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REVIEW

The pyruvate dehydrogenase complex as a therapeutic target for age-related diseases

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Summary

Considerable research has been conducted on mitochondrial biology as it pertains to aging. However, relatively little attention has been accorded the pyruvate dehydrogenase complex (PDC) relative to how we grow old and acquire age-related diseases. The purpose of this review is threefold: first, to describe the physiological chemistry of the PDC and define its place in normal cellular bioenergetics; second, to compare and contrast the pathogenesis and clinical features of congenital PDC deficiency with discrete examples of age-associated dysfunction of the complex; and third, to summarize recent findings in *Caenorhabditis elegans* that shed additional new light on the significance of the PDC to the aging process.

Key words: aging; Alzheimer's disease; *Caenorhabditis elegans*; cancer; dichloroacetate; glucose intolerance; mitochondria; pyruvate dehydrogenase complex.

Introduction

Interest in the association between mitochondrial dysfunction and the pathobiology of aging and age-related disorders has only waxed since the free radical theory of aging was posited over half a century ago (Harman, 1956). Modern interpretations of this theory emphasize the importance of genetically or environmentally induced disruption of mitochondrial electron transport and inadequate antioxidant defense mechanisms in causing abnormal accumulation of damaging reactive oxygen species (ROS) (Balaban *et al.*, 2005). Indeed, the term 'mitochondrial disease' is most commonly applied to congenital or acquired defects in the terminal steps of oxidative phosphorylation (OXPHOS) embodied in the five complexes of the respiratory chain of enzymes (DiMauro *et al.*, 2006). These complexes, comprised of nuclear DNA and mitochondrial DNA-encoded proteins, enable the stepwise transfer of electrons from reducing equivalents (NADH and $FADH_2$) to molecular oxygen and result ultimately in the synthesis of ATP. Less frequently considered is the impact of more proximal steps in mitochondrial fuel metabolism that can dramatically influence the generation of free radicals and energy. Prominent among these early mitochondrial reactions is that catalyzed by the pyruvate dehydrogenase complex (PDC), which functionally links glycolysis in the cytoplasm to OXPHOS in the mitochondrion.

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The pyruvate dehydrogenase complex

The PDC is distributed heterogeneously within the mitochondrial matrix (Margineantu *et al.*, 2002) and catalyzes the irreversible oxidation of pyruvate to acetyl CoA (Fig. 1). The reaction is rate-limiting under aerobic conditions for the oxidative removal of glucose and pyruvate and for other 3-carbon metabolites (alanine and lactate) in equilibrium with pyruvate. As befitting such a critical gatekeeper enzyme, the PDC is highly regulated. Rapid changes in catalytic activity are achieved primarily by reversible phosphorylation by PDC kinases (PDKs) and phosphatases (PDPs). Humans possess at least four PDK and two PDP isoforms that are expressed differentially among tissues (Linn *et al.*, 1969; Bowker-Kinley *et al.*, 1998). End products of the PDC-catalyzed reaction, acetyl CoA and NADH, each increase the activity of PDKs, leading to phosphorylation and inactivation of the PDC, as does a rise in intramitochondrial ATP. In contrast, pyruvate inhibits PDK activity as do several halogenated xenobiotics that are structurally similar to pyruvate. One of these analogs, dichloroacetate (DCA), has been used extensively in the laboratory and clinically to modulate PDC activity (reviewed in Stacpoole, 2011). In turn, the activity of PDPs may be positively regulated by insulin and by magnesium and calcium ions.

Congenital PDC deficiency

It may not appear intuitively obvious why a treatise on the PDC's role in aging should include a discussion of the fate of children born with loss-of-function mutations in the complex. However, the natural history of congenital PDC deficiency (reviewed in Patel *et al.*, 2011) and the biochemical concomitants of this rare disease provide insight into the clinical presentation and underlying mechanisms of many age-related disorders. Several cardinal clinical features of PDC deficiency are remarkably similar to those associated with aging. For example, neurocognitive and neuromuscular complications, such as mental retardation, hypotonia, ataxia, peripheral neuropathy and exercise intolerance, are common findings in PDC-deficient children and neuroimaging frequently reveals structural brain abnormalities, including cerebral atrophy and ventriculomegaly. No proven therapies exist for congenital PDC deficiency, and most affected patients die within the first two decades of life.

Studies using cultures of skin fibroblasts from patients harboring various mutations in the PDC E1α subunit have shown that these cells exhibit high rates of glycolysis and lactate production compared to similarly treated fibroblasts from healthy donors (Simpson *et al.*, 2006). In PDC deficiency, glucose carbon is diverted from acetyl CoA synthesis to oxaloacetate formation via pyruvate carboxylase, although overall flux through the tricarboxylic (TCA) cycle is reduced. The metabolic abnormalities are reversed on treatment with the prototypic PDK inhibitor DCA. These data indicate that aerobic glycolysis is a prominent feature of PDC deficiency but that, in at least some cases, dephosphorylation of the mutated enzyme can increase residual enzyme activity and shift glucose metabolism from glycolysis toward increased OXPHOS. E1α-deficient cells also accumulate superoxide (O_2^-) from the Qo site of complex III of the

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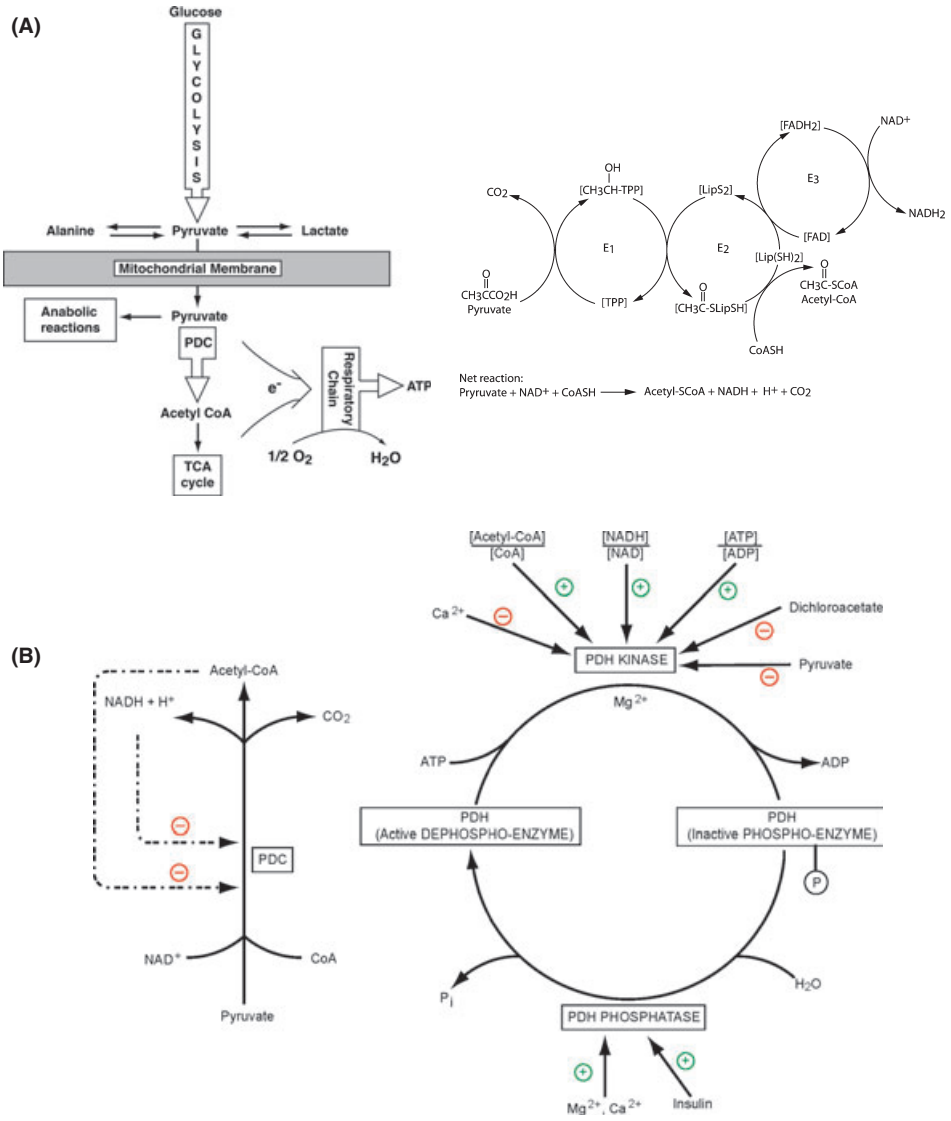

Fig. 1 Panel A – The 9.5M Da eukaryotic complex is organized into multiple copies of 3 enzymatic components (Zhou *et al.*, 2001; Smolle *et al.*, 2006). The heterotetrameric ($\alpha 2\beta 2$) pyruvate dehydrogenase (E1) decarboxylates pyruvate in the presence of thiamine pyrophosphate (TPP). Dihydrolipoamide acetyltransferase (E2) transfers the acetyl group to a lipoic acid moiety that synthesizes up to 60 molecules of acetyl CoA from reduced coenzyme A per macromolecular complex. Reduced lipoate is reoxidized by dihydrolipoamide dehydrogenase (E3) in a coupled redox reaction in which NADH is generated. The pyruvate dehydrogenase complex (PDC) also utilizes an E3 binding protein (E3BP) to tether the E3 component to the complex's core (Brautigam *et al.*, 2006). The net reaction thus provides glucose-derived acetyl CoA for the tricarboxylic cycle and reducing equivalents (NADH) for the respiratory chain or for anabolic reactions, such as lipid synthesis. Five requisite cofactors enable pyruvate oxidation (thiamine; B1) and the synthesis of coenzyme A (pantothenic acid; B5), acetyl CoA (lipoic acid), and NADH (riboflavin; B2 and niacin; B3). The gene for the E1α subunit is located on the X chromosome, and all components of the complex are nuclear encoded. Panel B – Rapid regulation of the PDC is mediated primarily by reversible phosphorylation of up to three serine residues on the E1α subunit, rendering the complex inactive. Phosphorylation of E1α is facilitated by a family of four pyruvate dehydrogenase kinase isoforms (PDK 1–4), whereas two pyruvate dehydrogenase phosphatase isoforms (PDP 1 and 2) dephosphorylate, and activate, the PDC. PDKs themselves are activated by a rise in the intramitochondrial ratio of acetyl CoA:CoA and NADH:NAD^+, as well as by an increase in cellular energy charge (ATP:ADP). Pyruvate and certain structurally related halogenated analogs, such as dichloroacetate (DCA), inhibit PDK activity. PDPs are positively regulated by insulin or magnesium ions and PDP1 can be activated by calcium ions. PDK and PDP isoforms are differentially expressed in tissues and PDK isoforms exhibit variable sensitivity to pyruvate and DCA (Bowker-Kinley *et al.*, 1998).

respiratory chain. Pathological accumulation of $O_2^{\cdot-}$ may be due mainly to its underutilization, because the activity of mitochondrial manganese superoxide dismutase (MnSOD) is also reduced in PDC-deficient cells (Glushakova *et al.*, 2011). A particularly intriguing and unexpected finding in PDC-deficient fibroblasts was the overexpression of hypoxia inhibitory factor 1α (HIF1α). HIF1α transactivates numerous genes involved in critical pathways of cell metabolism, growth and survival (Gordan *et al.*, 2007; Semenza, 2011), including those encoding glucose transporters and most glycolytic enzymes. It also transactivates PDK (Kim *et al.*, 2006), thereby down-regulating the PDC and OXPHOS. Together, HIF1α's effects on glucose metabolism provide crucial insight into the molecular mechanisms of the Warburg effect, a phenomenon first described in tumor cells almost a century ago (Warburg, 1930). The mechanism for HIF1α overexpression in PDC deficiency is unknown, although ROS generated by complex III are thought to be required for activation of HIF1α under conditions of hypoxia (Klimova & Chandel, 2008). In addition, glycolytic metabolites, such as pyruvate, stabilize HIF1α by inhibiting its degradation by cytoplasmic prolyl hydroxylases (Lu *et al.*, 2005), creating a positive feedback loop

whereby HIF1α activity in PDC deficiency is maintained by increased glycolytic flux. Regardless of the precise mechanism, HIF1α overexpression may contribute to the Warburg effect operative in PDC-deficient cells and to further inhibition of residual PDC activity.

Congenital defects in the PDC and respiratory chain enzymes share many common clinical features (Patel *et al.*, 2011; Scaglia *et al.*, 2004). Thus, it could be argued that acquired PDC deficiency is no more relevant to the aging process than acquired pathological changes in other OXPHOS enzymes. However, what distinguishes the PDC is evidence that mitigation or reversal of the phenotype in several age-related disorders, such as glucose intolerance (Stacpoole *et al.*, 1978), ischemia–reperfusion injury or heart failure (Bersin & Stacpoole, 1997), pulmonary arterial hypertension (Bonnet *et al.*, 2006), neurodegeneration (Stacpoole, 1997) and cancer (Archer *et al.*, 2008), is achievable by therapeutic targeting of the complex. Each of these conditions is pathologically distinct, yet, together, find common ground as disorders of metabolic integration in which PDC dysregulation figures prominently, as described more fully by the following examples.

Glucose intolerance

Blood glucose concentration is maintained within well-defined limits by mechanisms regulating its uptake, storage, and utilization. Remodeling of glucose metabolism, leading to progressive tissue resistance to insulin action and glucose utilization, is a well-recognized concomitant of aging and contributing environmental factors, such as diet and physical activity. In 1963, Randle *et al.* (1963) proposed a 'glucose-fatty acid cycle' that described fuel selection in mammals and posited a reciprocal relationship between the utilization of glucose and long-chain fatty acids derived from the diet or tissue stores (Fig. 2). Multiple enzyme control points were identified through which the metabolism of glucose or fat imposed inhibitory effects on the oxidation of the other substrate. One such crucial control point is the PDC, whereby NADH, acetyl CoA, and ATP generated by fatty acid oxidation inhibit the complex and contribute to the suppression of mitochondrial glucose oxidation. Since this seminal work, the glucose–fatty acid cycle has undergone extensive scrutiny and revision (reviewed in Hue & Taegtmeyer, 2009), while maintaining the relevance of the PDC as an important factor in the processes of fuel selection and fuel flux.

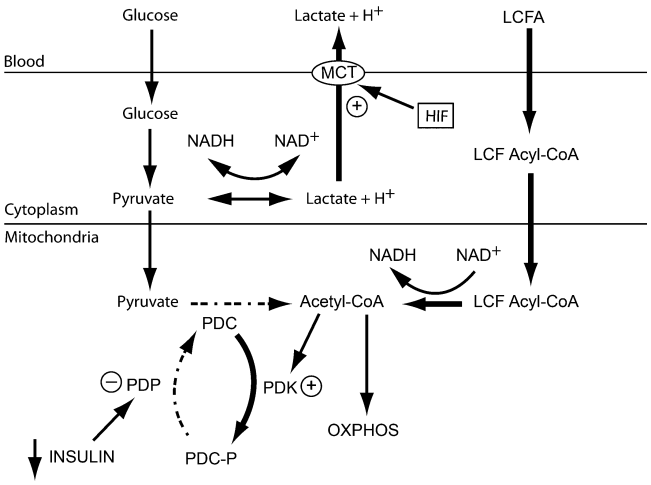

Fig. 2 Metabolic remodeling in glucose intolerance. In aging, an increase in muscle long-chain fatty acid (LCFA) beta-oxidation (β-ox) raises intramitochondrial concentrations of acetyl CoA and reduced nicotinamide dinucleotide (NADH) and contributes disproportionately to tricarboxylic acid cycle flux and oxidative phosphorylation (OXPHOS). The resulting increased ratios of acetyl CoA:CoA and $NADH/NAD^+$ increase the activity of PDK isoforms, particularly in insulin-sensitive tissues, such as skeletal and cardiac muscle, thereby inhibiting the pyruvate dehydrogenase complex (PDC) and contributing to the age-associated decline in peripheral insulin sensitivity. PDC inhibition also increases production of lactic acid, which exits cells mainly by two H^+/lactate monocarboxylate transporters (MCT) 1 and 4, the latter being regulated by HIF1α (Le Floch *et al.*, 2011; Ullah *et al.*, 2006). In addition, decreased insulin secretion by the pancreas and/or insulin action at peripheral tissues may contribute to inhibition of the PDC by decreasing tonic inhibition on PDK and tonic stimulation of PDP, which helps maintain the PDC in its unphosphorylated, catalytically active, form.

In vivo and *in vitro* studies in mammalian skeletal muscle and heart, two tissues in which the glucose-fatty acid cycle is particularly robust (Nuutila *et al.*, 1992), have shown that an age-related decline occurs in the activity of the PDC that may contribute to the metabolic 'inertia' in stimulating aerobic glucose oxidation during the transition from rest to exercise (Gurd *et al.*, 2008), but this transition can be accelerated by pharmacological inhibition of muscle PDK with DCA (Howlett *et al.*, 1999). This finding is consistent with the drug's glucose and lactate-lowering effects in patients with type 2 diabetes mellitus (Stacpoole *et al.*, 1978). Euglycemic insulin clamp experiments in 21- and 71-year-old healthy adults demonstrate increased plasma free fatty acid concentration, lipid turnover, and lipid oxidation but decreased glucose oxidation in elderly subjects at all insulin levels administered (Bonadonna *et al.*, 1994). Not surprisingly, knockout of skeletal muscle PDK4 in mice is associated with improved peripheral glucose tolerance and insulin sensitivity and with increased glucose but decreased fatty acid oxidation in muscle (Jeoung & Harris, 2008). Moreover, the age-related increase in circulating glucose and free fatty acid levels observed in rats parallels the age-related decline in total PDC activity in heart and sarcopenic skeletal muscle (Nakai *et al.*, 1997; Martin *et al.*, 2007). These changes are also associated with an increase in mitochondrial ROS and a decrease in MnSOD activity (Martin *et al.*, 2007), reminiscent of the biochemical abnormalities associated with congenital PDC deficiency. Insulin secretion also requires a coupled PDC-OXPHOS system (Krus *et al.*, 2010), and genetically induced inhibition of beta-cell PDC leads to decreased glucose-stimulated insulin secretion and hyperglycemia (Srinivasan *et al.*, 2010).

Cancer

Cancer is the archetypical disease of aging, with 60% of newly diagnosed cancers found in people over 65 years of age and 70% of cancer-related deaths occurring in this same population (Cancer Trends Progress Report, 2009/2010). Yet, despite its complex biology and protean manifestations, a striking property shared by most cancers is a reliance on aerobic glycolysis to provide the energy required to survive and grow (Gatenby & Gillies, 2004). Warburg originally postulated that mitochondrial defects in fuel metabolism were central to carcinogenesis and tumor progression (Warburg, 1930). Our modern understanding of the molecular mechanisms underlying the relationships between aerobic glycolysis and cancer informs that mitochondrial dysfunction in cancer is potentially reversible. Once again, the PDC is relevant both to the pathogenesis of the Warburg effect in tumors and to its reversal.

Normoxic overexpression of HIF1α in most, if not all, human cancers stimulates glucose uptake, glycolysis, and also PDK, which inhibits the PDC. Consequently, OXPHOS is suppressed and pyruvate accumulates, which stabilizes HIF1α, creating a positive feedback loop between HIF1α and glycolysis (Lu *et al.*, 2002, 2005) that can be reversed by knockdown of PDK (McFate *et al.*, 2008). In a landmark study, Bonnet *et al.* (2007) investigated downstream metabolic consequences of the Warburg effect in various human tumors in cell culture or implanted into nude athymic rats. Compared to normal cells, cancer cells exhibited the expected

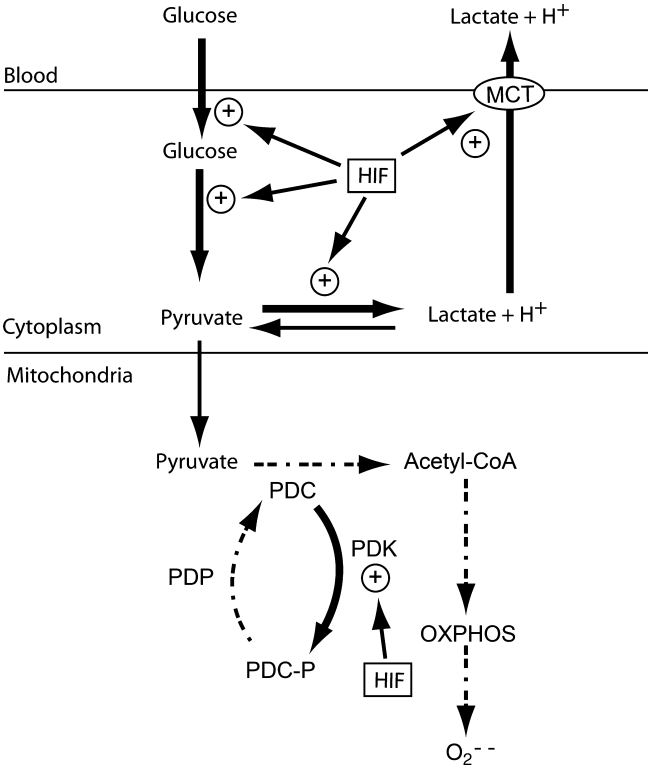

Fig. 3 Metabolic remodeling in cancer. Up-regulation and stabilization of the transcription factor hypoxia inducible factor-1α (HIF1α) provides the molecular mechanism for the Warburg effect in cancer. Up-regulation of HIF-1α increases glucose uptake, glycolysis, and lactate in cytoplasm and activates PDK, inhibiting the pyruvate dehydrogenase complex (PDC) and causing cancer cells to rely on glycolysis for energy, rather than on oxidative metabolism. The reduction in OXPHOS decreases superoxide ($O_2^{\cdot-}$) production by the respiratory chain, resulting in perturbation of redox signaling mechanisms and inhibition of apoptosis (Bonnet *et al.*, 2007; Archer *et al.*, 2008). In addition, MCT 1 and 4 allow cellular egress of lactate and protons, thereby reducing tumor acidosis and promoting tumor survival. MCT4 is regulated by HIF1α (Le Floch *et al.*, 2011; Ullah *et al.*, 2006).

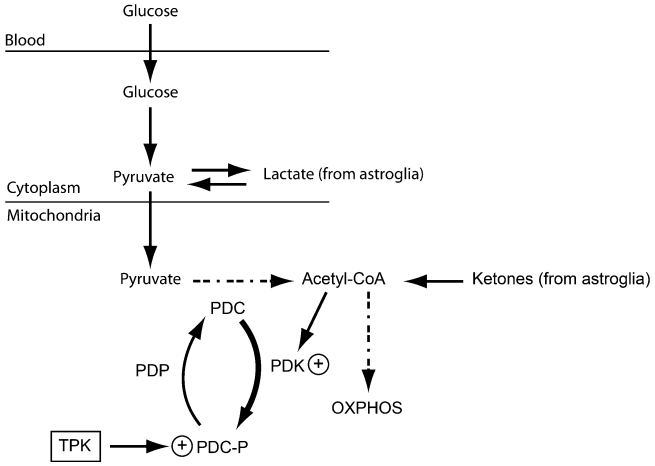

Fig. 4 Metabolic remodeling in Alzheimer's disease (AD) neurons. Neuronal pyruvate dehydrogenase complex (PDC) activity may be inhibited by at least two mechanisms. First, oxidation of ketones provided by astroglial cells as an energy substrate for neurons may increase the mitochondrial ratio of acetyl CoA:CoA, which activates PDK and inhibits the PDC. Second, accumulation of beta-amyloid in AD cells causes pathological activation of tau protein kinase I/glycogen synthase kinase β (TPK), which is also capable of phosphorylating the PDC. Consequently, glucose oxidation is inhibited in AD neurons, resulting in diminished OXPHOS and energy failure.

up-regulation of PDK and inhibition of OXPHOS, leading to reduced production of $O_2^{\cdot-}$ (Fig. 3). In addition, cancer cells had high mitochondrial membrane potential and low expression of the oxygen-sensitive potassium channel Kv1.5, both of which contributed to apoptosis resistance. DCA inhibited PDK in tumor cells, reactivated the PDC, and reversed the Warburg effect, thus decreasing glycolysis and increasing OXPHOS and $O_2^{\cdot-}$. The drug also selectively up-regulated Kv1.5 channels and induced apoptosis only in tumor cells by a mechanism involving inhibition of nuclear factor of activated T cells. Qualitatively similar findings have been obtained in several other human tumor types exposed to DCA (reviewed in Papandreou *et al.*, 2011). DCA appears to inhibit PDK by two mechanisms: by directly inhibiting the kinase (Roche & Hiromasa, 2007; Li *et al.*, 2009) and by decreasing the expression and stability of HIF1α (Archer *et al.*, 2008; Sun *et al.*, 2011). Proof-of-concept validation of these preclinical reports was recently demonstrated in five patients with glioblastoma multiforme who received oral DCA for up to 15 months (Michelakis *et al.*, 2010). Together, these data indicate that the PDC and its regulatory kinases are not only fundamental to the pathobiology of cancer cell metabolism but are also exciting new targets for therapy.

The magnitude of ROS accumulation in cancer and their pathophysiological role in the disease are controversial. Bonnet's findings of decreased $O_2^{\cdot-}$ accumulation are at variance with some results reported for other cancers (reviewed in Gogvadze *et al.*, 2010) and for congenital PDC deficiency (Glushakova *et al.*, 2011), despite concordance in demonstrating aerobic glycolysis and suppression of MnSOD in these diseases. An important consideration is the degree to which ROS accumulates in these disorders, because $O_2^{\cdot-}$ levels in PDC-deficient fibroblasts were not sufficient to cause evidence of oxidative changes in cellular lipids or proteins or to DNA (Glushakova *et al.*, 2011), whereas ROS-associated damage to cellular components has been reported in cancer (reviewed in Anastasiou *et al.*, 2011; Hamanaka & Chandel, 2011).

Alzheimer's disease

Brain glucose oxidation and oxygen consumption decline with aging (Martin *et al.*, 1991; Kalpouzos *et al.*, 2009). Studies employing magnetic resonance spectroscopy and infusions of stable isotopes of glucose and acetate in healthy young and elderly subjects suggest that brain neuronal glucose oxidation is decreased and nonoxidative glucose removal is increased in the elderly, whereas aging appears to have comparatively less impact on astrocytic energetics (Boumezbeur *et al.*, 2010). These findings are consistent with the observed age-related metabolic shift toward aerobic glycolysis and ketone body oxidation in rodent brain (Ross *et al.*, 2010; Yao *et al.*, 2010) and with a decrease in unphosphorylated (active) PDC (Zhou *et al.*, 2009) (Fig. 4). Although the latter experiments were conducted using whole brains of rats, it is likely that the major effect of aging on PDC activity is exerted on neurons. This is because PDK is normally highly expressed and the PDC is strongly inhibited in astrocytes from rat brain, whereas neuronal PDC activity is close to maximum levels because of lower PDK expression (Halim *et al.*, 2010). This metabolic dichotomy makes sense from a teleological standpoint, considering that glia are considered to be an important provider of lactate used as oxidative fuel by neurons (reviewed in Magistretti, 2006) and that mammalian neuronal PDC activity normally operates at near-maximum levels to maintain vital energetic functions (reviewed in Robinson, 2001). In addition,

many neurodegenerative diseases occurring in mid- to late-life are associated with abnormal brain oxidative metabolism. Although the etiology of mitochondrial dysfunction in neurodegenerative diseases is undoubtedly multifactorial (reviewed in Coskun *et al.*, 2011; Green *et al.*, 2011) intriguing new data implicate reduced PDC activity and up-regulation of aerobic glycolysis in several of these disorders, particularly Alzheimer's disease (AD).

It has long been known that diminished brain glucose metabolism in patients with AD precedes the appearance of overt clinical manifestations of the disease. Cognitively normal subjects who are homozygous for the *APOE* ε4 allele that confers heightened risk of developing AD show decreased glucose metabolism in the same brain regions as do patients with AD (Small *et al.*, 1995; Reiman *et al.*, 1996). Postmortem analysis of brains from patients with AD have repeatedly demonstrated significant decreases in the activities of the PDC and α-ketoglutarate dehydrogenase, a TCA cycle enzyme structurally and functionally similar to the PDC (Blass *et al.*, 2000; Bubber *et al.*, 2005). Reduced PDC activity and intramitochondrial respiration have been recapitulated in a transgenic mouse model of AD (Yao *et al.*, 2009). The brains of these animals contained extracellular aggregates of β-amyloid peptide (Aβ) and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau protein, both of which are considered important in the pathogenesis of AD (Sato *et al.*, 2002). Aβ exposure activates tau protein kinase I/glycogen synthase kinase 3β (TPKI/GSK-3β), which phosphorylates tau protein into forms typically found in AD brains. Although the E1α subunit of the PDC is reported to be a substrate for TPKI/GSK-3β (Hoshi *et al.*, 1996), it is difficult to understand how this cytoplasmic enzyme could exert regulatory control over the PDC. Nevertheless, regional reductions in cerebral glucose metabolism correlate with the magnitude of deposition of neurofibrillary tangles and, hence, of abnormal tau protein (Planel *et al.*, 2004). Furthermore, studies in human cancer cells have revealed that the PDC exists not only within the mitochondrial matrix but also on the outer mitochondrial membrane (Hitosugi *et al.*, 2011). Thus, it is possible that TPK1/GSK-3β could exert regulatory influence on PDC molecules 'exposed' to the cytoplasmic environment. Precise localization of the PDC in AD brains has not been reported.

Recent findings using positron emission tomography applied to healthy young adults provide new insight into regional brain metabolism that might first appear inconsistent with some of the earlier results obtained in aged or AD individuals. Aerobic glycolysis and mitochondrial oxidative metabolism appear to be differentially located in the normal resting brain (Vaishnavi *et al.*, 2010) and can account for up to 15% of glucose metabolism in adults (Powers *et al.*, 1998). Moreover, regional variations in aerobic glycolysis are not tightly correlated with brain metabolic activity, implying that such regions rely on a comparatively inefficient pathway of energy generation to maintain normal resting function. However, the spacial distribution of aerobic glycolysis in normal young adults also correlates with Aβ deposition both in subjects with overt AD and in cognitively normal individuals with elevated levels of Aβ (Vlassenko *et al.*, 2010). Although the significance of brain Aβ accumulation to the Warburg effect remains controversial (c.f. Newington *et al.*, 2011), most evidence strongly supports an age- and disease-dependent decline in brain mitochondrial function, in which reduced activity of the PDC plays a major role.

On aging worms and the PDC

Caenorhabditis elegans has been a useful model by which to study mechanisms of aging, including studies of the relationship between aging and energy metabolism. Induced loss-of-function mutations of complex I cause lactic acidosis, oxidative stress and decreased OXPHOS, fecundity, and survival. This pathology can be mitigated by dietary supplementation with certain water-soluble vitamins or with DCA, which decreases lactate concentrations and increases fecundity and survival (Grad & Lemire, 2004). Although the effect of vitamins might be rationalized on the basis of their actions as cofactors for OXPHOS enzymes or as antioxidants, the effect of DCA in animals with complex I mutations is harder to explain. The drug has no known direct effect on any respiratory chain complex. Moreover, it might be assumed that increasing the mitochondrial $NADH/NAD^+$ ratio by stimulating flux through the PDC and the TCA cycle might worsen a condition in which reoxidation of NADH is already diminished. However, anecdotal reports of biochemical and clinical benefit of DCA in children with congenital deficiency of complex I or other respiratory chain components (Stacpoole *et al.*, 1997) suggest that increasing PDC activity might improve mitochondrial energetics, providing there was sufficient residual activity of the downstream mutated enzyme to accommodate the increased provision of reducing equivalents. So might it be for the lowly nematode. Indeed, exposing normal worms to DCA preserves locomotive activity and improves their lifespan (Schaffer *et al.*, 2011). These salutary effects are probably mainly due to inhibition of PDK and subsequent stimulation of the PDC, because *C. elegans* survival is reduced by knockout of PDC but is enhanced by knockout of PDK (Mouchiroud *et al.*, 2011).

Summary

The PDC is central to mitochondrial fuel metabolism and, thus, to organismal health and survival. Deficiency of the complex, either through normal aging or by the imposition of congenital or acquired diseases, displays a strikingly similar pathology and affords stature to the PDC and its regulatory kinases as potential therapeutic targets for multiple rare and common disorders. Such age-associated conditions as sarcopenia, glucose intolerance, neurodegenerative diseases, and cancer represent fertile areas for continued research into the pathophysiological significance of how this fascinating macromolecular complex is perturbed and how it can be therapeutically manipulated.

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