atrophy 1; OXPHOS, oxidative phosphorylation; PD, Parkinson's disease; PDH, pyruvate dehydrogenase; PDK1, pyruvate dehydrogenase kinase 1; PET, positron emission tomography; PFK-1, phosphofructokinase-1; PGC-1α, proliferator activator receptor γ coactivator-1 α; PolyQ, polyglutamine; PQ, paraquat; RNA, ribonucleic acid; ROS, reactive oxygen species; SCO2, synthesis of cythocrome c oxidase 2; SDH, succinate dehydrogenase; SNCA, α-synuclein; TCA, tricarboxilic acid; TFAM, mitochondrial transcription factor A; VEGF, vascular endothelial growth factor.

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protein subunits of the respiratory chain: NADH dehydrogenase (ND)1, ND2, ND3, ND4, ND4L, ND5, and ND6 of complex I, cytochrome *b* of complex III, COI, COII, and COIII of complex IV, and subunits A6 and A8 of the ATP synthase complex. The remaining 24 genes encode two ribosomal ribonucleic acids (RNAs) (12S and 16S), and 22 transfer RNAs are required for mitochondrial translational machinery.

The majority of proteins required for electron transport chain (ETC) and normal mitochondrial function (~900 proteins) are encoded by the nuclear genome and imported into the mitochondria by specialized import systems [Mokranjac and Neupert, 2005]. In human cells, each mitochondrion contains multiple copies of mtDNA, although the copy number can vary between different cell types [Gilkerson, 2009].

Mitochondrial genomes are tightly associated with proteins forming structures called nucleoids [Legros et al., 2004; Chen and Butow, 2005; Kucej and Butow, 2007]. Nucleoids are widely distributed inside the matrix of the mitochondria and consist of 2–8 mtDNA molecules associated with several different proteins. Some major proteins that can be found in the nucleoids are mitochondrial single-stranded DNA-binding protein, mitochondrial polymerase γ, twinkle helicase, and the mitochondrial transcription factor A (TFAM) [Garrido et al., 2003]. TFAM is the major protein of these complexes and is important for the regulation of mtDNA copy number, mtDNA packaging, and maintenance [Alam et al., 2003; Ekstrand et al., 2004; Kanki et al., 2004; Kaufman et al., 2007].

THE 'LIGHT AND DARK SIDE' OF MITOCHONDRIAL FUNCTION

ATP Production

Adenosine triphosphate (ATP) is the molecular currency of energy transfer in a cell. The major consumers of ATP within the cell include the sodium potassium pump and macromolecular synthesis including protein synthesis, DNA replication, and transcription [Buttgereit and Brand, 1995; Wieser and Krumschnabel, 2001]. ATP is produced by mitochondria as a result of sequential reactions through the electron transport chain, which generate a proton gradient that is harvested by the F1F0 ATP synthase. During this process, electrons liberated by the oxidation of nicotinamide adenine dinucleotide (NADH) and/or $FADH_2$ during metabolism of nutrients in the TCA cycle are transferred to complex I (NADH dehydrogenase or NADH:ubiquinone oxidoreductase) or from succinate to complex II (succinate dehydrogenase or succinate:ubiquinone oxidoreductase). A pair of electrons is donated to ubiquinone (coenzyme Q), which then is reduced to ubisemiquinone and then to ubiquinol. Electrons from ubiquinol are transferred to complex III (ubiquinone:cytochrome *c* oxidoreductase or the bc_1 complex), which transfers them to complex IV (cytochrome *c* oxidase, COX) through cytochrome *c*. The final acceptor of the electrons is oxygen, which through a four-electron addition, is reduced to water.

ROS and mtDNA Damage

During the ETC, electrons are occasionally captured by oxygen to produce superoxide anion radicals ($O_2^{\bullet-}$). Within the mitochondria, these superoxide radicals are converted to hydrogen peroxide by the action of manganese superoxide dismutase. Hydrogen peroxide in the mitochondria is broken down to water by the action of glutathione peroxidase or peroxiredoxins (Fig. 1). Former estimates based on isolated highly energized mitochondria have suggested as much as 2–4% of the oxygen consumed by mitochondria is liberated as superoxide or hydrogen peroxide [Boveris et al., 1972]. More recent studies as well as extrapolation to whole cells suggest that these early estimates are too high, and it has been estimated that mitochondrial under normal physiological cellular conditions probably produced one to two orders lower amounts of reactive oxygen species (ROS) [St-Pierre et al., 2002; Murphy, 2009]. Complexes I and III have been demonstrated to be the main sites of superoxide [Brandon et al., 2006]. Because superoxide is negatively charged, it cannot cross the inner mitochondrial membrane, whereas hydrogen peroxide is freely diffusible and its release into media has been used to show dysfunctional mitochondria [Santos et al., 2003]. Careful analysis of the topology, in which superoxide is generated, has indicated that as much as 30% of the superoxide generated at complex III is in the inner membrane space, whereas 70% is generated in the matrix [St-Pierre et al., 2002]. It is of interest to note that in 2000, McLennan and Esposti demonstrated that when the complex II activity is inhibited ~80% by carboxin, a potent inhibitor of this complex, a decrease of mitochondrial ROS production is observed [Brandon et al., 2006]. It would therefore appear that complexes I, II, and III are all capable of generating ROS during oxidative phosphorylation (OXPHOS).

Besides the antioxidant enzymatic activities mentioned earlier, cells have nonenzymatic (GSH, vitamin E, vitamin C, and ubiquinone) scavengers to protect them against ROS. However, in certain conditions of high-radical production or lower antioxidants, often found in pathological conditions, these increased ROS can then affect cell integrity, oxidizing proteins, lipids, and DNA. The result of an imbalance between ROS production and antioxidant action is called oxidative stress [Ott et al., 2007; Scherz-Shouval and Elazar, 2007] and is reviewed in more detail by Jones in this issue.

mtDNA is more susceptible to oxidative damage than nuclear DNA [Yakes and Van Houten, 1997; Mandavilli et al., 2002]. We and others have proposed that chronic mtDNA damage causes a vicious cycle of ROS production and serves to amplify oxidant injury during disease

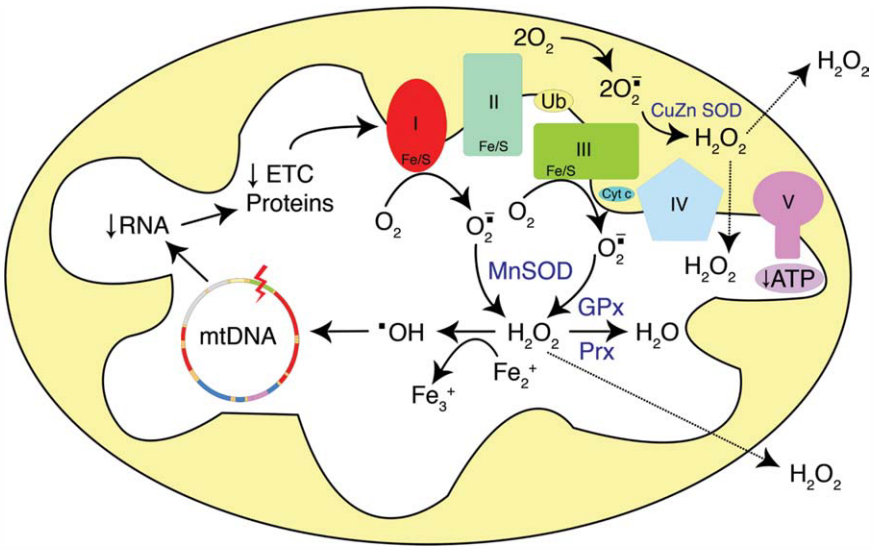

Fig. 1. Schematic model of mitochondrial ROS production. During mitochondrial respiration, a small amount of the molecular oxygen consumed by cells is converted into superoxide anion ($O_2^{\bullet-}$) by complexes I and III as toxic by-products of OXPHOS. Superoxide dismutase (SOD) enzymes (MnSOD and CuZn SOD) convert $O_2^{\bullet-}$ to hydrogen peroxide (H_2O_2), which can be sequentially converted into H_2O by glutathione peroxidase (GPx) or peroxiredoxin enzymes. Also, H_2O_2 can react with Fe^{2+} to generate a hydroxyl radical ($^{\bullet}OH$). This radical can attack all molecules including mtDNA and consequently cause a decrease in mitochondrial mRNA and altered expression of mitochondrial proteins essential for ETC and ATP synthesis. Defects in mitochondrial proteins affect ETC activity culminating in a vicious cycle of ROS production. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

[Ishii et al., 2006; Van Houten et al., 2006; Ott et al., 2007] (Fig. 1.). Damaged mtDNA causes a decrease in transcription and the synthesis of the 13 polypeptides associated with the electron transport [Ballinger et al., 1999, 2000]. This inhibition of ETC proteins can cause a subsequent increase in ROS resulting in a decrease in the mitochondrial membrane potential, loss of ATP, and energy collapse and subsequent cell death [Mandavilli et al., 2002; Santos et al., 2003]. Thus, mitochondrial dysfunction and ROS are intimately linked in a cellular death spiral that underlies a large number of human pathologies [Van Houten et al., 2006]. The following sections provide evidence that dysfunctional mitochondria, alterations in mitochondrial dynamics, increased ROS, mtDNA damage, and the loss of energy production are important contributors to the pathophysiology associated with several neurodegenerative diseases and cancer.

MITOCHONDRIA AND NEURODEGENERATIVE DISEASES

Neurodegenerative diseases are associated with neuronal death and progressive loss of synapses in vulnerable areas in the brain and spinal cord. The major effects of these illnesses are memory loss, emotional alterations, problems with body balance, and movements. Neurodegenerative diseases are a consequence of genetic mutations and/or environment factors and are strongly associated with age [Mandemakers et al., 2007; Jellinger, 2009]. After years of intense studies, a considerable amount evidence has accumulated that demonstrates an important role of mitochondrial dysfunction and oxidative stress to development of the more common neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) [Enns 2003; Mandemakers et al., 2007; Sas et al., 2007; Gogvadze et al., 2009; Jellinger, 2009].

Alzheimer's Disease

According to the Alzheimer's Association, Alzheimer's disease (AD) is the most common form of age-related neurodegenerative disorders and is responsible for the majority of cases of dementia (www.alz.org) [Ott et al., 1995; Cotter, 2007; Kester and Scheltens, 2009]. This cognitive impairment is the result of progressive neuronal loss in the cortex and hippocampus, combined with two brain lesions: the accumulation of senile plaques composed by amyloid-β (Aβ) and neurofibrillary tangles (NFT) is made of hyperphosphorylated protein tau (Fig. 2).

Genetically, AD can be classified as either familial or sporadic. Familial forms of AD usually occur at an early age of onset (before 60–65 years) and are quite rare, ultimately responsible for less than 2% of all AD cases [Jakob-Roetne and Jacobsen, 2009]. These autosomal–dominant forms are caused by mutations in three genes related to Aβ-peptide proteolysis: *APP*, *PSEN*1, and *PSEN*2. *APP* encodes for amyloid precursor protein (APP) that, after sequential cleavage by β- and γ-secretases, generates Aβ-peptide. *PSEN*1 and *PSEN*2 encode

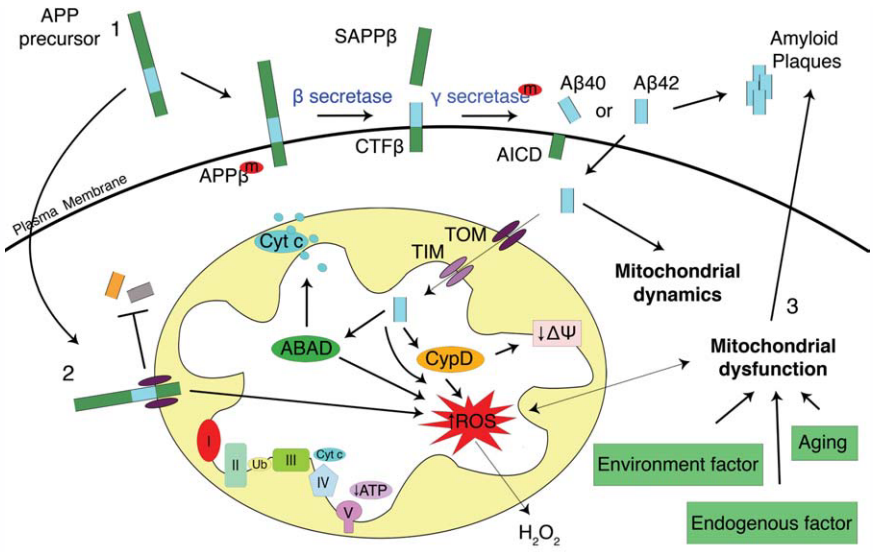

Fig. 2. Alzheimer's disease (AD) and mitochondria. Possible mechanisms that lead to mitochondrial dysfunction in AD. (**1**) Autosomal inheritance hypothesis for AD development. This hypothesis states that mutations of the APP precursor or γ secretase genes (PS1 and PS2) lead to the accumulation of the Aβ40 and Aβ42 peptides and subsequent formation of amyloid plaques. Aβ42 and Aβ40 peptides can go into the cell and interfere with mitochondrial dynamics. Also, these peptides can be translocated into the mitochondria and cause several problems. Aβ can interact with Aβ-binding alcohol dehydrogenase (ABAD) promoting a cytochrome c release. Aβ interaction with cyclophilin D (CypD) promotes a decrease mitochondrial membrane potential. Aβ alone or in association with ABAD or CypD increase ROS production. (**2**) APP precursor has a mitochondrial target sequence; thus, it can be translocated into mitochondria. However, if its translocation is impaired, APP will block the TOM channel preventing translocation of other proteins. This impairment can increase ROS production, which can affect mitochondrial function (see Fig. 1). (**3**) Moreover, mitochondrial dysfunction caused by increased ROS levels, environment/endogenous factors, and/or aging can cause amyloid plaques deposition. In this way, mitochondrial dysfunction is the basis for the sporadic hypothesis for AD. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

for presenilin 1 (PS1) and presenilin 2 (PS2) polypeptides, respectively, both components of the γ-secretase complex [Moreira et al., 2006; Bertram and Tanzi, 2008; Jakob-Roetne and Jacobsen, 2009]. Mutations in these genes lead to the accumulation of the Aβ42 peptide as an intraneuronal and extracellular species resulting in early amyloidosis of the brain. Aβ42 peptide is the long form of Aβ and is considered more toxic than the short-form Aβ40 [Burdick et al., 1992]. Aβ deposition is the basis for the amyloid hypothesis [Hardy and Higgins, 1992; Selkoe, 2000], which states that Aβ formation is the first pathological event to AD, triggering a cascade of inflammatory response, oxidative injury, and synaptic dysfunction with neurotransmitter deficits leading to dementia. In this way, mitochondrial dysfunction is a secondary consequence. However, the amyloid hypothesis cannot be applied to the sporadic form of AD, because patients with this common type of disease do not present mutations on *APP*, *PSEN*1, or *PSEN*2 genes. The sporadic form of AD is caused by environmental and/or endogenous factors and manifests late in life [Baloyannis, 2006; Bertram and Tanzi, 2008]. In 2004, Swerdlow and Khan [2004] proposed a hypothesis to explain sporadic AD. The authors state that sporadic AD is not caused by the accumulation of Aβ, but instead is a consequence of a decline in mitochondrial function with age. These impaired mitochondria eventually reach a functional threshold that triggers several events such as Aβ deposition, synaptic loss, and degeneration and NFT formation [Moreira et al., 2006; Swerdlow and Khan, 2009].

Some studies have suggested that Aβ can contribute to the functional impairment of mitochondria in AD. APP has a mitochondrial-signal sequence that targets the peptide to mitochondria, but its incomplete translocation and accumulation on the mitochondrial membrane leads to an oxidative dysfunction [Anandatheerthavarada et al., 2003]. As mentioned earlier, APP is cleaved to Aβ by the action of the γ-secretase complex, also identified within mitochondria [Ankarcrona and Hultenby, 2002; Hansson et al., 2004]. Aβ can directly interact with Aβ-binding alcohol dehydrogenase (ABAD), promoting a release of cytochrome *c* and an increase in ROS production [Lustbader et al., 2004]. Aβ can interfere with mitochondrial membrane potential through interaction with cyclophilin D (CypD), a component of the mitochondrial permeability transition pore (mPTP). The process of CypD translocation from the mitochondrial matrix to the inner membrane triggering the opening of the mPTP is induced by ROS generated by Aβ itself or by Aβ-ABAD interaction [Lustbader et al., 2004; Du et al., 2008]. However, Aβ-CypD interaction per se increases the production and accumulation of ROS, forming a vicious cycle.

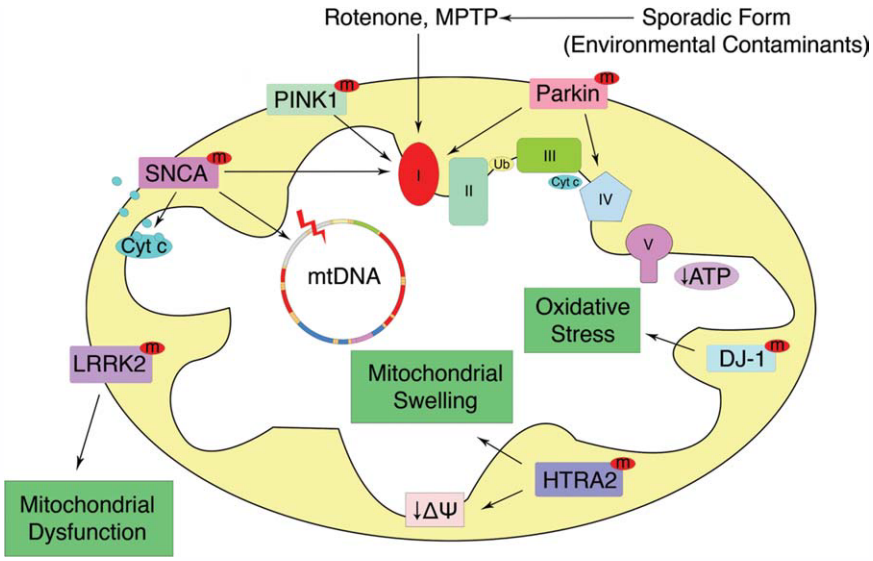

Fig. 3. Parkinson's disease (PD) and mitochondria. Sporadic form of PD is attributed to environmental contaminants. Substances like rotenone and MPTP inhibit complex I and cause Parkinson-like symptoms, suggesting an important role for this complex in PD. Mutations in several genes (SNCA, PINK1, Parkin, DJ-1, HTRA2, HTRA2, and LRRK2) associated with familiar forms of PD are found to affect mitochondrial function. Mutations in the SNCA gene promotes complex I dysfunction, cytochrome c release, and mtDNA mutations. Abnormal PINK1 gene is associated with a decrease in complex I activity. Mutated Parkin affects complex I and IV. Mutation in the DJ-1 gene leads to an increase in the oxidative stress. Dysfunction in the HTRA2 protein was correlated to a decrease in membrane potential as well as mitochondrial swelling. Mutated LRRK2 was found to lead to mitochondrial dysfunction. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Zhu and colleagues [Wang et al., 2008] showed another way that Aβ could interfere with mitochondrial function by altering its dynamics. Using M17 cells, the authors demonstrated that overexpression of Aβ causes an alteration in the mitochondrial fission and fusion proteins. They observed a decrease in DLP1 and optic atrophy 1 (OPA1), an increase in Fis1, and no alterations in Mfn1 and Mfn2 levels. DLP1 and Fis1 proteins are required for mitochondrial fission, whereas OPA1, Mfn1, and Mfn2 are required for mitochondrial fusion. This imbalance between fusion and fission proteins results in mitochondrial dysfunction, mitochondrial fragmentation, an increase in ROS and ATP production, and reduced mitochondrial membrane potential. In this case, APP-induced mitochondrial dysfunction is apparently initiated by mitochondrial fragmentation, which contributes to a vicious cycle of ROS generation [Wang et al., 2008].

Parkinson's Disease

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder after AD [George et al., 2009; Naoi et al., 2009; Winklhofer and Haass, 2009]. Pathologically, it is characterized by the extensive and progressive loss of dopaminergic neurons in the substantia nigra pars compacta as well as an accumulation of intraneuronal inclusions (Lewy bodies) in the surviving neurons. Patients with PD exhibit motor abnormalities including resting tremor, gait difficulties, postural instability, and rigidity in addition to nonmotor symptoms such as depression, cognitive, and autonomic problems [Hardy et al., 2006; D'Amelio et al., 2009].

Despite intense study, the possible cause(s) of PD is still unknown since about 90% of the cases are probably caused by environmental toxins and are not linked to a specific genetic mutation [George et al., 2009]. However, several lines of evidence have linked mitochondrial dysfunctions and oxidative stress with PD (Fig. 3). The first evidence of chemically induced Parkinsonian syndrome was shown in 1983, when drug addicts developed rapid onset PD-like symptoms after injecting heroin contaminated with 1-methyl-4-phenyl-1,2,3,6-*tetra*-hydropyridine (MPTP) [Langston et al., 1983]. MPTP blocks complex I [Langston et al., 1983; Vila and Przedborski, 2003] of the ETC and also promotes cytochrome *c* release from the inner membrane [Perier et al., 2005; Banerjee et al., 2009; George et al., 2009]. Studies using two pesticides [rotenone and paraquat (PQ)], commonly used in farming, have shown an association linking them with dopaminergic alterations in humans [Jones and Miller, 2008]. Rats continually exposed to rotenone, a complex I inhibitor, presented similar characteristics to PD, as dopaminergic degeneration and formation of α-synuclein (SNCA)-positive cytoplasmic aggregate in

nigral neurons [Betarbet et al., 2000; Sherer et al., 2003]. PQ, an herbicide MPP^+-analog also used in animal models, causes degeneration of dopaminergic neurons, dopamine depletion, and increased production of oxidative stress [Cicchetti et al., 2005; George et al., 2009].

About one tenth of all PD cases can be traced to both dominant and recessive mutations in six nuclear genes encoding proteins that can interact with mitochondria [DiMauro and Schon, 2008]. The dominantly inherited genes are SNCA encoded by PARK1/PARK4 and LRRK2 (dandarin) encoded by PARK8. Three-point mutations have been identified in the SNCA gene: A53T, A30P, and E46K; in addition, gene duplication and triplication are involved with PD. SCNA, the major component of Lewy bodies, has a natural tendency to form aggregates, and the mutations as well as the gene amplification seem to enhance such characteristics [Gasser, 2009]. Studies suggest that oxidative damage to SNCA enhances its aggregation potential and causes subsequent cell death [Dalfo et al., 2005; Henchcliffe and Beal, 2008]. SNCA mutations seem to promote severe damage in mtDNA and mitochondrial function [Martin et al., 2006; Henchcliffe and Beal, 2008; Shavali et al., 2008]. Mutations in the LRRK2 gene are the most common cause of Mendelian PD [Henchcliffe and Beal 2008; Gasser, 2009], despite the fact that a link between clinical phenotype and these mutations has not been established [Yao and Wood, 2009]. However, its association with the mitochondrial outer membrane suggests a possible role of LRRK2 in mitochondrial dysfunction [Henchcliffe and Beal, 2008; Yao and Wood, 2009].

Parkin, PINK1, DJ-1, and Omi/HTRA2 are the genes associated with autosomal recessive PD and are localized in mitochondria. Mutations in *PARK2*, which encodes the parkin protein, are related to early-onset development of PD. Parkin is a E3 ubiquitin ligase associated with the mitochondrial outer membrane that has been suggested to play a role in mitochondrial morphology [Poole et al., 2008] as well as complex I and IV activity [Muftuoglu et al., 2004; Palacino et al., 2004]. Mutations in *PARK6*, the gene that encodes for PINK1, are the second most common mutations found in PD. PINK1 is a mitochondrial kinase; however, its substrates are still unknown [Valente et al., 2004]. PINK1 seems to be a neuroprotective molecule against apoptosis [Petit et al., 2005], and PINK1 dysfunction promotes a decrease in complex I activity and increase in oxidative damage [Henchcliffe and Beal, 2008]. DJ-1 is encoded by *PARK7* and is responsible protection of neurons from oxidative stress [Winklhofer and Haass, 2009]. Omi/HTRA2 is a serine-protease, encoded by PARK13, that is localized to the mitochondrial intermembrane space. Besides PD, Omi/HTRA2 is also associated to AD once it can interact with presenilin-1 and AD-associated amyloid β [Gray et al., 2000; Park et al., 2004].

Huntington's Disease

Huntington's disease (HD) is a progressive neurodegenerative disorder, which differs from AD and PD in that it is exclusively caused by a genetic factor. HD is inherited as autosomal dominant disorder and is one of the nine diseases generated by abnormal expansions of an unstable CAG trinucleotide repeat sequence encoding a polyglutamine (polyQ) tract [Gatchel and Zoghbi, 2005]. The CAG repeat within the N-terminal region of the huntingtin protein, encoded by the *HD* gene, causes a conformational change in the protein, leading to neurological impairments [Imarisio et al., 2008]. The CAG repeat is common to all individuals, but the number of repeats is what determines the pathology of HD. The CAG distribution in normal people is from 10 to 26 and in HD patients is from 40 to 80 [Myers, 2004]. Also, the age of onset for HD is related to the length of the CAG repeat, where individuals, presenting 60 or more repeats, manifest HD symptoms early, at age 20 or younger [Myers, 2004; Andresen et al., 2007]. HD is characterized by involuntary movements and cognitive and psychiatric decline arising from neuronal loss in the caudate and putamen of the striatum and cortex [Vonsattel and DiFiglia, 1998].

Mitochondrial dysfunction has been strongly linked to HD development (Fig. 4). For example, a decrease in glucose metabolism in the basal ganglia and cerebral cortex in HD patients was detected by positron emission tomography (PET) [Kuwert et al., 1990; Andrews and Brooks, 1998]. In the same region of the brain, elevated lactate production was seen [Reynolds et al., 2005; Browne, 2008], and, in muscles, there was a reduction in ATP production [Lodi et al., 2000]. Some groups observed a reduction in the enzymatic activity of aconitase, pyruvate dehydrogenase (PDH), succinate dehydrogenase, and cytochrome oxidase. Furthermore, an analysis of postmortem HD brain showed reduced activity in complex II, III, and IV of the electron transport chain [Brennan et al., 1985; Gu et al., 1996; Browne et al., 1997; Benchoua et al., 2006].

Experiments using 3-nitropropionic acid (3-NPA), an irreversible inhibitor of succinate dehydrogenase, suggest that defects in complex II can contribute to the pathophysiology of HD [Brouillet et al., 2005]. 3-NPA has been shown to cause an increase in ROS production and subsequent increase in damage to mtDNA, but not nuclear DNA in PC12 cells [Mandavilli et al., 2005]. When complex II was blocked by constant administration of 3-NPA, rats and nonhuman primates presented degeneration in the striatal neurons, mimicking the HD phenotype in humans [Beal et al., 1993; Brouillet et al., 1995, 2005; Acevedo-Torres et al., 2009; Damiano et al., 2010]. Furthermore, in both a 3-NPA model and a CAG repeat mouse model of HD, increased ROS damage and mtDNA damage were observed [Acevedo-Torres et al., 2009]. This data strongly

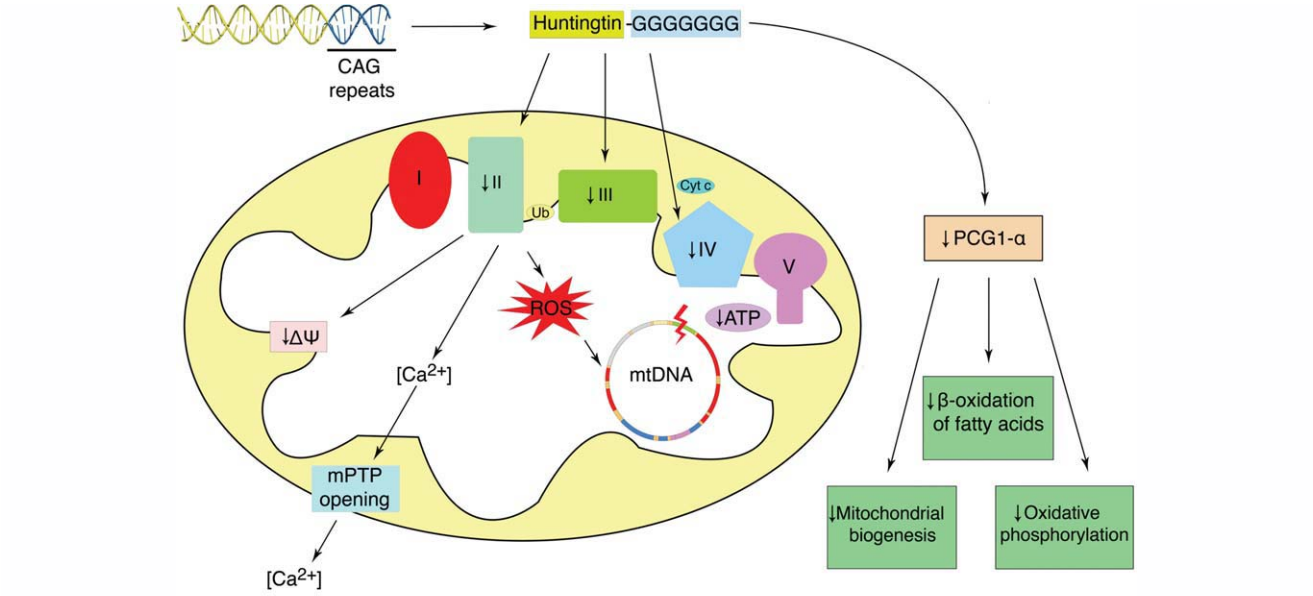

Fig. 4. Huntington's disease and mitochondria. HD is caused by an abnormal expansion of CAG repeats in the N-terminal region of *HD* gene that encodes huntingtin (htt) protein. A conformational change in htt can cause a direct effect of mitochondrial function through a decrease in activity of mitochondrial complexes II, III, and IV. An impairment of complex II affects the mitochondrial membrane potential and mPTPs, promoting a mitochondrial depolarization by Ca^{2+} release. Also, defects in complex II can trigger ROS production that can generate damage to mtDNA and initiate a vicious cycle of damage (see Fig. 1). Indirectly, an abnormal htt interfere with mitochondrial metabolism and mitochondrial biogenesis by repressing PGC-1α gene transcription. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

suggests that increased ROS, mtDNA damage, and mitochondrial dysfunction all contribute to HD. The sensitivity to 3-NPA also seems to be proportional to CAG repeats. Treatment with 3-NPA caused a higher rate of cell death in SH-SY5Y neuroblastoma cells overexpressing huntingtin with 82 repeats when compared with cells with just 23 repeats [Ruan et al., 2004].

Brouillet and coworkers showed that a decrease in complex II/succinate dehydrogenase (SDH) activity is not related to mitochondrial loss once levels of other subunits of mitochondria complex did not change, but is due to the presence of polyQs in the N-terminal of the huntingtin protein. They also showed that defects in complex II/SDH activity could cause a decrease in mitochondrial membrane potential, corroborating other studies [Benchoua et al., 2006]. The results obtained by Ruan and coworkers [2004] cited earlier suggest that the cell death observed in SH-SY5Y cells overexpressing mutated huntingtin is not caused by apoptosis, but by mitochondrial calcium overload, the opening of mPTPs, and the loss of mitochondrial membrane potential. Using lymphoblast mitochondria from HD patients, Greenamyre and colleagues observed a reduced mitochondrial membrane potential in these mitochondria when compared with control mitochondria. Also, the CGA repeat number seems to interfere with mitochondrial depolarization, because the Ca^{2+} amount needed to depolarize mitochondria from a patient with 65 repeats was smaller than one needed for 46 repeats and for the control. The same results were obtained in experiments using HD transgenic mice [Panov et al., 2002].

Another way that huntingtin can interfere with mitochondrial metabolism has also been proposed. In 2006, Krainc and coworkers [Cui et al., 2006] showed that mutation in this protein represses proliferator activator receptor γ coactivator-1 α (PGC-1α) gene transcription, a protein that regulates some metabolic process such as β-oxidation of fatty acids, mitochondrial biogenesis, and oxidative phosphorylation [Puigserver et al., 1998]. The relation between HD and PGC-1α was first suggested by Spiegelman and coworkers using PGC-1α knockout mice [Lin et al., 2004], where the authors observed that these mice displayed behavior alterations and lesions in their striatal neurons similar to those found in HD. A few months later, a similar result was reported by Kelly and coworkers [Leone et al., 2005].

In summary, studies presented in this section have demonstrated how mitochondrial dysfunction is intimately linked to several neurodegenerative diseases and is perhaps a direct cause of the disease progression. Oxidative stress, alterations in apoptosis, or impairment of ETC complexes contribute to neurodegenerative diseases, and, in the next section, we will explore how mitochondrial dysfunction and alterations in mitochondrial metabolism contribute to the development of the cancer cell.

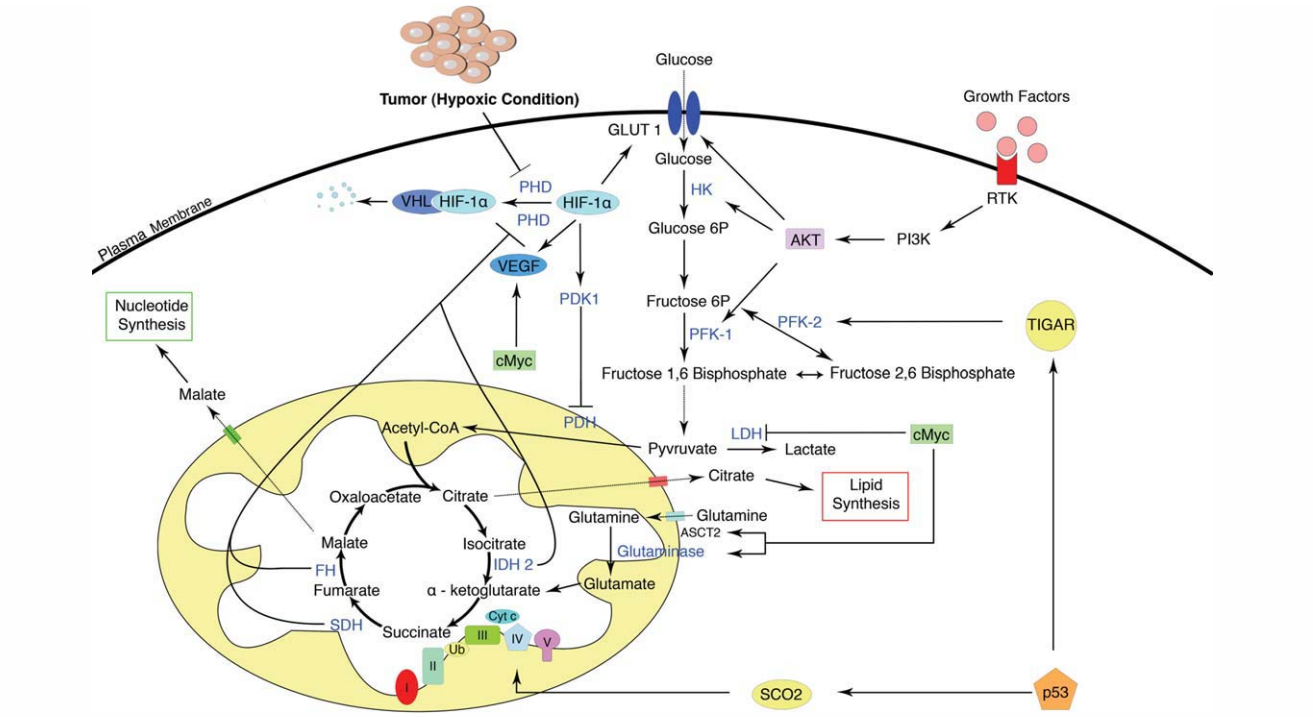

Fig. 5. Metabolic alteration in cancer cells. The rapid growth of tumors cells outstripping their vasculature creates a stressful state of hypoxia that leads to the release of hypoxia-related factors. These factors favor a shift toward a more glycolytic metabolism by the stabilization of HIF-1α and inhibition of PDH. Besides HIF-1α, oncogenes and tumor suppressors also promote a more glycolytic metabolism. c-Myc as well as HIF-1α regulate angiogenesis by the induction in the expression of VEGF. c-Myc can also interferes with glutamine metabolism through the induction of the glutamine transporter ASCT2 and glutaminase. p53, a tumor suppressor, enhances the expression of SCO2, which is necessary for the assembly of COX complex. TIGAR, a gene that inhibits glycolysis by downregulating phosphofructokinase-2 is also under p53 control. Akt also plays a key role in cancer cell metabolic changes. Growth factors activate Akt in a 3-phosphoinoside-inositol dependent-manner and, once activated, can increase the uptake of glucose by directing GLUT1 to the plasma membrane. Moreover, Akt upregulates HK and PFK-1, thus enhancing glycolysis. The fate of some TCA intermediates also varies in cancer cells. Malate and citrate, for example, are allocated to nucleotide and lipid synthesis, to act as building blocks as well as energy production. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

MITOCHONDRIA AND CANCER

At first glance, cancer seems to be an extremely different disease when compared either with PD, HD, or AD. However, as described below in the following sections, some studies have demonstrated several important links between cancer and neurodegeneration.

Warburg Hypothesis

In 1924, Otto Heinrich Warburg made an important discovery that has influenced the field of cancer research. Measuring the metabolism of normal and tumor cells, he observed a higher glucose consumption and higher lactate production by tumor cells even in the presence of sufficient oxygen, suggesting that these cells preferentially use glycolysis to produce ATP [Warburg 1956a,b]. Based on these observations, he proposed that alterations to respiratory capacity generated by mitochondrial impairment could be the origin of cancer. This phenomenon is known as "aerobic glycolysis" or the "Warburg hypothesis" [Warburg 1956a]. The increase in glucose uptake has been demonstrated in many types of tumors by PET using [^{18}F] 2-fluoro-2-D-glucose (FDG), a glucose analog [Mankoff et al., 2007].

Over the years, the Warburg hypothesis has been hotly debated, as his original assumption that the mitochondria are not functional in tumor has been refuted [Pedersen, 1978, 2007]. It is widely accepted that increased glycolytic potential is one hallmark of cancer [Matsumoto et al., 2008; Frezza and Gottlieb, 2009]. The current challenge is to determine whether metabolic changes in tumors are a cause or a consequence of neoplastic transformation [Garber, 2004; DeBerardinis, 2008; Frezza and Gottlieb, 2009].

Metabolic Changes in Cancer Cells

Although it is clear that tumor cells have altered metabolism when compared with normal cells, it is difficult to understand why tumors cells prefer to generate ATP through glycolysis, even though oxygen is still present. Glycolysis, although it produces 16-fold less ATP than

OXPHOS, has a high flux and can rapidly produce ATP, which is required for higher rates of cell growth and proliferation in tumor [DeBerardinis, 2008; Ortega et al., 2009]. It has also been suggested that cancer cells rather than burning the metabolic intermediates in the TCA cycle for energy production use these intermediates as important precursors to macromolecular synthesis. For example, citrate is used to make lipids and malate for de novo synthesis of nucleotides [DeBerardinis, 2008; Deberardinis et al., 2008].

Uncontrolled cell proliferation within a developing tumor often outstrips its blood supply. Consequently, oxygen availability drops, but this physical barrier is not sufficient to deprive cells from glucose [Gillies and Gatenby, 2007]. To cope with the lack of oxygen (hypoxia) and still produce energy, cells switch their metabolism to glycolysis. In addition, a prolonged hypoxic state leads to the stabilization of the hypoxia-inducible transcription factor (HIF-1α), which will help cells adapt to stressful environment by transcribing and synthesizing ~70 hypoxia-related factors [Hsu and Sabatini, 2008; Trayhurn et al., 2008]. HIF-1α is an important regulator of pyruvate dehydrogenase kinase 1 (PDK1). Under hypoxic conditions, HIF-1α induces PDK1 expression that in turn inhibits PDH, responsible for converting pyruvate to acetyl coenzyme A [Kim et al., 2006; Papandreou et al., 2006; DeBerardinis, 2008]. To increase the glucose uptake as a way to compensate for low-ATP yield of glycolysis, HIF-1α promotes the overexpression of the GLUT1 transporter [Airley and Mobasheri, 2007; Trayhurn et al., 2008]. However, HIF-1α is not the only way to regulate glycolysis as mutations in signaling kinases, oncogenes, and/or tumor suppressor genes also have implications on metabolic changes in cancer cells [DeBerardinis, 2008; Hsu and Sabatini, 2008; Yeung et al., 2008].

c-Myc is overexpressed in ~20% of cancers and plays an important role in the proliferation of tumor cells [Prochownik, 2008]. In addition, this oncogene can enhance biosynthesis of precursors and glycolysis [Dang, 1999; DeBerardinis, 2008]. c-Myc also regulates angiogenesis and vasculogenesis, as depletion of this gene in mice is early embryonic lethal and embryonic stem (ES), and yolk sacs cells showed a decrease in vascular endothelial growth factor (VEGF) expression [Baudino et al., 2002]. Studies have been demonstrated that cells use glutamine as a source of glutamate in the TCA cycle [DeBerardinis et al., 2007; Wise et al., 2008; Heiden et al., 2009] and that c-Myc contributes to the regulation of glutamine metabolism. Thompson and coworkers, used shRNA to knock down Myc expression in tumor cells and showed a 80% reduction in glutamine consumption. They also observed that Myc is able to induce the glutamine transporter sodium-dependent neutral amino acid transporter type 2 (ASCT2), LDH-A, and glutaminase, the first enzyme in glutamine metabolism [Wise et al., 2008]. Lazebnik and coworkers observed that glutamine, but not glucose depletion, promoted apoptosis in Myc-dependent manner [Yuneva et al., 2007]. These results suggest an increase reliance on mitochondrial TCA cycle in Myc overexpressing cells. In support of this hypothesis, Hockenbery and coworkers have shown that Myc expression may help coordinate metabolic networks and stimulate oxidative phosphorylation to allow rapid entry into the cell cycle [Morrish et al., 2008]. Future studies are necessary to determine how Myc mediates its control over metabolism and the bioenergetics of cells.

In normal conditions, the tumor suppressor protein p53 induces apoptosis, cell-cycle arrest, DNA repair, and senescence in response to cellular stress [Bensaad and Vousden, 2007]. In this way, under hypoxia conditions, the loss of p53 function can be an advantage to tumor cells. Interestingly, p53 is found to be the most mutated or deleted gene in ~50% of all solid tumors [Royds and Iacopetta, 2006]. In 2006, Hwang and coworkers described a link between p53 and mitochondrial respiration, where p53 loss favors glycolysis [Matoba et al., 2006]. They showed a proportional decrease in oxygen consumption in $p53^{+/+}$, $p53^{+/-}$, and $p53^{-/-}$ cells, a fact that was observed in mitochondria from mice liver and in isogenic human colon cancer HCT116 cells. Serial analysis of gene expression showed that p53 induced the gene, synthesis of cytochome c oxidase 2 (SCO2), which is necessary for the assembly of the mitochondrial COX II subunit into the COX complex. Therefore, it has been suggested that the lack of p53 interferes with ETC assembly, promoting a shift in cancer cell metabolism to a more glycolytic state [Matoba et al., 2006]. Besides the *SCO2* gene, p53 also regulates TP53-induced glycolysis and apoptosis regulator [Bensaad et al., 2006]. This gene indirectly inhibits glycolysis by downregulating fructose-2,6-bisphosphate levels, an allosteric regulator of phosphofructokinase-1 (PFK-1). In this way, cells with mutant or inactive p53 have a higher level of glycolysis and escape hypoxia-induced apoptosis [Corcoran et al., 2006; Young and Anderson, 2008].

Three isoforms of serine/threonine kinase acute transforming retrovirus thymoma (Akt) are found in humans: Akt1 (Aktα), Akt2 (Aktβ), and Akt3 (Aktγ). These three proteins play an important role in cellular processes such as cell proliferation, metabolism, and apoptosis [Manning and Cantley, 2007]. Akt is activated by insulin and growth factors in a phosphatidylinositol 3-kinase-dependent manner, followed by phosphorylation of residues T308 and S473 by 3-phosphoinoside-dependent protein kinase 1 and 2, respectively [Shiojima and Walsh, 2002]. Activation of Akt is commonly observed in many cancer cells and believed to help mediate changes in metabolism. Akt, as well as HIF-1α, contributes to increase glucose uptake by directing the glucose transporters GLUT1 and GLUT4 to plasma membrane. In addition, Akt promotes hexokinase I and II translocation to the mitochondrial

outer membrane [Plas and Thompson, 2005; Manning and Cantley, 2007].

mtDNA Mutations and Changes in Mitochondrial Function in Cancer

About a decade ago, two groups independently showed an accumulation of mitochondrial DNA (mtDNA) mutations in colon cancer [Polyak et al., 1998] as well as bladder, head and neck, and primary lung tumors [Fliss et al., 2000]. Since then, a number of reports have shown increased mutations in a large variety of solid tumors and hematological malignancies [Carew and Huang, 2002; Copeland et al., 2002; Brandon et al., 2006].

The current challenge is to determine if the mutated mitochondrial genomes contribute to the tumor progression. Recently, Sidransky and coworkers [Dasgupta et al., 2008] showed that a mitochondrial cytochrome B gene mutation promoted growth of bladder tumor cells both in vitro and in vivo in a xenograft model. They re-engineered a 21-bp cytb deletion mutation to be expressed in the nucleus of either a mouse carcinoma cell line or an immortalized human uroepithelial cell line. The protein was transported to the mitochondria using a mitochondrial leader sequence, where its overexpression caused increase ROS production and increased cell growth through nuclear factor kappa-light-chain-enhancer of activated B cells signaling. They also noted increased glycolysis, and surprisingly cells expressing the mutant cytochrome B gene also showed increased oxygen consumption. Although they were unable to determine whether this increase in oxygen consumption was directly due to alterations in OXPHOS, which would be inconsistent with the Warburg hypothesis.

Using a slightly different approach, Hayashi and coworkers [Ishikawa et al., 2008] used cybrid technology to evaluate the metastatic potential of cells lines derived from Lewis lung carcinoma cell line. They replaced the endogenous mtDNA of P29 cell line that has low-metastatic potential, with the mtDNA from a highly metastatic A11 cell line, and vice versa. Cybrids with A11 mtDNA showed high-metastatic potential, whereas cybrids with P29 lost their potential for metastatic growth. These results suggest that mutations in mtDNA could contribute to alterations in mitochondrial function and metastatic potential in cancer cells. Using the same methodology, Wong and coworkers [Ma et al., 2010] fused 143B rho^0 osteosarcoma cell line with mitochondria derived from different breast cancer cell lines. They observed a decrease in cell viability, oxygen consumption, and reduced activity of mitochondrial complexes, suggesting that dysfunctional mitochondria can also drive the metabolic changes in breast cancer cells. Future studies are necessary to understand the precise events that cause a change in mitochondrial function during the development of a tumor.

CANCER AND NEURODEGENERATIVE DISEASES

Mutations in the TCA Cycle Are Associated with Cancer and Neurodegeneration

Germline mutations in one allele of SDH cause inherited phaeochromocytomas and paragangliomas [Zanssen and Schon, 2005], whereas mutations in both alleles cause a childhood encephalomyopathies [Briere et al., 2005a,b]. Mutations in another TCA enzyme, fumarate hydratase (FH), are also associated with childhood encephalomyopathies and in a heterozygous state cause cutaneous and uterine leiomyomas as well as renal cell carcinomas [Tomlinson et al., 2002]. HIF1-α plays an important role in these two cancer syndromes [Maynard and Ohh, 2007]. Mutations in SHD and FH promote an accumulation of succinate and fumarate, respectively, two TCA cycle enzymes. Succinate is one of the end products of prolyl hydroxylase activity, the enzyme that catalyzes HIF hydroxylation and subsequent degradation by von Hippel–Lindau tumor suppressor protein. Thus, succinate accumulation can block proly hydroxylase function and cause an accumulation of HIF-1α [Gottlieb and Tomlinson, 2005; Dahia, 2006], and the induction of genes involved in tumorigenesis [Gottlieb and Tomlinson, 2005]. Malate accumulation also interferes with prolyl hydroxylase activity, leading to HIF1-α stabilization [Esteban and Maxwell, 2005]. In addition, dysfunction of the TCA cycle promotes an imbalance on ETC leading to ROS production and HIF1-α stabilization [Enns 2003; Gottlieb and Tomlinson, 2005]. In 2008, Kinzler and coworkers [Parsons et al., 2008] identified in glioblastoma a recurrent mutation in the gene that encode for isocitrate dehydrogenase 1 enzyme (IDH1). Similar results were founded in gliomas [Yan et al., 2009] and other types of brain tumors [Balss et al., 2008]. This enzyme catalyzes decarboxylation of isocitrate to α-ketoglutarate, but deficiencies of its activity can stabilize HIF1-α [Thompson, 2009].

Links Between PD and Cancer

As mentioned earlier, a small fraction of PD cases is due to inherited mutations in genes, which may also affect cellular transformation [D'Amelio et al., 2009]. MG63 cells overexpressing SNCA showed a lower protein kinase C activity. After treatment with phorbol ester, protein kinase C activity was restored together with proteasome activity, which stopped cellular differentiation. Also, these cells showed an inverse correlation between cellular levels of SNCA and proteasome activity. These results suggest that SNCA may have a role in tumor differentiation [Fujita et al., 2007]. Other genes, besides SNCA, may also play a role in cancer differentiation. Analysis of loss of heterozygosity in 40 breast and ovar-

ian cancer cells identified the parkin gene region as a hot spot for genomic loss. Furthermore, mutation analysis showed that the expression of parkin is compromised in these breast and ovarian cancer samples. Therefore, a decreased expression of parkin may lead to initiation/progression of cancer [Cesari et al., 2003]. Moreover, Chiba and collaborators observed that the absence of parkin decreases apoptosis and stimulates cell growth, thus promoting hepatic tumor development [Fujiwara et al., 2008]. These studies indicate that parkin may have an important role as tumor suppressor. Ubiquitin carboxyl-terminal esterase L1, a product of PARK-5, is also found to be correlated in several cellular process related to cancer development [D'Amelio et al., 2009]. DJ-1, a protein correlated to a young form of parkinsonism, seems to play a role in tumorigenesis [D'Amelio et al., 2009], besides serum levels against DJ-1 may be used prognostic marker in breast cancer [Le Naour et al., 2001]. PINK1, another protein related to the early onset of PD, has also been showed to be related to cancer, a fact that maybe explained by PINKs role in the regulation of cell cycle [D'Amelio et al., 2009].

The discovery that PD can be caused by mutations in genes that otherwise are associated with cancer, lead to epidemiological studies about a possible correlation between cancer and PD. Those studies suggest that PD patients have an overall lower risk of contracting some types of cancer in comparison with control patients, whereas higher risks for other types of cancer [Driver et al., 2007; D'Amelio et al., 2009]. It has been observed that PD patients have a lower frequency of smoking and nonsmoking-related cancers [Driver et al., 2007; Zanetti et al., 2007; D'Amelio et al., 2009]. Interestingly, smoking it is not a risk factor among PD patients, only among controls. Detoxifying polymorphisms in the enzyme P450 D6 (CYP2D6 polymorphism) are usually correlated with PD, a fact that may lead to an overrepresentation in PD patients, contributing to lower rates observed of smoke-related cancers in PD patients [Elbaz et al., 2002; Driver et al., 2007; Zanetti et al., 2007]. Breast cancer, thyroid cancer, and melanomas have shown to be more common in PD patients [Driver et al., 2007; D'Amelio et al., 2009]. Melanomas may have a higher frequency in PD patients, a fact that some investigators attribute to the use of levodopa in PD treatment. They claim that genetic-susceptible patients may develop melanomas, because levodopa is a substrate to melanin synthesis [D'Amelio et al., 2009]; however, this hypothesis has not yet been experimentally supported [Zanetti et al., 2007]. There is skepticism about the higher percentage of breast cancer in PD patients. Some claim that this is just due to the fact that PD patients are more likely to see a doctor; therefore, they have a higher probability of being diagnosed with another disease.

CONCLUSIONS

Mitochondrial function is important for two major classes of diseases that affect millions of people around the world: cancer and neurodegenerative disorders. Mitochondrial dysfunction has an indisputable role in three major neurodegenerative disorders—Alzheimer's, Parkinson's, and Huntington's disease. Mitochondrial dysfunctional seems to be the cause of sporadic form of AD, whereas inherited forms of AD seem to be a consequence amyloid accumulation. In PD, mitochondria can also be a cause or a consequence, because mutations in nuclear genes that encode mitochondrial proteins or impairment of ETC complex I by environment factors can lead to this disease. Although Huntington's disease is caused by an increase in the number of CAG repeats, its development seems to have a mitochondrial component. Dysfunction of complex II can cause an increase in ROS production and consequential mtDNA damage, which is linked to HD development.

After 70 years, the Warburg hypothesis is again the focus of research to explain cancer development. Alterations of mitochondrial function and, in some cases, a decline in mitochondrial function clearly contribute to neoplastic transformation and/or metastasis. Also, mutations in ETC enzymes as well as alteration in the expression levels of oncogenes and/or tumor suppressor genes can trigger metabolic shifts from OXPHOS to glycolysis, which may contribute to tumor progression. Continued insights into the role of mitochondrial dysfunction in these and other diseases will help in the development of potential targets for drugs and intervention therapies.

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