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FORUM REVIEW ARTICLE

Strategic Role for Mitochondria in Alzheimer's Disease and Cancer

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Abstract

Significance: Detailed knowledge about cell death and cell survival mechanisms and how these pathways are impaired in neurodegenerative disorders and cancer forms the basis for future drug development for these diseases that affect millions of people around the world. ***Recent Advances***: In neurodegenerative disorders such as Alzheimer's disease (AD), cell death pathways are inappropriately activated, resulting in neuronal cell death. In contrast, cancer cells develop resistance to apoptosis by regulating anti-apoptotic proteins signaling via mitochondria. Mounting evidence shows that mitochondrial function is central in both cancer and AD. Cancer cells typically shut down oxidative phosphorylation (OXPHOS) in mitochondria and switch to glycolysis for ATP production, making them resistant to hypoxia. In AD, for example, amyloid-β peptide (Aβ) and reactive oxygen species impair mitochondrial function. Neurons therefore also switch to glycolysis to maintain ATP production and to produce molecules involved in antioxidant metabolism in an attempt to survive. ***Critical Issues***: One critical difference between cancer cells and neurons is that cancer cells can survive without OXPHOS, while neurons are dependent on OXPHOS for long-term survival. ***Future Directions:*** This review will focus on these abnormalities of mitochondrial function shared in AD and cancer and discuss the potential mechanisms underlying links that may be key steps in the development of therapeutic strategies. *Antioxid. Redox Signal.* 16, 1476–1491.

Introduction

Cancer and Alzheimer's disease (AD) are two of the most heinous diseases that continue to take a major toll on the lives of millions of people around the globe. Recent discoveries show an inverse relationship between dementia of the AD type and cancer (15, 135). A lower incidence of cancer diagnosis was detected for individuals with AD and a decreased risk for developing AD was detected for individuals with a cancer history (136), although the reduced risk did not apply to all types of cancer (70). These data suggest that the development of AD and many types of cancers may be related via common molecular mechanisms. For example, excessive apoptosis has been associated with AD, whereas inhibition of apoptosis is associated with cancer.

Mitochondria play essential and diverse roles in the physiology of eukaryotic cells. Besides ATP production, mitochondria participate in numerous intermediate metabolic reactions and play a central role in calcium homeostasis, apoptosis, cell signaling, proliferation, and differentiation. Impairment of mitochondrial functions has been implicated in a wide variety of human diseases (144), including cancer and dementia, suggesting that these two diseases may result from a common basic abnormality despite the different regulation in cell apoptosis, like the two sides of a coin. Reduced brain glucose metabolism, reduced activity of tricarboxylic acid (TCA) cycle enzymes and cytochrome c oxidase (COX), reduced numbers of mitochondria, and accumulation of amyloid-β peptide (Aβ) inside mitochondria are early detectable defects in AD (129). Reduced brain glucose metabolism was recently linked to a maternal family history of AD, again suggesting the involvement of mitochondria (in this case mtDNA) in AD (109).

Cancer cells are typically protected against cellular energetic depression by a phenomenon called the Warburg effect, characterized by suppression of oxidative phosphorylation (OXPHOS) combined with activation of aerobic glycolysis as the main pathway for ATP synthesis (55, 175). Understanding the strategic role of mitochondria in cancer and AD would be important for the development of efficient therapy. In this review, we will focus on the abnormalities of mitochondrial function shared in these diseases and discuss the link in between that could help to keep this coin balanced without falling to one side. Different aspects of AD and cancer will be discussed separately under each paragraph.

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Apoptosis–Caspase Activity

In AD and other neurodegenerative disorders, an inappropriate and excessive degeneration of neurons occur in specific regions of the brain. Several evidences show that apoptotic cell death mechanisms are responsible for the death of these neurons (1, 2, 60, 92). In cancer cells, it is well established that apoptotic signaling pathways are shut down, allowing cancer cells to proliferate and form tumors.

Caspases are a family of cysteine proteases that play essential roles in apoptosis, necrosis, and inflammation. Based on their function, the size of their pro-domain or cleavage specificity, they can be classified into an inflammatory group (caspase-1, -4, and -5) or a group regulating apoptosis. Caspases regulating apoptosis are divided into two classes: initiator caspases (caspase-2, -8, -9, and -10) and effector caspases (caspase-3, -6, and -7). When activated, effector caspases target a broad spectrum of cellular proteins, ultimately leading to apoptosis. Mitochondria are central in apoptotic signaling and in caspase activation. Upon signaling both via the intrinsic (mitochondria-mediated) and extrinsic (receptor-mediated) pathways, cell death proteins (*e.g.,* cytochrome c, Omi/HtrA2, Smac/DIABLO) are released from the intramembrane space, leading to activation of caspase-3. Interestingly, active caspases-3, earlier thought to be exclusively activated during apoptosis, have recently also been shown to be activated in a transient fashion mediating neuronal plasticity, including long-term depression, synaptic reorganization, and neurite retraction in the healthy brain without completion of the apoptotic program (40, 53, 90, 102). Furthermore, caspase-3/7 and caspase-8 have been shown to regulate microglia activation, also without execution of the apoptotic program (19). Therefore, it is suggested that certain cell types (*e.g.,* neurons and microglia) utilize apoptotic signaling pathways to regulate processes such as plasticity or activation. Keeping caspases active in this transient fashion must be heavily controlled to hinder massive caspase activation. At present, little is known about the factors involved in regulation of this process. However, X-linked inhibitor of apoptosis (XIAP) might be one of the players. It has dual functions, both being a potent inhibitor of caspase activation and function as an E3 ubiquitin ligase targeting caspases for degradation (115).

Alzheimer's disease

Several lines of evidence indicate excessive caspase activation in the AD brain, and recently XIAP was shown to be inactivated by nitric oxide (NO) modification (112). Activity of different caspases has been demonstrated in postmortem brain as well, and in the cerebrospinal fluid of sporadic and familial AD patients (1, 2, 60, 92). Moreover, caspase activation and apoptosis have been linked to synaptic loss and neurodegeneration in human AD brain (92, 153). Inhibition of caspase activity has been found to be neuroprotective as demonstrated in the triple transgenic AD mice model lacking pathology when overexpressing anti-apoptotic protein Bcl-2 (137). In addition, caspase cleavage of tau has been shown to induce mitochondrial dysfunction and also to be required for tangle formation *in vivo* (40, 125). Several lines of evidence also suggest a correlation between caspase activation and elevated amyloid-β peptide (Aβ) production (163, 177). We have recently investigated this relationship and demonstrated in an *in vitro* cell model that caspase cleavage of presenilin-1 (PS1) gives rise to an elevation in intracellular Aβ42/Aβ40 ratio (67). PS1 is one of four components of the γ-secretase complex, which together with β-secretase, generates Aβ from the amyloid-β precursor protein (AβPP). Our study proposes that γ-secretase complexes containing caspase-cleaved PS1 alters the cleavage properties of the protease, changing the cleavage preferences of AβPP and resulting in elevation of Aβ42. However, it is not known if this truncation of PS1 also changes the enzymatic activity in respect to other substrates. For example, PS1 has been shown to regulate P53 expression (3) and this regulation is lost by AD-related PS1 mutations generating increased levels of p53 and thereby cell death (94). Furthermore, PS1 also regulates lysosomal proteolysis and autophagy which also has been shown to be compromised by AD-related PS1 mutations (87). Caspase cleavage of PS1 reflects a scenario that may take place in the brain since active caspase-3 and -6, which both can cleave PS1 (77, 168), have been found in the AD brain. This truncation of PS1 accompanied with changed enzymatic property could be of relevance in the development of AD.

Cancer

Evasion of apoptosis is considered to be one of the hallmarks of human cancers and is characterized by the capability to adjust the mitochondria-mediated or the receptor-mediated caspase cascade. Cancer cells have many ways of hindering apoptosis, for example, by upregulating anti-apoptotic genes, including Bcl-2 and Bcl-XL. The anti-apoptotic Bcl-2 protein prevents the release of cytochrome c from the mitochondria (78, 179). Bcl-XL has been shown to interact and maintain VDAC in an open configuration and thereby hinder mitochondria permeability transition (MPT) (150). Furthermore, mutations in the p53 gene, which is one of the genes found to be most frequently mutated in cancer, have been found to silence mitochondrial activity (18, 101) and thereby make the cell less susceptible for mitochondrial-mediated cell death (55). Moreover, mitochondrial dysfunction has also been shown to impair p53 expression and function (32). Thus, through suppression of the mitochondria, cancer cells evolve a resistance to apoptotic cell death. This will be discussed later in this review.

Mitochondrial Dynamics

Mitochondrial function is directly linked to the dynamic properties of mitochondria (117), including mitochondrial fusion, fission, transport, and mitophagy. Abnormalities in mitochondrial dynamics are associated with human diseases such as AD and cancer (28, 30, 58, 62). Mitochondria are dynamic organelles from several aspects. First, they are engaged in repeated cycles of fusion and fission, which serve to mix the lipids and contents of a mitochondrial population. Second, mitochondria are actively recruited to subcellular sites, such as the axonal and dendritic processes of neurons. Finally, the quality of a mitochondrial population is maintained through mitophagy, in which defective mitochondria are selectively degraded. These dynamic processes regulate mitochondrial function and enable mitochondria to adapt readily to changes in cellular requirements.

Alzheimer's disease

Neurons are metabolically active cells with high energy demands at locations distant from cell body. As a result, these

cells are particularly dependent on mitochondrial function, especially on the properties of mitochondrial dynamics. Recent evidence suggests that an imbalance in mitochondrial dynamics may contribute to both familial and sporadic neurodegenerative diseases (172). Abnormal mitochondrial structure (7) and an impaired balance of mitochondrial fusion and fission is found in the AD brain (172). Therefore alterations in mitochondrial dynamics may play a crucial role in the pathogenesis of AD (79). Exposure of neuronal cells in culture to conditioned medium from cells stably expressing mutant forms of AβPP or exposure to synthetic Aβ induces mitochondrial fragmentation and abnormal distribution, which results in mitochondrial fission, loss of dendritic spines, and eventually cell death (9, 140, 173). Recently, it was reported that excessive nitric oxide (NO) production, induced by $A\beta_{25-35}$ exposure, stimulates S-nitrosylation of Drp1 (dynamin-related protein 1). The formation of SNO-Drp1 leads to increased GTPase activity and excessive fission, resulting in mitochondrial fragmentation and neurodegeneration (29, 111). In the same study it was also reported that SNO-Drp1 levels were higher in AD brain and the AD tg2576 mouse model (29). However, these data were recently challenged by Bossy and colleagues showing that SNO-Drp1 did not induce GTPase activity and that SNO-Drp1 levels are not specifically increased in AD brain (14). Also, mitochondrial degradation by mitophagy is suggested to be dysfunctional in AD. Lysosomal proteolysis and autophagy have been shown to require PS1, and AD-related PS1 mutations disrupt this degradation pathway (87). Despite the evidence showing the role of mitochondrial dynamics in AD, the underlying mechanisms remain to be further elucidated.

Cancer

Mitochondrial alternations observed in cancer cells could also be linked to unbalanced mitochondrial fission or fusion events. Since mitochondrial dynamics are essential for preserving the integrity and function of the organelle, it is highly possible that mitochondrial dynamics alternations could participate in tumorgenesis. First, proteins involved in the fusion/fission machinery were recently found to regulate the intrinsic apoptotic pathway and may therefore participate in the resistance of cancer cells to apoptotic stimuli. Bcl-2 family proteins, which regulate mitochondrial permeabilization, functionally associate with mitochondrial fission and fusion proteins, and could thus modulate the morphology of mitochondria. However, the mechanism whereby Bcl-2 family proteins regulate these events remains to be elucidated (6). Second, shaping of mitochondria could impact mitochondrial function and cell metabolism. While mitochondrial fusion and elongation may be associated with increased OXPHOS (139, 181), mitochondrial fission has been suggested to be triggered by OXPHOS dysfunction (12), a hallmark of cancer cells. In addition, mitochondrial dynamics change during normal cell cycle progression (99). It was suggested that alterations of mitochondrial dynamics during cell cycle may contribute to enhancement of ATP supply needed in nuclei during cytokinesis and for proper distribution of mitochondria during cell division (12). While cancer cells lose the control and regulation of cell cycle progression, neuronal cells in AD brain may engage in cell death after the reactivation of the cell cycle (34). It is far from clear whether the abnormality of cell cycle progression is primarily due to defects in mitochondrial dynamics or is the direct consequence of an impairment of energy production (58).

The Roles of AβPP and Aβ

Alzheimer's disease

The amyloid cascade hypothesis states that it is the generation and aggregation of Aβ that initiates the pathological process in AD (98). It is now commonly believed that the oligomeric/fibrillar forms of Aβ cause toxicity to synapses and neuronal degeneration (142). Several evidences point towards a role of Aβ toxicity in mitochondrial dysfunction detected in AD tissue. We and others have shown that Aβ accumulates in mitochondria from postmortem AD brain, in living patients with cortical plaques, and in TgAβPP mice (27, 65, 93, 96). In TgAβPP mice, mitochondrial Aβ accumulation occurs prior to plaque formation, indicating that this is an early event in the pathogenesis (27). *In vitro* studies with isolated mitochondria suggest that $A\beta_{1-42}$ inhibits COX activity in a copper-dependent manner (33). Furthermore, mitochondrial Aβ-binding alcohol dehydrogenase (ABAD) has been found to be upregulated in neurons from AD patients (93) and Aβ has been shown to interact with ABAD, resulting in free radical production and neuronal apoptosis. ABAD is localized to the mitochondrial matrix and has an essential physiological role in mitochondria. It was identified as an Aβ-binding protein in a yeast two-hybrid screen (93). ABAD–Aβ complexes were detected in AD brain and in Tg mutant AβPP/ABAD (Tg mAβPP/ABAD) mice. Cortical neurons cultured from Tg mAβPP/ABAD mice show increased production of ROS and decreased mitochondrial membrane potential, ATP levels, and activity of respiratory chain complex IV. Consistently, these neurons displayed DNA fragmentation and caspase-3 activity resulting in cell death by day 5–6 in culture (160).

Aβ has also been shown to specifically interact with cyclophilin D (CypD), a mitochondrial matrix protein that associates with the inner membrane during opening of the mitochondrial permeability transition pore (mPTP) (43). Cortical mitochondria from CypD-deficient mice are resistant to Aβ- and calcium-induced mitochondrial swelling and permeability transition. Moreover, Tg mAβPP/CypD-null mice had improved learning and memory and synaptic function both in 12- and 24-month-old animals (43, 44).

Recently, it was shown that presequence protease (PreP) is responsible for the degradation of the accumulated Aβ in mitochondria (47). PreP was originally found and characterized in *Arabidopsis thaliana* (155) as a protease degrading targeting peptides that are cleaved off in mitochondria after completed protein import, as well as other unstructured peptides up to 65 amino acid residues in length, but not small proteins (108, 156). Recombinant hPreP completely degrades both Aβ40 and Aβ42, as well as Aβ Arctic protein (E22G) at unique cleavage sites, including several sites in a very hydrophobic C-terminal Aβ (29–42) segment that is prone to aggregation. Interestingly, PreP is an organellar functional analogue of the human insulin-degrading enzyme (IDE), implicated in AD as it cleaves Aβ before insoluble amyloid fibers are formed (84, 143, 161). The importance of PreP in AD was recently strengthened when its activity was shown to be decreased in AD brain (2a).

The presence of Aβ in mitochondria indicates that it is either produced inside mitochondria and/or taken up from the outside. Both AβPP (4) and γ-secretase complexes (64) have been detected in mitochondria and thus it is possible that Aβ is produced locally in mitochondria. This remains however to be proven. AβPP has been shown to accumulate in AD brain mitochondria via arrested import, leaving a large C-terminal part outside (4). Under these circumstances, AβPP is stuck in the mitochondrial protein import pore, consisting of the translocases of the outer (TOM) and inner membrane (TIM), causing impairment of mitochondrial function and eventually cell toxicity. The import of AβPP is arrested due to an acidic domain at amino acids 220–290, leaving the Aβ region outside the import pore. Recent *in vitro* data from our laboratory show that the C-terminal part of AβPP can be inserted into the outer mitochondrial membrane (OMM) and that the mitochondrial γ-secretase cleaves AβPP to generate AβPP intracellular domain (AICD) which was detected in the inter membrane space (122). Since we mainly detected C83 fragments of AβPP, which is the result of α-secretase cleavage, the subsequent cleavage by γ-secretase would produce P3 fragments and not Aβ. Therefore, Aβ is most likely taken up by the mitochondria after vesicular transport within the cell (5). We investigated the mechanisms of Aβ uptake using isolated rat mitochondria treated with Aβ in the absence or presence of antibodies or inhibitors directed to various mitochondrial translocases and pores (65). The uptake of Aβ was not affected by the presence of antibodies directed towards the voltage-dependent anion channel (VDAC) nor in the presence of cyclosporine A which is an inhibitor of the mPTP. Interestingly, import of both $A\beta_{1-40}$ and $A\beta_{1-42}$ was prevented when import competent mitochondria were pre-incubated with antibodies directed towards proteins of the TOM complex (*i.e.*, Tom20, Tom40, and Tom70). Aβ import was not affected by the addition of valinomycin, an ionophore that causes depolarization of the mitochondrial inner membrane, indicating that the Aβ import was not dependent on the ψ_{mit}. After import, Aβ was mostly localized to mitochondrial cristae and associated with the inner membrane fraction. In summary, these data show that Aβ is imported via the TOM complex where Tom 20 and Tom70 are receptors and Tom40 the pore-forming subunit in the OMM.

Cancer

Interestingly, AβPP processing and Aβ also have a role in cancer. It has been reported that AβPP may be related to the malignant progression of human astrocytic tumors (110), and it has been shown that intra-tumoral injection of Aβ potently inhibits the angiogenesis of human glioblastoma and thus inhibits the growth of the tumor (120, 121). The γ-secretase complex is a key enzyme for the generation of Aβ and a target not only for AD but also for human T cell acute lymphoblastic leukemia (89). While chemotherapy increases the activity and expression of the γ-secretase complex, the γ-secretase inhibitor renders colon cancer cells more sensitive to chemotherapy (104). AβPP processing is ubiquitous, and Aβ is produced by almost all types of cells (61), although the highest production is observed in neuronal tissue and neuronal cells (146). Aβ generation may be a defensive consequence of an underlying disease mechanism (126). Investigations by Zhao *et al*. (182) in cultured cells revealed direct inhibition of breast and skin cancer cell proliferation by naturally secreted Aβ from mammalian cells. Various species of Aβ showed different degrees of cellular toxicity, although it was not clear which exact species played the dominant inhibitory effects on the tumor cell proliferation. These findings would suggest that AD patients might be at lower risk for cancer occurrence, although there is no strategy to overcome the risk of having AD by increasing Aβ levels in a hope to decrease cancer development.

Inhibition of mitochondrial energy metabolism alters the processing of AβPP to generate amyloidogenic derivatives (51, 102) and oxidative stress has been shown to increase the generation of Aβ (50, 107, 119). This will link the Aβ levels to cancer. Understanding the mechanism underlying the effects of Aβ on tumor cell proliferation would reveal novel targets for therapeutic interventions of tumor cell growth, in concert with the consideration of AD.

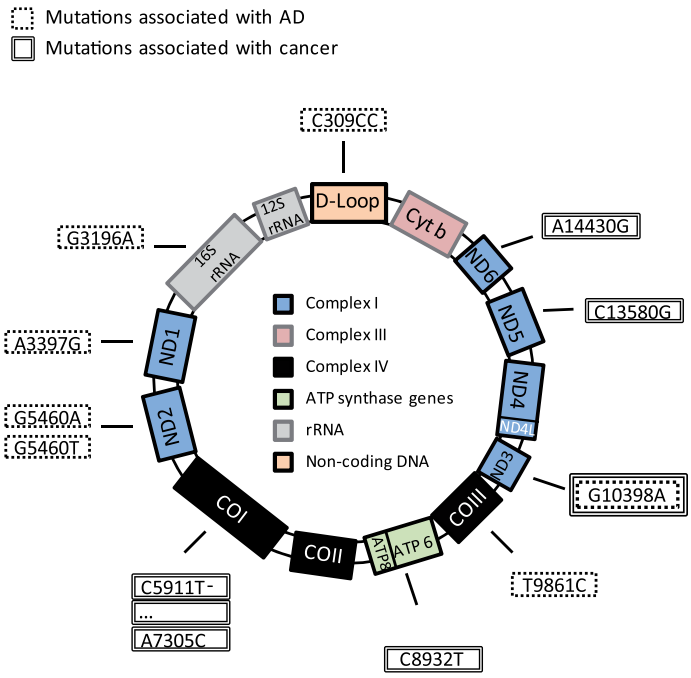
Mitochondrial Genome in AD and Cancer

The prevalence of both cancer and neurodegenerative diseases increase with age. Somatic mitochondrial DNA (mtDNA) mutations occur during cell transformation and aging. MtDNA is more susceptible to oxidative damage than nuclear DNA, partly due to the lack of histones and the production of reactive oxygen species (ROS) inside mitochondria (97, 178). It was found that accumulation of mtDNA mutations is a key mechanism of aging (75). MtDNA mutations can cause alternations in the encoded proteins (167) and may as a consequence compromise the respiratory chain function and stimulate ROS production (71, 72). Reports confirmed that accumulated mtDNA mutations is the cause of subsequent mitochondrial function alternations including oxidative OXPHOS deficiency, ROS overproduction, and finally upregulation or aberration of signaling pathways associated with cell maturation, proliferation, and cell death (10, 24, 35, 42).

Studies on mtDNA mutations have been expanded rapidly in metabolic disease diagnosis. Several somatic point mutations in the human mitochondrial genome database (mitomap.org) have been reported to be associated to cancer or AD (Fig. 1) (91, 154). The mtDNA G10398A polymorphism alters the structure of Complex I in the mitochondrial electron transport chain. African-American and Indian women carrying the 10398A allele have an increased risk for breast cancer (22, 39, 106). However, a fourth study did not support the hypothesis that the mtDNA G10398A polymorphism is a marker for breast cancer risk in African-American women (145). The 10398A allele appears to increase the risk of AD (169) and the 10398G allele decrease the risk for Parkinson's disease (PD) (170). In aging cells, mtDNA accumulates both point mutations and deletions, which could affect cell defense mechanisms. Moreover, the mitochondrial haplogroups with certain inherited SNPs (*e.g.*, the G10398A polymorphism) may predispose individuals more susceptible to certain mitochondrial diseases, such as cancer or AD (8, 26, 127).

Metabolic Alterations

The impact of mtDNA mutations in the aging process has been studied in the prematurely aging mtDNA mutator mice which express a proofreading-deficient version of mitochondrial DNA polymerase γ (POLG), resulting in accumulation of mtDNA mutations, premature aging, and reduced life span (82, 138). In this model, the premature aging phenotypes have been suggested not to be caused by increased levels of ROS (165) and



REGION	MUTATION	AD	CANCER
D-Loop	C309CC	AD weakly associated	
16S rRNA	G3196A	AD/PD	
ND1	A3397G	AD/PD	
ND2	G5460A	AD/PD	
	G5460T	AD	
COI	C5911T		Prostate cancer
	G5913A		Prostate cancer
	A5935G		Prostate cancer
	G5973A		Prostate cancer
	G6081A		Prostate cancer
	G6150A		Prostate cancer
	T6253C		Prostate cancer
	G6261A		Prostate cancer
	G6267A		Prostate cancer
	G6285A		Prostate cancer
	C6340T		Prostate cancer
	G6480A		Prostate cancer
	A6663G		Prostate cancer
	G7041A		Prostate cancer
	T7080C		Prostate cancer
	A7083G		Prostate cancer
	A7158G		Prostate cancer
	A7305C		Prostate cancer
ATPase	C8932T		Prostate cancer
COIII	T9861C	AD	
ND3	G10398A	AD risk factor	Breast cancer
ND5	C13580G		Thyroid cancer
ND6	A14430G		Thyroid cancer

FIG. 1. Mut**ations associated with AD and cancer in the mitochondrial genome.** The double-stranded DNA molecule of the human mitochondria is circular and contains 16,569 nucleotide pairs. It encodes 2 rRNA genes, 22 tRNA genes, and 13 protein-coding sequences. In the schematic picture, the protein-coding sequences, the noncoding region (D-loop), and rRNA genes are shown. Mutations in mtDNA are associated with several different diseases. Here we have summarized point mutations in protein-coding genes, rRNA genes, and D-loop region that have been reported to be linked to AD or cancer according to mitomap.org (http://mitomap.org/bin/view.pl/MITOMAP/MutationsCodingControl, 2011-06-23). cytochrome c oxidase genes, Cyt b; ubiquinol: cytochrome c oxidoreductase gene. ND1-6; NADH dehydrogenase genes, COI-III; (To see this illustration in color, the reader is referred to the web version of this article at www.liebertonline.com/ars).

instead explained by a decline in aerobic respiration caused by random point mutations (45). Recently, Ross and co-workers, using proton magnetic resonance spectrometry, found a twofold increase in brain lactate levels before the appearance of overt aging phenotype in both mtDNA mutator mice and wild-type mice. This elevation was shown to be caused by a metabolic shift from aerobic respiration to glycolytic metabolism, resulting in a change in transcription of lactate dehydrogenase isoforms (increased LDH-A and decreased LDH-B) promoting pyruvate to lactate conversion (138). Studies on MILON and MitoPark mice indicate that neurons can survive only a limited time with dysfunctional mitochondria. In the MILON mice, oxidative phosphorylation was shut down by removal of the mitochondrial transcription factor A (Tfam) in the forebrain (151). At 5–5.5 months of age, neurodegeneration was initiated and progressed rapidly in hippocampus and neocortex, causing death shortly thereafter. In the MitoPark mice, the deprivation of Tfam was restricted to the dopaminergic neurons, resulting in severe respiratory chain deficiency in these neurons accompanied with adult onset of slowly progressive neurodegeneration with parkinsonian phenotype (46). These studies provide evidence for mitochondrial dysfunction caused by age-related accumulation of mtDNA mutations in development of neurodegenerative diseases.

Alzheimer's disease

As discussed above, the inability to utilize energy in a proper way is a major characteristic of aging tissue. Interestingly, this is also seen in AD manifested as glucose hypometabolism (105), insulin resistance, and glucose intolerance (103, 174). The activities of several enzymes in the glycolytic-, TCA- and OXPHOS-pathways are altered in AD or in AD mouse models (Fig. 2). Some enzymes have increased activity (13, 17, 100, 118, 138, 141, 157) while others have decreased activity (13, 17, 23, 49, 134, 147, 148, 157, 162, 180), although controversy exists (Table 1). Recent findings imply that protein modifications, including carbonyl, 3-nitrotyrosin, 4-hydroxy nonenal (HNE), and S-glutathionyl, could regulate the activity of the metabolic enzymes. Many of these modifications result in significant inhibition of enzyme activity (20, 59, 123, 131, 132, 158) and are therefore suggested to be involved in the dysregulation of metabolic pathways in AD (Fig. 2). The brain has a high energy demand, and since 15 times more energy is produced from respiration as compared to glycolysis, OXPHOS is the main pathway used for energy production. Neurons can utilize glucose, lactate, and ketone bodies as energy sources (73, 74). Cellular energy production is highly regulated, keeping the activities of glycolysis, TCA, and respiration integrated through feedback inhibition via ATP (Pasteur effect) and citrate controlling the rate of glycolysis. During hypometabolism (as is the case in AD brain), the brain cells will elicit compensatory mechanisms, increasing the activity of glycolytic proteins to override transient energy deficits and hypoxic environment. The transcription factors hypoxia-inducible factor-1α (HIF-1α) and c-MYC affect the activity of glycolytic enzymes, glucose transporters (GLUTs), and the pentose phosphate pathway (PPP) (36, 164). For

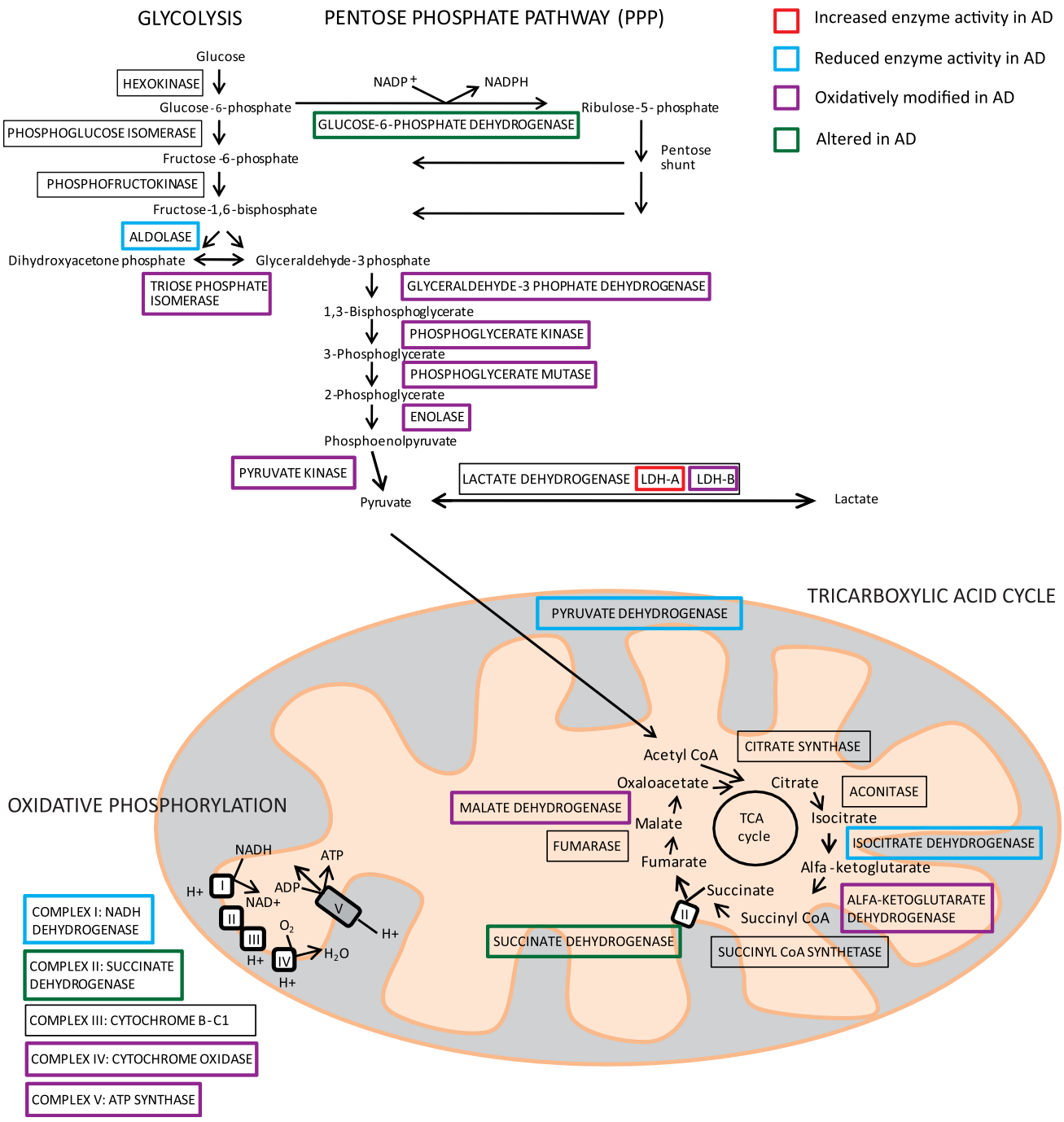


FIG. 2. Enzymes in the energy metabolism that are altered in AD. (To see this illustration in color, the reader is referred to the web version of this article at www.liebertonline.com/ars).

example, C-MYC elevates mRNA levels of several glycolytic enzymes, including GLUT1, phosphofructokinase, and enolase in order to restore energy deficits or oxygen deprivation (116). However, increased c-MYC activity could also have devastating consequences for neurons, since it could drive postmitotic neurons into cell cycle re-entry and thereby cause cell death (86). Interestingly, nonprocessed PS1 inhibits the expression of c-MYC (128) and in case of PS1-FAD mutation the control of neuronal cell cycle is lost (95). Furthermore, PS1 is suggested to be involved in the regulation of HIF-1. Fibroblast lacking PS1 or expressing the M146V PS1 FAD mutation had an impaired metabolic induction of HIF-1 (41).

Increased glycolytic activity requires increased GLUTs. GLUTs are stored in cytoplasm, regulated by HIF-1, and recruited to plasma membrane upon demand. From the blood, glucose is transported over the blood-brain barrier (endothelial cells and astrocytes) via GLUT1 transporter and subsequently transported into neurons via GLUT3 (4, 8). HIF-1 has been shown to be activated upon Aβ exposure, resulting in a shift from OXPHOS to glycolysis and PPP (152). This shift

Table 1. Summary of Cellular Pathways Altered in Alzheimer's Disease and Cancer

Mechanisms	*Pathways*	*Enzyme*	*AD*	*Cancer*
Metabolism	General glucose metabolism		↓(109)	↑(55)
	General glycolytic activity		↓(20, 131-132)	↑(55, 57, 80, 133)
		Hexokinase		↑(55)
		Phosphofructokinase		↑(55)
	Glycolysis	Triose phosphate isomerase	↑(157) Ox-modification (59)	
		Glyceraldehyde 3 phosphate dehydrogenase	↓(147) ↑(157) Ox-modification (20)	
		Phosphoglycerate mutase	↓(157) Ox-modification (158)	↑(80, 133, 171)
		Enolase	↑(157) Ox-modification (21, 132, 158)	↑(83)
		Phosphoglyceratekinase	Ox-modification (131)	
		Pyruvate dehydrogenase	↓(17, 180)	↓(55)
		Pyruvate kinase	↑(13) Ox-modification (131)	↓(31)
		Aldolase	↓(157)	
		Lactate dehydrogenase	↑(13, 138) Ox-modification (131)	↑(48, 57, 69, 76, 85, 149)
	PPP		↑(100, 118, 141), ↓(13)	
	TCA cycle enzymes	Isocitrate dehydrogenase	↓(17)	↓TCA activity (55, 88)
		Alf a-ketoglutarate dehydrogenase	↓(17) Ox-modification (148)	
		Succinate dehydrogenase	↑(17) ↓(49)	↓(55)
		Malate dehydrogenase	↑(17) Ox-modification (132)	
	General OXPHOS activity		↓(23, 49, 134, 180)	↓OXPHOS (55, 88, 101)
	OXPHOS	Complex I	↓(134)	
		Complex II	↑(17) ↓(49)	↓(55)
		Complex IV	↓(23, 134) Ox-modification (131)	↓(55)
		ATP synthase	↓(162) Ox-modification (131)	↓(55)
Calcium homeostasis	Calcium regulation		Aberrant (68, 81, 166)	Aberrant (124)
Oxidative stress	Oxidative stress		↑(100, 118, 123, 141),	↓↑ (55, 85)
Cell death	Caspase activity		↑(1-2, 52, 60, 92)	↓(78, 179)
	Apoptosis		↑(92, 102, 112, 153)	↓(55, 78, 130, 179)
Mitochondrial dynamics	Fisson		↑(14, 29, 79, 111, 140, 172-173)	↑(6, 12, 58)

Arrows indicate if enzyme activity is increased (↑) or decreased (↓). Reference numbers are indicated in parentheses.
OXPHOS, oxidative phosphorylation; PPP, pentose phosphate pathway; TCA, tricarboxylic acid cycle.

protects against oxidative stress; however, as a consequence it will increase the sensitivity to glucose starvation. Recently, neuronal cells that utilize the Warburg effect were shown to be resistant to Aβ toxicity (113). Also, HIF-1 activity has been shown to prevent neuronal death after exposure to mitochondrial toxins (114). In the PPP pathway, glucose-6-phosphate dehydrogenase is the rate limiting enzyme and is activated in AD (100). PPP produce reducing power in form of NADPH that can be used to regenerate antioxidant systems, including glutathione reductase and thioredoxin reductases. Both oxidative stress and Aβ have been shown to shift glycolysis to PPP. However, PPP is dependent on glycolysis and might not be as effective later on in AD when damage to glycolytic enzymes occur.

Recent data from Suzuki and colleagues supports the hypothesis that glycolysis is not enough for neuronal viability and survival in the long run (159). This study emphasizes the importance of lactate in synaptic plasticity. Lactate is produced by astrocytes (from glucose or glycogen metabolism) and transported to the neurons via monocarboxylate

transporters. The inhibition of these channels either on the astrocyte or neuronal side caused impairment of long-term potentiation (LTP), substantiating the importance of a functional oxidative metabolism in neuronal plasticity (159).

Cancer

Multiple mechanisms for controlling the balance between mitochondrial and glycolytic ATP production have also been reported in cancer cells (Fig. 3). Many enzymes in the glycolytic pathway have increased activity (57, 69, 85, 133) whereas the activities of several enzymes in the TCA cycle and respiratory chain are decreased (55, 76, 101) (Table 1). The metabolic shift from OXPHOS to glycolysis is primarily based on the activation of HIF-1α, driven by specific oncogenes such as RAS, Src, HER-2/Neu, c-MYC, and p53 that are activated in response to diverse stresses (38, 48, 101). Activated c-MYC upregulates the LDH-A isoform (48, 149), whereas activated RAS, Src, and HER-2/Neu trigger induction of glycolytic enzymes through stabilization of HIF-1α. Both HIF-1α and c-MYC induce expression of PDK1 that suppress OXPHOS by decreasing the activity of pyruvate

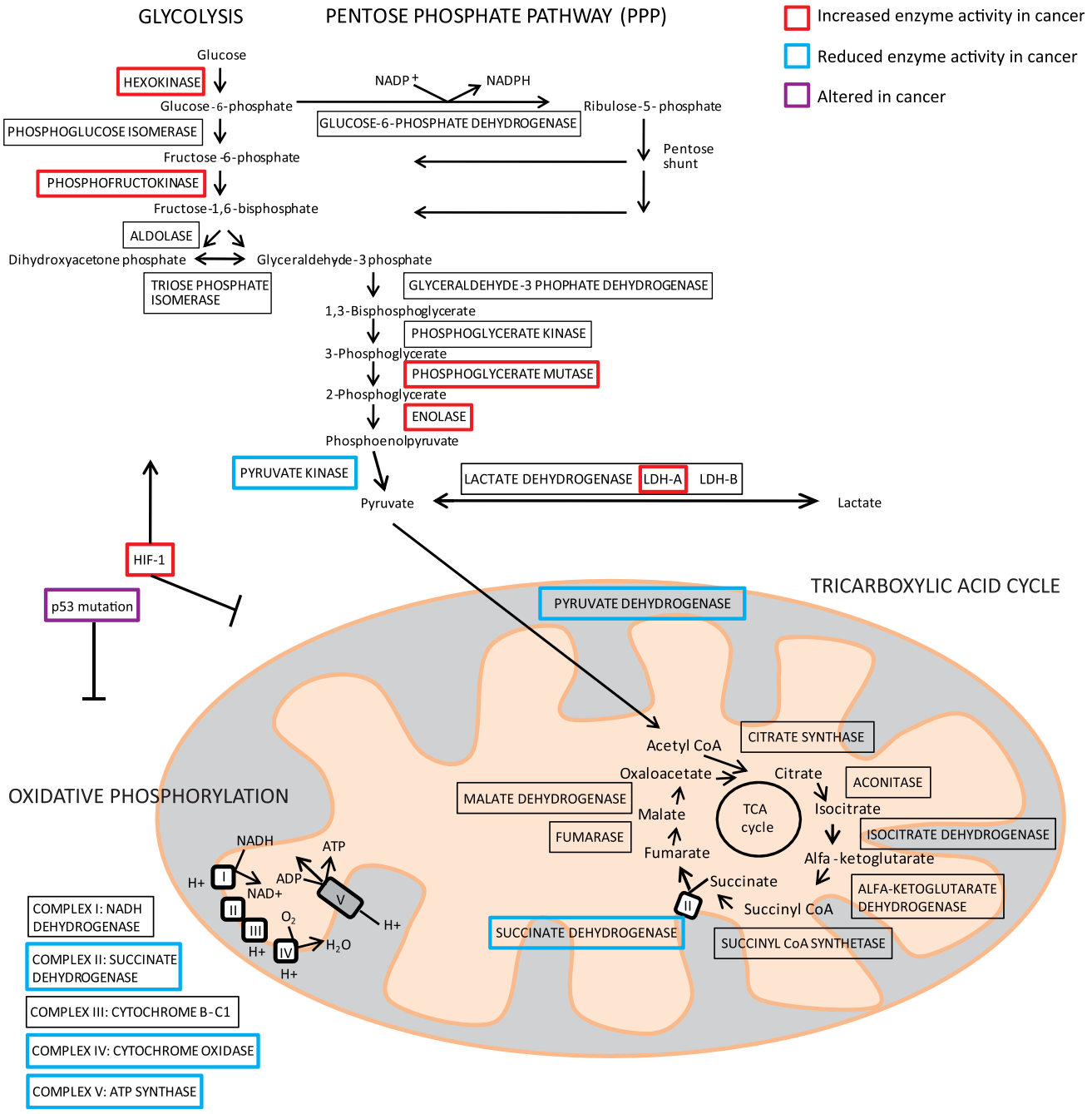


FIG. 3. Enzymes in the energy metabolism that are altered in cancer. (To see this illustration in color, the reader is referred to the web version of this article at www.liebertonline.com/ars).

dehydrogenase (37). Suppression of OXPHOS and activation of glycolysis are feed-forward processes. All these HIF-1α-mediated mechanisms strongly promote carcinogenesis in different cell types.

P53-mediated pathways are of importance to promote the metabolic shift (80, 88, 101). Normally, activation of p53 leads to stimulation of OXPHOS and mitochondrial respiration (101), thus acting as a negative regulator of glycolysis (80, 88). In cancer cells, p53 functions are more or less lost due to the mutations, among many consequences, resulting in impaired coordination between OXPHOS and glycolysis (80, 88). Finally, the impairment of the coordination can be stimulated by changes in cytoplasmic adenine nucleotides, as energy stress activates the AMP-kinase through increased AMP in the cytoplasm, stimulating biosynthesis of glycolytic enzymes in cancer cells. Since mitochondria also play a central role in triggering and establishing apoptosis, by skipping the dependence of mitochondria, cancer cells appear to attenuate or even switch off the mitochondria-dependent pro-apoptotic mechanisms.

Oxidative Stress

As discussed above, mtDNA mutations accumulate when the endogenous antioxidant systems are overwhelmed and the levels of ROS and reactive nitrogen species (RNS) increase in the cell. ROS are generated mainly in the mitochondria but also by the NADPH oxidase (NOX) and oxidative enzymes in ER as well as xanthine oxidase (11, 56, 66). The main production of ROS occurs during OXPHOS where up to 2% of the electrons passing through the electron transport chain, mostly at complex I and complex III, react with oxygen and yield superoxide anions ($^{\cdot}O_2^-$) which then can be converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD). The presence of Fe^{2+} accelerates the decomposition of H_2O_2 to hydroxyl radicals ($^{\cdot}OH$), and nitric oxide ($NO^{\cdot}$) reacts with $^{\cdot}O_2^-$ to produce peroxynitrite ($ONOO^{\cdot}$). Mitochondria are at the same time the major source of ROS production and the major target of ROS damage. The mitochondria are particularly susceptible to damage and have a mutation rate estimated to be 10 to 20 times higher than that of the nuclear DNA. The sensitivity of mtDNA is due to the lack of protective histones and the limited repair mechanisms (16). For protection, the inner mitochondrial membrane (IMM) incorporates a number of free radical scavengers, such as vitamin E, ascorbate, and glutathione. There is also enzymatic removal of free radicals by MnSOD in the mitochondria and by SOD1 in the cytoplasm. All the13 genes in the mitochondrial genome are essential for execution of normal OXPHOS. Therefore, maintenance of integrity of mtDNA with age is critical for the survival of individuals since breakdown of the mitochondrial genome would cause severe problems. Nevertheless, in the aging process the mitochondrial pool weakens due to accumulation of mitochondrial DNA mutations. Some of the effects seen after mitochondrial damage include decreased energy production, altered mitochondrial distribution, increased production of ROS accompanied by increased oxidative stress, decreased calcium buffering, and induction/inhibition of apoptosis.

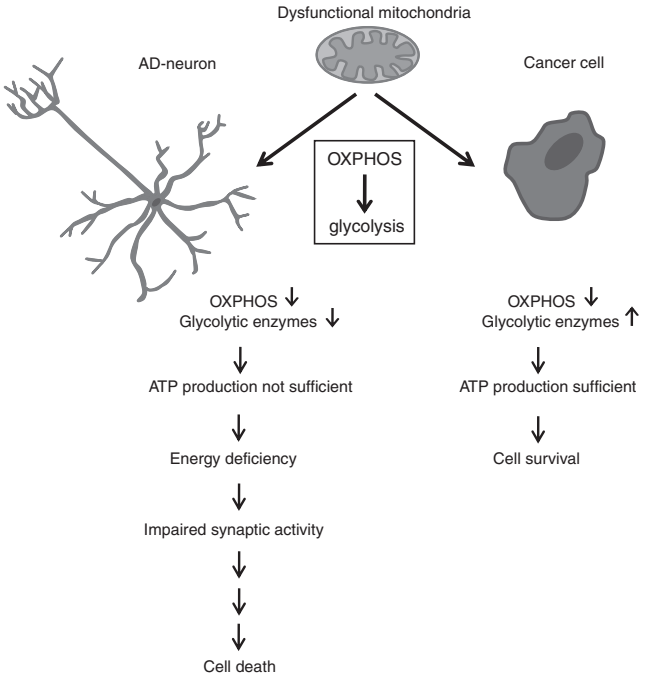


FIG. 4. Schematic hypothetic illustration of the consequences of dysfunctional mitochondria in AD and cancer pathology.

Alzheimer's disease

Neurons are vulnerable to oxidative insult since they have a high rate of energy and oxygen utilization, poor concentrations of classical antioxidants, high levels of redox active metals, and high content of polyunsaturated lipids. Damage to mitochondria in neurons is detrimental since there is limited or no regeneration/replacement capacity of neurons in the brain. Dysfunctional mitochondria could therefore result in loss of brain function in, for example, AD where neurons gradually degenerate. It is possible that the shift from OXPHOS to glycolysis that occurs in AD neurons temporally can provide enough ATP to keep neuronal function. However, the brain has a high energy demand, and decreased glucose uptake in AD brain in combination with dysfunctional mitochondria may eventually result in synaptic failure and neuronal loss.

Cancer

Unlike cell death caused by oxidative stress or calcium overload or other mechanisms that are induced by suppression of mitochondrial ATP synthesis in neurodegenerative diseases, cells in cancer shift the metabolism from OXPHOS to glycolysis. In this way cancer cells gain tolerance to hypoxic microenvironment, ability to control ROS levels, and avoidance of apoptosis. Cancer cells thus has a great advantage over normal cells which assures their viability, autonomous growth, migration, and chemoresistance (25, 63, 130, 176, 183).

Conclusion

Basic research suggests that the development of AD and of many cancers may be related via one or more common molecular mechanisms (Table 1). Both AD and cancer involve disruption of physiologic cell death programs and signaling pathways that associate with mitochondrial structure,

dynamics, and function. A metabolic shift from OXPHOS to glycolysis occurs in both diseases (Fig. 4). We hypothesize that since the activities of several OXPHOS and glycolytic enzymes are impaired in specific AD brain neurons, the ATP production in these neurons is not sufficient for proper synaptic function and neuronal survival. This means that a shift from OXPHOS to glycolysis in AD neurons would only be a transient attempt to rescue neurons. Cancer cells shut down OXPHOS and mitochondria-mediated apoptotic signaling, making them resistant to apoptotic cell death and independent of mitochondrial ATP production. The activities of glycolytic enzymes are increased in cancer cells, and the ATP produced is sufficient for cell survival. In both types of diseases, the mitochondrial function is impaired, the difference is that cancer cells evolve to survive without OXPHOS while neurons can neither function properly nor survive without OXPHOS.

Potential drug targets for both neurodegenerative disorders and cancer include mitochondria, glycolytic enzymes, glucose transporters, and proteins involved in apoptotic signaling. Moreover, both ROS and Aβ toxicity have been linked to these disorders and highly considered as targets for drugs already tested in clinical trials. In this review, we have discussed the strategic role of mitochondria in AD and cancer. Increased understanding of the role of mitochondria in these devastating diseases would open new possibilities for drug development.

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Abbreviations Used

Aβ = amyloid-β peptide
AβPP = Aβ precursor protein
ABAD = Aβ-binding alcohol dehydrogenase
AD = Alzheimer disease
COX = cytochrome c oxidase
Drp1 = dynamin-related protein 1
FAD = familial AD
HIF1 = hypoxia inducible factor 1
IMM = inner mitochondrial membrane
MPT = mitochondrial permeability transition
mtDNA = mitochondrial DNA
OMM = outer mitochondrial membrane
OXPHOS = oxidative phosphorylation
PD = Parkinson disease
PPP = pentose phosphate pathway
PreP = presequence protease
PS1 = presenilin-1
ROS = reactive oxygen species
TCA = tricarboxylic acid