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REVIEW ARTICLE

Age-dependent metabolic dysregulation in cancer and Alzheimer's disease

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Abstract Age is the main risk factor for cancer and neurodegeneration; two radically divergent diseases. Yet selective pressure to meet cellular metabolic needs may provide a common mechanism linking these two disorders. The exclusive use of glycolysis, despite the presence of oxygen, is commonly referred to as aerobic glycolysis and is the primary metabolic pathway of cancer cells. Recent evidence suggests that aerobic glycolysis is also a key regulator of synaptic plasticity in the brain that may positively influence cognition. Elevated aerobic glycolysis is a contributing factor to the development of cancer as increased glycolytic flux plays an important role in the biosynthesis of macromolecules and promotes proliferation. In contrast, decreased aerobic glycolysis in the brain occurs with age and could lead to a loss of cell survival mechanisms that counter pathogenic processes underlying neurodegeneration. In this review we discuss the recent findings from epidemiological studies demonstrating an inverse comorbidity of cancer and Alzheimer's disease. We summarize evidence linking the two diseases through changes in metabolism over the course of normal aging. We discuss the key steps and regulatory mechanisms of aerobic glycolysis and mitochondrial oxidative phosphorylation which could be exploited for the development of novel therapies. In addition, we outline the regulation of aerobic glycolysis at the transcriptional level by HIF-1α and Pin1 and their roles in cancer and neurodegeneration. Finally, we provide a possible explanation for metabolic dysregulation that occurs with age, and how it may be a contributing factor to age-related diseases. Determining how metabolism becomes dysregulated over time could lead to the development of effective interventions for ensuring metabolic homeostasis and healthy aging.

Keywords Metabolism · Cancer · Neurodegeneration · Alzheimer's disease · Aerobic glycolysis · Oxidative phosphorylation · Warburg effect · Mitochondria

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Introduction

In developed countries, age is the single greatest risk factor for late-onset diseases, including cardiovascular disease, cancer, and neurodegenerative disorders. The ageing process can perturb molecular pathways regulating cellular homeostatic mechanisms, ultimately promoting disease states. Cancer and neurodegenerative disorders are classes of disease that emerge from opposite ends of the biological spectrum: cancer is characterized by uncontrolled cellular proliferation whereas neurodegeneration is typified by uncontrolled

cell death. Interestingly, epidemiological studies have revealed an inverse relationship between cancer and neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). The incidence of cancer is lower among patients with AD, while the prevalence of AD is lower among survivors of cancer (DeSouky 1992; Yamada et al. 1999; Roe et al. 2005, 2010; Driver et al. 2012). One longitudinal study found people with cancer had a 43 % lower risk of developing AD, whereas those with AD had a 69 % lower risk of cancer incidence (Roe et al. 2010). Another study suggested that cancer survivors had a 33 % lower risk of developing AD (Driver et al. 2012). Further studies have demonstrated inverse relationships between PD and cancer (Jansson and Jankovic 1985; Ben-Shlomo and Marmot 1995; Moller et al. 1995; Vanacore et al. 1999; Minami et al. 2000), as well as HD and cancer (Sørensen et al. 1999). The link between motor neuron diseases, such as amyotrophic lateral sclerosis (ALS), and cancer have led to conflicting results with some studies showing association (Freedman et al. 2005; Baade et al. 2007) while others have not (Fois et al. 2010). Regardless, the majority of studies have shown, to varying degrees, an inverse association between cancer and many neurodegenerative diseases, especially AD.

Given that different disease states can exist in distinct cellular populations of the same individual, the search for a link between cancer and neurodegenerative disorders requires evaluation from a systemic biological perspective. This concept has previously been explored with a focus on certain common genetic factors implicated in both diseases; although a mechanism to explain the inverse co-morbidity between cancer and neurodegeneration was not formally proposed (Plun-Favreau et al. 2010). A recent theory posits that sporadic forms of both diseases may arise from the age-related metabolic dysregulation triggered by cell selection based on bio-energetic requirements (Demetrius and Simon 2013). In cancer, a shift toward enhanced glycolysis arises to selectively enhance production of molecular building blocks for proliferation and to confer a survival advantage against competing cellular populations. In AD, the opposite effect occurs whereby a compensatory increase in mitochondrial respiration arises in response to age-related reduced energy production in impaired neurons (Demetrius and Simon 2013). Thus, cancer and AD may occur as a result of metabolic reprogramming adopted by cells to compensate for age-dependent diminished energy production. In this review, we propose that cancer and neurodegeneration arise through the age-associated dysregulation of a common molecular pathway that controls metabolic programming which either favours or hinders the survival of different cellular populations. Understanding the differences and commonalities in metabolism between these two disease types has practical applications for developing therapies to maintain metabolic homeostasis during the course of ageing.

Metabolic reprogramming in cancer

Cellular metabolism is a complex process regulated by many intrinsic and extrinsic factors. Metabolic reprogramming can be defined as a persistent shift in cellular metabolic pathways towards or away from respiration in the mitochondria. Shifts in metabolic states occur naturally in order to meet the energy demands of active cellular processes while responding to a dynamic environment and changing nutrient availability. Metabolic reprogramming may also contribute to the development of several age-related diseases as nutrient sensing and metabolic regulatory mechanisms decline with age. The key toward healthy aging may be achieved by proper homeostasis of glucoregulatory mechanisms, whereas a disproportionate shift towards either enhanced aerobic glycolysis or oxidative phosphorylation (OxPhos) may promote the incidence of cancer or AD, respectively (Fig. 1).

Under normal conditions, the majority of glucose consumed by the cell is oxidized to carbon dioxide and water in the mitochondria to yield large amounts of ATP to support cellular functions. However, a characteristic feature of many cancer cells is the extensive reliance on glycolysis, even under normoxic conditions, with production of lactate as a by-product. In cancer cells, this type of metabolism is known the Warburg effect in recognition of its discovery by Warburg (1956). The reliance on glycolysis in the presence of oxygen is commonly referred to as aerobic glycolysis and is a characteristic feature of cancer, or cells in the developing fetus. Originally it was believed that aerobic glycolysis was up-regulated in cancer cells in response to the hypoxic conditions of

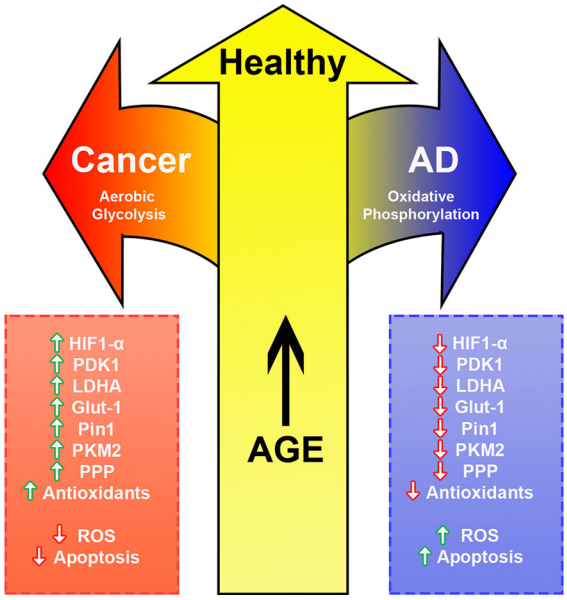

Fig. 1 Balanced cellular metabolism is key to healthy aging. A shift toward aerobic glycolysis increases the incidence of cancer, whereas the shift toward OxPhos likely increases the incidence of AD. Factors directly contributing to either pathology include HIF-1α, PDK1, LDHA, Glut-1, Pin1, PKM2, pentose phosphate pathway (PPP), antioxidants, and reactive oxygen species (ROS). Cancer is characterized by a decrease in apoptotic signalling (associated with heightened aerobic glycolysis), whereas an elevation in apoptotic signalling (linked to elevated OxPhos) increases the likelihood of developing AD. The homeostatic regulation of aerobic glycolysis and OxPhos is critical for maintaining health and preventing disease with age

tumours, or as a mechanism to compensate for dysfunctional mitochondria (Gatenby and Gillies 2004). However, human leukemia cells in the circulating blood and lung tumours are highly glycolytic despite a higher oxygen environment than in peripheral tissues (Nolop et al. 1987; Gottschalk et al. 2004). In addition, substantial evidence suggests that mitochondrial metabolism is required for tumorgenesis and that mitochondrial-derived reactive oxygen species (ROS) can promote cell proliferation (Weinberg et al. 2010; Giang et al. 2013).

It is now understood that a high glycolytic rate has several advantages for rapidly proliferating cells: First, computer simulation studies of competition between cell types have shown that, despite its low efficiency at producing ATP compared to OxPhos in the mitochondria, glycolysis can generate ATP at a faster rate when the supply of glucose is abundant (Pfeiffer et al. 2001). As such, cancer cells are highly dependent on glucose availability and inhibiting glucose import or metabolism can enhance the efficacy of chemo- and radiotherapy (El Mjiyad et al. 2011). Second, proliferating cells require metabolites to support the biosynthetic requirements of mitosis and glycolytic intermediates can provide the carbon building blocks for the *de novo* synthesis of nucleotides, lipids, and non-essential amino acids (Hume and Weidemann 1979; Lunt and Vander Heiden 2011). The pentose phosphate pathway (PPP) is a metabolic branch of glycolysis that can be exploited for the production of reducing equivalents in the form of NADPH molecules, as well as generating nucleotide and lipid precursors. In addition to glycolysis in the cytosol, the supply of acetyl-CoA and glutamine to the TCA cycle within mitochondria drives the production of metabolites that can be siphoned off to the cytosol and participate in the anabolic metabolism of amino acids and lipids (Lunt and Vander Heiden 2011). Finally, the maintenance of biosynthesis in proliferating cells requires the regeneration of NAD^+, which is partially supported by the conversion of pyruvate to lactate. NAD^+ is an important cofactor for continued glycolytic flux as well as nucleotide and amino acid biosynthesis.

A more recent theory termed the "reverse Warburg effect" has also been proposed (Pavlides et al. 2009) in which aerobic glycolysis occurs primarily in neighbouring stromal fibroblasts that surround tumor cells. Decreased expression of caveolin-1 (Cav1), a scaffolding protein, in stromal fibroblasts triggers loss of mitochondria via mitophagy (the autophagic destruction of mitochondria), forcing these cells to undergo aerobic glycolysis and produce high levels of pyruvate, lactate and ketone bodies (Lisanti et al. 2010). These metabolites are subsequently taken up by cancer cells and processed via OxPhos. Thus, in this model, the Warburg effect occurs in fibroblasts, and not in cancer cells, contrary to the original theory proposed by Otto Warburg. Evidence has been found in support of both theories suggesting that cancer-associated metabolic reprogramming is likely cell type and context dependent.

In general, glucose availability is not rate limiting and cancer cells can effectively use aerobic glycolysis or OxPhos. However, when glucose is scarce but constant, oxidative OxPhos has a selective advantage by producing ATP in a more efficient manner to meet the metabolic needs of cancer cells. The entropic

selection principle is a mathematical model which postulates that the outcome of competition between cells for metabolic resources is predicted by differences in evolutionary entropy, and is contingent on the abundance and diversity of resources (Demetrius and Simon 2012). Thermodynamic entropy pertains to aggregates of inanimate matter such as solid, liquid or gas and describes the number of ways that the molecules of a system can be arranged to achieve the same total energy. Accordingly, thermodynamic entropy is a measure of the degree of disorder. Evolutionary entropy pertains to aggregates of living entities. In this context, metabolic networks (i.e., glycolysis or OxPhos) can be considered living entities. Evolutionary entropy of metabolic networks describe the number of distinct pathways of energy flow within the network (Demetrius 1997). When resources are diverse and abundant then high entropic systems will replace low entropic systems. In contrast, when resources are restricted to a singular source which is subject to large variations in abundance then low entropic systems will prevail. Applying these principles to cellular metabolism; when resources are diverse and constant, cells using OxPhos (high entropy) will have a selective advantage. However, when the resource is restricted to a singular fuel source that varies in abundance (i.e., glucose), then cells using glycolysis (low entropy) will prevail.

The predictions of the entropic selection principle have recently been experimentally validated in a study in which cancer cells, which are normally grown in complete media with high glucose, were continually grown in low glucose containing media (Birsoy et al. 2014). Cancer cells that successfully adapted to this form of selection exhibited a pronounced change in metabolism whereby they switched from glycolysis to OxPhos to generate ATP. In this manner, changes in metabolism can be considered a direct consequence of the cell adapting appropriately to its environment. In light of the fact that cancer cells are highly proliferative, due to mutations in genes controlling cell cycle regulation or tumor suppression, when glucose in abundant a shift to aerobic glycolysis provides cancer cells with a competitive growth advantage over neighbouring cells.

In the brain, there may exist two populations of neurons: those with normal OxPhos and those with high OxPhos (Demetrius and Simon 2012). An age-related decline in either the production of metabolic substrates or their transport will select for neurons that have elevated OxPhos. However, inefficient electron transport in older neurons with elevated OxPhos will also result in elevated ROS production and increased susceptibility to various pathological neurotoxins in this subset of neurons (as discussed later). In contrast, neurons that favour aerobic glycolysis (low OxPhos) will be less susceptible to toxins as long as substrate availability is not rate-limiting.

Aerobic glycolysis and OxPhos in the human brain

Emerging evidence now suggests that aerobic glycolysis may play a critical role in neuronal development as well as memory processing in the adult brain. Aerobic glycolysis predominates in the developing brain during embryogenesis to provide biosynthetic materials necessary for the proliferation of neuronal and astrocytic stem cells, and accounts for approximately one-third of glucose consumed in the brain during early childhood to maintain axon growth and myelination (Bauernfeind et al. 2013; Settergren et al. 1976). In the resting adult human brain, aerobic glycolysis can account for approximately 10–12 % of all glucose consumed but quickly declines past the age of 20 years and virtually disappears in the elderly (Raichle et al. 1970; Boyle et al. 1994; Powers et al. 2007; Vaishnavi et al. 2010). Thus, from embryogenesis to late adulthood, there is a progressive shift from aerobic glycolysis to OxPhos within the human brain (Fig. 2). Recent evidence suggests that metabolic reprogramming toward aerobic glycolysis, and the concomitant production of lactate, within certain regions of the CNS is associated with long-term memory formation and the maintenance of long-term potentiation of synaptic strength (Suzuki et al. 2011; Newman et al. 2011; Barros 2013). A multimodal positron emission tomography (PET) analysis identified high rates of aerobic glycolysis in cortical regions of the adult brain known to participate in cognitive control networks, although the study did not distinguish between metabolism in astrocytes versus neurons (Vaishnavi et al. 2010). A recent meta-analysis of whole-genome microarray data revealed a correlation between aerobic glycolysis and changes in gene expression associated with synapse formation and neurite growth in the adult brain (Goyal et al. 2014).

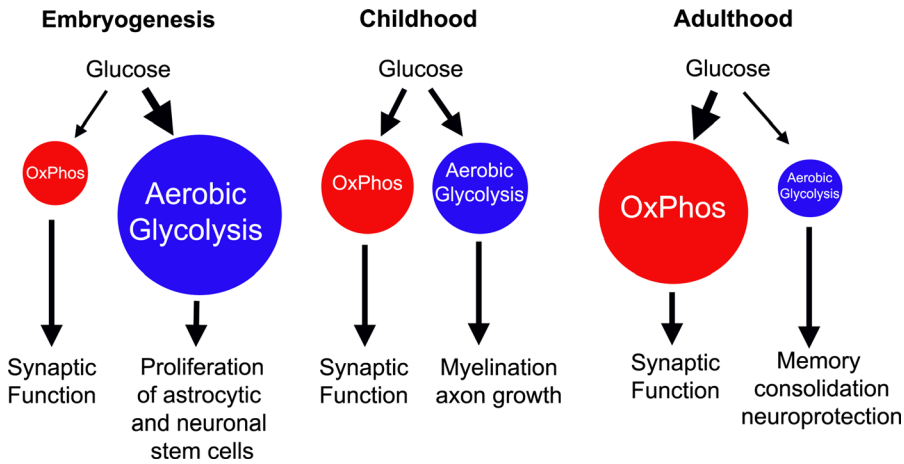

Fig. 2 Age-dependent shift in metabolism from aerobic glycolysis to OxPhos in the human brain. During embryogenesis, aerobic glycolysis is the predominate form of metabolism in the brain to generate metabolites required for astrocytic and neuronal stem cell proliferation. During childhood, aerobic glycolysis is predominately used to support axon growth and myelination. Finally, during adulthood aerobic glycolysis persists in certain regions of the brain to support memory networks and maintain neuronal viability. OxPhos is primarily used throughout human lifespan to support synaptic activity with a progressive increase in activity during aging

Aerobic glycolysis is also quickly up-regulated in active regions of the brain along with localized cerebral blood flow during periods of cognitive demand and can persist for at least 40 min despite the return to baseline conditions (Madsen et al. 1995; Fox et al. 1988; Vlassenko et al. 2006; Kasischke et al. 2004). Research into activity-induced aerobic glycolysis strongly implicates a role for astrocytes in removal of glutamate and Na^+ from firing synapses, which rely primarily on glycolysis to drive membrane-bound Na^+/K^+ ATPases (Pellerin and Magistretti 1994). A theory termed the astrocyte-neuron lactate shuttle hypothesis (ANLSH) posits that astrocytes can rapidly mobilize glucose from either glycogen stores, or directly from cerebral blood vessels, process it through glycolysis to generate lactate which is exported via monocarboxylate transporters and subsequently used as a fuel source for OxPhos in the mitochondria of neurons (Magistretti et al. 1981; Pellerin and Magistretti 1994; Magistretti 2006; Suzuki et al. 2011). Neurons have a reduced glycolytic capacity due to the continual degradation of 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase isoform 3 (Pfkfb3), an enzyme that plays a key role in the early stages of glycolysis (Bolaños et al. 2010). Thus neurons likely rely on astrocytes for the production of lactate which is subsequently used as an energy supply for OxPhos. However, the extent to which lactate is shuttled between astrocytes and neurons to meet the active energy requirements of the brain has been debated (Dienel 2012). It is possible that lactate supply from astrocytes may help to offset the energy requirements of neurons due the poor efficiency of glycolysis in this cell type. The reliance of neurons for astrocyte-derived lactate is, in a manner, analogous to the reverse Warburg effect postulated to exist between cancer cells and their surrounding stromal cells (Pavlides et al. 2009). It has been proposed that an inverse Warburg effect occurs in the brain in which the progressive age-related increase in OxPhos within neurons entails more reliance on astrocyte-derived lactate production (Demetrius and Simon 2012). However, glucose may also directly be taken up by neurons and preferentially processed via the PPP for antioxidant production, in addition to biosynthetic pathways required for growth and synaptic remodelling (Soucek et al. 2003; Goyal et al. 2014). Thus, neuronal cells make take up astrocyte-derived lactate to fuel OxPhos, concomitantly with glucose uptake to generate reducing equivalents via the PPP and augment antioxidant systems. Collectively, these findings indicate that aerobic glycolysis and astrocyte-neuron metabolic coupling are strongly associated with neuronal development and persist in certain regions of the adult brain to actively support antioxidant and biosynthetic requirements for synaptic plasticity and memory formation.

Alzheimer's disease and brain metabolism

AD is the most common form of dementia in the elderly and is strongly associated with a range of progressive cognitive deficits and memory loss. AD is characterized by widespread nerve cell death and accumulation of extracellular plaques and intracellular neurofibrillary tangles (NFTs) within the brains of affected individuals. The NFTs are composed of aggregated microtubules which arise from the hyperphosphorylation of the tau protein and are a late-stage AD pathology marker that correlates closely with neurodegeneration (Gómez-Isla et al. 1996). The plaques are primarily comprised of aggregated amyloid-β-peptide (Aβ) derived from the proteolytic cleavage of the amyloid precursor protein (APP) (Zhang et al. 2012). The Aβ peptide, particularly the 42 amino acid variant ($A\beta_{1–42}$), is highly prone to undergo oligomerization and promote mitochondrial dysfunction, oxidative stress, and synaptic damage in affected neurons (Tillement et al. 2011). The amyloid cascade hypothesis posits that AD arises from the abnormal deposition, or improper clearance, of Aβ in the brain (Hardy and Higgins 1992). This was largely supported by the discovery that familial, early-onset versions of AD are caused by autosomal dominant mutations within the APP gene itself or within genes that directly affect APP processing in favor of $A\beta_{1–42}$ production (Bagyinszky et al. 2014). Yet, the vast majority of AD patients in the general population have a sporadic, late-onset dementia, in which the strongest risk factors for cognitive decline are age, genetics, lifestyle, education, and cardiovascular disease (Imtiaz et al. 2014). Cognitive decline in humans correlates poorly with regional deposition of insoluble plaques, but correlates well with soluble Aβ and synaptic loss (Wang et al. 1999; Terry et al. 1991). However, therapeutic strategies to either limit the production of Aβ or enhance its clearance have generally proved to be ineffective in clinical trials (Marchesi 2012). These studies have prompted the search for non-amyloid based strategies to treat AD.

Due to the difficulty in altering cognitive decline in AD patients already displaying symptoms of dementia, in recent years a large initiative toward prevention of AD in the general population has been undertaken (Sperling et al. 2011). The goal is to discover the earliest reliable biomarker for probable AD in order to implement therapeutic or lifestyle interventions for at-risk individuals before the onset of dementia. Initial analyses of the dominantly inherited Alzheimer's network (DIAN) have revealed the appearance of amyloid deposits in the brain and increased tau concentrations in cerebral spinal fluid nearly 15 years before the onset of clinical symptoms (Bateman et al. 2012). A recent study using magnetic resonance imaging (MRI) and PET estimated that fibrillar deposits of amyloid in the brain of sporadic individuals can begin up to 25 years before cognitive impairment (Villemagne et al. 2013). Collectively, these findings suggest that the human brain can tolerate a certain level of amyloid deposition, beyond which synaptic dysfunction and neural cell loss can no longer support normal cognitive function. In support of this view, it has been well established that approximately 30 % of the elderly are cognitively normal yet have pathology indistinguishable from AD patients of the same age (Burns et al. 1997; Price and Morris 1999; Aizenstein et al. 2008). Several factors can contribute to an individual's tolerance to AD pathology, yet proper regulation of glucose metabolism is an emerging and promising candidate for maintaining brain function over the course of age.

Cerebral hypometabolism has traditionally been perceived as a hallmark feature of the AD brain at the stage of mild cognitive impairment (MCI), which correlates temporally with symptom severity and has high predictive value for onset of dementia (Mosconi et al. 2008). This observation can be accounted for by a decrease in glucose transport and phosphorylation rates in affected brain regions, and may be due to a decreased energy demand related to synaptic dysfunction at later stages of the disease (Friedland et al. 1989; Jagust et al. 1991; Piert et al. 1996). However, Pittsburg compound B (PiB) and ^{18}F-Fluorodeoxyglucose (^{18}F-FDG)-PET imaging of cognitively normal people at risk for AD revealed area-specific increases in both Aβ deposition and glucose metabolism in individuals before MCI, which may represent an early compensatory event in the AD cascade in response to the presence of Aβ (Johnson et al. 2014). Moreover, a recent PET study of autosomal dominant AD mutation carrier individuals revealed regionally higher glucose uptake ~25 years before the estimated age of onset (EAO) (Benzinger et al. 2013). Although reduced glucose metabolism was observed 5–10 years before EAO in many cortical areas with Aβ deposition, a divergent pattern was observed

subcortically; the caudate and palladium did not show either metabolic decline or atrophy, despite markedly elevated PiB uptake (Benzinger et al. 2013). Thus, aerobic glycolysis may be elevated in certain regions of the brain as a compensatory mechanism in response to Aβ accumulation that occurs during aging or in familial cases of AD. Loss of this protective mechanism may render certain areas of the brain susceptible to Aβ-induced neurotoxicity.

Recent multimodal PET imaging studies have revealed a strong correlation between the spatial distribution of elevated aerobic glycolysis and Aβ deposition in the brain tissue from patients with both sporadic AD, as well as cognitively normal individuals with high levels of Aβ-deposition (Vlassenko et al. 2010). Recent evidence from our lab revealed that nerve cells resistant to Aβ toxicity undergo metabolic reprogramming and shift toward aerobic glycolysis through the stabilization of hypoxia-inducible factor 1-α (HIF1-α) and up-regulation of pyruvate dehydrogenase kinase-1 (PDK1) and lactate dehydrogenase A (LDHA) (Soucek et al. 2003; Newington et al. 2011). Over-expression of either PDK1 or LDHA enzymes in nerve cell lines represses mitochondrial respiration and confers resistance to Aβ and other neurotoxins, whereas chemical or genetic inhibition of these enzymes results in re-sensitization of resistant lines to Aβ toxicity (Newington et al. 2011, 2012). Moreover, mitochondrial-derived ROS, which are closely associated with Aβ toxicity, are markedly diminished in resistant relative to sensitive cells. By repressing mitochondrial respiration, Aβ-resistant cells are less likely to produce ROS and are more resistant to mitochondrial depolarization; two events tightly linked to induction of apoptosis. These experiments support the notion that aerobic glycolysis may constitute a resistance mechanism against the toxic effects of Aβ in the AD brain. However, an outstanding question is whether any increase in aerobic glycolysis in the human brain, possibly as a compensatory response to Aβ accumulation, occurs preferentially in either astrocytes or neurons. Elevated aerobic glycolysis in astrocytes would lead to increased lactate production which, in turn, could be used as a resource to fuel OxPhos in adjacent neurons. Alternatively, increased aerobic glycolysis in neurons could be used to drive the PPP and generate reducing equivalents to enhance antioxidant defence systems which protect against Aβ induced toxicity.

Linking cancer and neurodegeneration through metabolism

Under healthy conditions, cellular metabolic homeostasis is tightly regulated and responds appropriately to a changing environment and energetic demand. However, regulatory processes lose fidelity as a consequence of changes that occur during the aging process. Through mechanisms that remain to be fully characterized, an imbalance in glucose regulation may steer cellular metabolism either toward aerobic glycolysis or OxPhos. A persistent shift toward aerobic glycolysis could provide a growth advantage to cancerous cells, while an age-dependent decline in aerobic glycolysis, and an increase in OxPhos, could predispose neural populations toward neurodegeneration (Fig. 3). Some studies have suggested that during aging a reduction in OxPhos and a concomitant increase in aerobic glycolysis occurs in tissues such as liver and skeletal muscle (Hagen et al. 1997; Trounce et al. 1989). It remains to be determined whether the gain or loss of aerobic glycolysis in cancer and neurodegeneration results as a compensatory mechanism, or as a consequence of the aging process itself. Investigation of metabolic regulatory enzymes and pathways in the context of health, ageing, and disease states could reveal novel molecular targets for the tipping the balance in favour of corrected homeostasis. Here we discuss the key steps that direct metabolism towards aerobic glycolysis or OxPhos via enzymes under strict regulation at the transcriptional and post-translational level.

Glucose transporters

The first rate-limiting step in glucose metabolism is the facilitated transport of glucose across the plasma membrane. This is mediated by the Glut-family of integral membrane proteins of which there are 14 members in humans, each with different affinities for glucose and related sugars (Macheda et al. 2005). Glut-1 and Glut-3 play an essential role in the insulin-sensitive homeostasis of glucose transport in the mammalian brain (McEwen and Reagan 2004). Glut-1 is primarily expressed in astrocytes and the capillary endothelium that form the blood–brain barrier, while Glut-3 is the major neuronal glucose transporter (Schubert 2005). Glut-1 is frequently over-

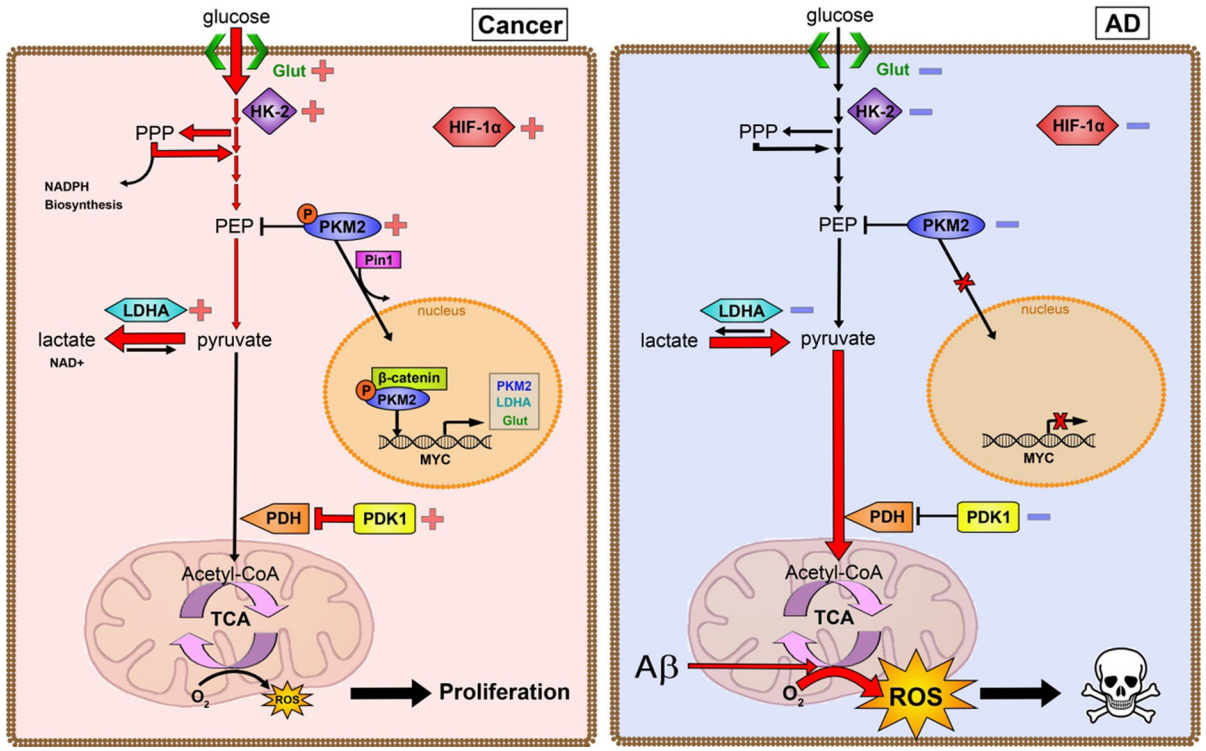

Fig. 3 The role of aerobic glycolysis in cancer and AD. In cancer (*left*), increased HIF-1α activity increases expression of glycolytic enzymes Glut-1, HK-2, PKM2, and LDHA, as well as the regulatory enzyme PDK1. Increased expression of these enzymes collectively lead to elevated aerobic glycolysis, enhanced PPP activity and associated production of NADPH, increased lactate levels and decreased mitochondrial respiration. PKM2 is translocated to the nucleus through the action of Pin1, where it binds β-catenin as a cofactor and induces MYC-directed expression of LDHA, Glut-1, and PKM2 in a feed-forward mechanism. Low levels of ROS from decreased mitochondrial respiration act as a second messenger to promote proliferation and contribute to a cancerous phenotype. In the context of AD (*right*), a natural decline in aerobic glycolysis associated with old age, or from decreased levels of HIF-1α, results in reduced expression of glycolytic enzymes and increased metabolic flux through mitochondrial respiration. A decline in PKM2 levels reduces the likelihood of phosphorylation and translocation to the nucleus with subsequent activation of glycolytic genes. Lactate may be used by neurons as an alternate fuel source to compensate for reduced glucose import which feeds directly into the mitochondria through increased activity of PDH. In the presence of Aβ, cellular respiration produces large amounts of ROS which induces apoptosis

expressed in cancers, which correlates with increased (^{18}F-FDG) uptake in PET scans of human carcinomas (Bos et al. 2002; Reske et al. 1997; Brown and Wahl 1993). Recently, a small-molecule inhibitor of Glut-1 was used to decrease the rate of glycolysis and induce cell-cycle arrest in cancer cell lines and in a nude mouse model (Liu et al. 2012). In contrast, Glut-1 and Glut-3 expression is decreased in the AD brain which correlates spatially with cerebral hypometabolism (Simpson et al. 1994; Harr et al. 1995; Mooradian et al. 1997; Liu et al. 2008). Glucose transport in the CNS is regulated by several factors including growth factor binding and gene expression. In response to insulin signaling, Glut-1 expression is elevated and targeted to the membrane by a signaling pathway mediated through activation of the serine/threonine kinase, Akt (Barthel et al. 1999). Glut-1 expression can also be up-regulated by HIF-1α in response to growth factor binding (i.e., bFGF, TNF, or VEGF), or directly in response to hypoxia (Boado et al. 1994; Mani et al. 2003; Okino et al. 1998). Glut-1 and Glut-4 expression steadily declines with age in skeletal muscle and may contribute to insulin insensitivity associated with sarcopenia in old age (dos Santos et al. 2012). However, it is currently unknown how the expression of glucose transporters in the CNS changes with age and contributes to the pathogenesis of neurodegeneration.

Hexokinase

Once glucose has entered the cell, it is phosphorylated to glucose-6-phosphate (G-6-P) in an essentially irreversible reaction. This reaction is catalyzed by the enzyme Hexokinase (HK). Four isoforms of HK have been characterized in mammalian tissue, each with a different expression pattern and different affinity for glucose as a substrate. One of the earliest adaptations observed in tumorgenesis is a switch to the high-affinity HK isoform (HK-2) and silencing of low-affinity isoforms (Rempel et al. 1994; Mayer et al. 1997). The regulation of HK-2 in tumors is primarily dependent on transcriptional activation by the c-Myc, HIF-1, and p53 transcription factors (Yeung et al. 2008). HK-2 also forms a complex with the pore-like voltage-dependent anion channel (VDAC) on the outer mitochondrial membrane. This provides HK-2 with several advantages including: preferential access to ATP generated by ATP synthase, enhanced binding affinity to ATP, and insensitivity to product-inhibition from G-6-P (Bustamante and Pedersen 1977, 1980; Bustamante et al. 1981; Arora and Pedersen 1988). As a result of this association, glucose is converted to G-6-P in a quick and efficient manner, which can then be funnelled into glycolysis or through the PPP for use in biosynthetic pathways. The HK-VDAC complex also plays a critical role in regulating apoptosis by preventing Ca^{2+} dependent induction of the mitochondrial permeability transition pore (MPTP) and cytochrome c release (Azoulay-Zohar et al. 2004; Majewski et al. 2004). HK binding to VDAC favours a closed state of the MPTP, while HK release promotes an open state that is more prone to release of pro-apoptotic factors (Azoulay-Zohar et al. 2004; Zaid et al. 2005). This constitutes a mechanism by which HK not only provides rapid energy and metabolite supply to the cell, but also reflects an anti-apoptotic defense mechanism. A recent study using amyloidogenic AD transgenic mouse models, as well post-mortem brain tissue from AD patients, demonstrated that VDAC1 was found to be over-expressed and levels of HK decreased in the hippocampus (Cuadrado-Tejedor et al. 2011). In addition, the hippocampus of AD transgenic mice at 12 months of age have increased levels of phosphorylated-VDAC1, which promotes its dissociation with HK and favours the release of apoptotic factors (Cuadrado-Tejedor et al. 2011). Despite its prominent role in promoting aerobic glycolysis and preventing apoptosis in cancer, functional analysis of HK-VDAC in the ageing brain awaits future investigation.

Pyruvate kinase

The final rate-limiting step in glycolysis is the conversion of phosphoenolpyruvate (PEP) and ADP into pyruvate and ATP. This is catalyzed by the enzyme pyruvate kinase (PK), of which there are four isoforms (M1, M2, L, and R). The L and R isoforms of PK are exclusively expressed in liver and red blood cells, respectively, while PKM1 and PKM2 are expressed in most adult tissues and arise from alternative splicing of the same M-gene under regulation of the oncogene c-myc (Mazurek et al. 2005; David et al. 2010). The PKM1 isoform assembles as a high activity tetramer for rapid substrate turnover (Jurica et al. 1998). In contrast, PKM2 is among the most tightly regulated enzymes of the glycolytic pathway and is important for controlling levels of ATP and glycolytic intermediates in the cell. PKM2 is expressed during embryonic development and can exist as a tetramer (high activity), or as a dimer (low activity). The dimeric form of PKM2 is characterized by low affinity for PEP which results in accumulation of glycolytic intermediates important for cancer growth (Christofk et al. 2008a). PKM2 is primarily regulated at the post-translational level, which influences its propensity to form either dimers or tetramers in order to respond quickly to a changing cellular environment. PKM2 can directly bind to activated growth factor receptors, including FGFR1, followed by phosphorylation to induce dimer (low activity) formation which promotes cell division and tumor growth (Christofk et al. 2008b; Hitosugi et al. 2009). PKM2 is acetylated under high glucose concentrations, which reduces its activity and targets PKM2 toward lysosome-dependent degradation (Lv et al. 2011). PKM2 can be inhibited by acute increases in intracellular concentrations of ROS through oxidation of C358, which promotes glucose flux through the PPP and facilitates the production of the reducing molecule NADPH (Anastasiou et al. 2011). PKM2 can also be regulated at the transcriptional level by HIF-1α, and through nuclear localization by Pin1, a finding which will be discussed in further detail below. Taken together, PKM2 activity is tightly regulated to respond

quickly to a changing metabolic environment and its dysregulation may lead to the progression of uncontrolled activation of biosynthetic pathways and cancer growth. PKM2 may also be an attractive target for modulation of glycolysis for treatment of neurodegenerative diseases.

Lactate dehydrogenase

As the end product of glycolysis, pyruvate has two major fates in the mammalian cell: transportation to the mitochondria and conversion to acetyl-CoA via the pyruvate dehydrogenase (PDH) complex to subsequently fuel the TCA cycle, or conversion to lactate in the cytosol via lactate dehydrogenase (LDH). LDH is a tetramer composed of two different subunits, LDHA and LDHB, which can assemble in different combinations depending on the relative expression levels of each subunit in the cell (Markert et al. 1975). LDHA catalyzes the forward reaction of pyruvate and NADH to lactate and NAD^+, while LDHB converts lactate back to pyruvate and permits the use of lactate as a nutrient source to fuel OxPhos or gluconeogenesis (Dawson et al. 1964). Originally it was believed that the excessive production and excretion of lactate in cancer cells was a result of the high glycolytic flux overwhelming the maximum PDH activity, thus leaving higher intracellular pools of pyruvate for processing by LDHA. However, the production of lactate has several benefits for a highly glycolytic cell. First, it generates NAD^+ which maintains the NADH/NAD^+ redox balance and permits continued glycolysis and biosynthetic reactions (Chiarugi et al. 2012). Second, the shift away from mitochondrial respiration towards lactate production reduces the production of ROS and prevents apoptotic signalling arising from oxidative stress (Le et al. 2010). In a cellular environment, lactate production from highly glycolytic cells can be transported to oxidative cells and offset the metabolic requirements of glucose, which can then be used in biosynthetic reactions to support proliferation. LDHA is commonly over-expressed in many tumours (Doherty and Cleveland 2013). Pyruvate dehydrogenase kinase 1 (PDK1), an enzyme which phosphorylates and inhibits PDH, is also highly expressed in cancer and functions to prevent mitochondrial metabolism in favour of lactate production (Lu et al. 2008). Emerging evidence now suggests that lactate can be a preferred fuel source for neurons and participates in signalling mechanisms that mediate long-term potentiation and memory consolidation (Suzuki et al. 2011; Newman et al. 2011; Barros 2013). Inhibition of LDHA is a promising therapeutic for the prevention of cancer, whereas its sustained activation could promote aerobic glycolysis and maintain synaptic function in the CNS.

HIF-1

Hypoxia-inducible factor 1 (HIF-1) has been a key target in cancer therapy for several decades due to its critical role in regulating cellular responses to oxygen and metabolic conditions. HIF-1 is a heterodimeric transcription factor comprised of two subunits: a constitutively expressed β subunit, and an α subunit, which is highly regulated by changing oxygen levels (Wang et al. 1995). Under normal oxygen conditions, HIF-1α is hydroxylated by prolyl hydroxylases and targeted for ubiquitin-mediated degradation (Salceda and Caro 1997). Under hypoxic conditions, HIF-1α is stabilized and translocates to the nucleus where it dimerizes with HIF-1β and induces expression of genes regulated by hypoxic response elements (Semenza et al. 1991). These genes include glucose transporters Glut-1 and Glut-3, as well as glycolytic enzymes and regulators HK, LDHA, and PDK1 (Semenza 2010). HIF-1α activation represents a well-characterized mechanism by which the cell can quickly respond to hypoxic environments by up-regulating glycolysis and inhibiting mitochondrial respiration in order to meet cellular energy demands. However, even when oxygen is abundant, HIF-1 can be stabilized and transcriptionally active during periods of rapid proliferation and increased metabolic demand. HIF-1α can be activated under normoxic conditions through the PI3 K/Akt/mTOR pathway, which results in transcriptional up-regulation of PKM2 and promotes cell proliferation and tumorgenesis (Sun et al. 2011). Expression of HIF-1α is induced by the glycolytic intermediates pyruvate, lactate and NAD^+, in addition to other TCA cycle metabolites (McFate et al. 2008; Semenza 2010). This feed-forward mechanism perpetuates HIF-1 activity and contributes to prolonged aerobic glycolysis commonly associated with proliferating cells. HIF-1α is over-expressed in many human cancers and loss of HIF-1α

dramatically slows tumor growth in nude mice (Maxwell et al. 1997; Jiang et al. 1997; Ryan et al. 1998; Zhong et al. 1999). HIF-1α activation promotes several cellular responses that are beneficial for a growing tumor, including vascular remodelling, increased glucose uptake, oxidative stress response, and cell survival. As such, it also directly opposes known deleterious effects of AD pathophysiology, including reduced cerebral blood flow, impaired glucose uptake and metabolism, increased oxidative stress, and uncontrolled cell death (Zhang et al. 2011).

Pin1

A recently emerging link between cancer and neurodegeneration is the peptidyl-prolyl isomerase, Pin1, which catalyzes the *cis*/*trans* conversion of pSer/Thr-Pro motifs on a specific set of proteins (Lu 2004). This change in shape alters the function of target phosphoproteins and has been implicated in regulation of several physiological processes including cell cycle progression, growth signal responses, cellular stress responses, germ cell development, and neuronal survival (Lu and Zhou 2007). Pin1 dysregulation is associated with pathological conditions including aging, cancer, and AD (Lee et al. 2011). Transgenic mice deficient in Pin1 display premature aging phenotypes, including reduced body size, telomere loss, germ cell depletion, and neuronal degeneration (Liou et al. 2003, 2002; Pastorino et al. 2006; Lee et al. 2009; Atchison et al. 2003; Atchison and Means 2003). Pin1 is often over-expressed in human cancer tissues where it functions as a catalyst for oncogenic pathways controlling the cell cycle and also inactivates many tumor suppressors or growth inhibitors (Wulf et al. 2001; Ryo et al. 2001; Bao et al. 2004). Pin1 can induce isomerisation of phosphorylated PKM2 in response to activation by EGFR, which facilitates its binding to importin-α5 and translocation to the nucleus. Nuclear PKM2 binds β-catenin and induces c-myc-mediated expression of glycolytic enzymes including Glut-1, LDHA, and PKM2 in a feed-forward mechanism (Yang et al. 2012). Thus, the correlation between Pin1 over-expression and cancer may be related to the ability of Pin1 to activate aerobic glycolysis. In contrast to over-expression in cancer, Pin1 is down-regulated in affected neuronal populations of AD patients; an event which correlates with neuronal loss (Liou et al. 2003). Pin1 binds directly to phosphorylated tau and restores its ability to bind microtubules and promote microtubule assembly (Lu et al. 1999). Pin1 also directly regulates APP processing in favour of non-amyloidogenic production of Aβ and over-expression of Pin1 reduces Aβ secretion from cell cultures (Pastorino et al. 2006). Knockout of the *PIN1* gene alone or in combination with transgenic mice over-expressing mutant APP results in elevated levels of toxic Aβ deposition in the brain in an age-dependent manner (Pastorino et al. 2006). Interestingly, polymorphisms in *PIN1* have been correlated with late-onset AD in some studies (Wijsman et al. 2004; Segat et al. 2007), but not in others (Poli et al. 2005; Nowotny et al. 2007), and polymorphisms resulting in increased Pin1 activity have been linked to a delayed onset of AD (Ma et al. 2012). These experiments strongly implicate Pin1 in the regulation of cellular pathways that promote cancer while inhibiting aging and neurodegeneration.

Age as a risk factor for cancer and neurodegeneration

Several decades ago it was first proposed that compromised mitochondrial homeostasis may be an underlying contributor to the aging process due to the deleterious effects of ROS production from cellular respiration (Harman 1972). Mitochondrial dysfunction is a hallmark characteristic of aging cells and likely precedes the development of several age-related diseases, including cancer and neurodegeneration (Chen 2012; Selfridge et al. 2013). The mitochondrion is an important organelle for regulation of cell survival or apoptosis which is largely mediated by changes in the production of ROS derived from cellular respiration. Basal levels of ROS can act as a second messenger to promote proliferation, while higher levels of ROS induce cellular damage and promote apoptosis. Moderate production of ROS from mitochondria is an important regulator of cellular proliferation and participates in cancer growth and tumorgenesis (Schumacker 2006; Hamanaka and Chandel 2010). Yet, in the context of AD, Aβ oligomers can accumulate in the mitochondrial matrix to interfere with electron transport and cause increased free radical production, leading to oxidative stress and

cellular death (Lustbader et al. 2004; Manczak et al. 2006; Petersen et al. 2008).

Mitochondrial dysfunction may arise naturally through the process of aging as mutations in mtDNA can accumulate over time or may be exacerbated by oxidative stress (Cottrell and Turnbull 2000). This theory is supported by the observation that mice expressing a mitochondrial DNA polymerase with a defective proof-reading function develop a premature aging phenotype (Trifunovic et al. 2004). In a follow up study, the authors demonstrated that there was no correlation between mtDNA mutation and ROS production or accumulation of oxidative damage (Trifunovic et al. 2005). This finding suggests that a mitochondrial regulatory mechanism other than oxidative stress is tied to the aging process. A recent study demonstrated the age-related decline in mitochondrial function was caused by a progressive decline in NAD^+ levels and sustained activation of HIF-1α in the skeletal muscle of mice (Gomes et al. 2013). This resulted in a decrease in transcription of mitochondrial genes for complexes of OxPhos and a decline in ATP production. The effect was mediated by the NAD^+-dependent deacetylase, Sirtuin 1 (SIRT1), which has previously been shown to inactivate HIF-1α by blocking p300 recruitment, thereby preventing transcriptional activation of HIF-1α target genes (Lim et al. 2010). Several different sirtuins have been reported to repress HIF-1α, including SIRT6 and SIRT7, which function by inhibiting HIF-1α activity and expression through a yet-unknown mechanism (Zhong et al. 2010; Hubbi et al. 2013). An age-dependent decline in NAD^+ levels has also been documented in several tissues in rats, including heart, lung, liver, and kidney, and in the pelvic skin of humans, and this decline correlated with increased oxidative stress and DNA damage (Braidy et al. 2011; Massudi et al. 2012). This trend is likely an underlying cause of age-related mitochondrial dysfunction, oxidative stress, and metabolic dysregulation, although the mechanism by which NAD^+ levels decline and whether this metabolic alteration occurs universally in all tissues remains to be determined. It has been suggested that the age dependent decline in NAD^+ levels and sirtuin activity promotes a shift towards aerobic glycolysis that favours carcinogenesis (Wu et al. 2014).

It is currently unknown if a similar mechanism exists in the brain and if it contributes to the development of neurodegenerative disorders linked to old age. An age-dependent decrease in NAD^+ levels in the brain could limit the extent to which neurons can use aerobic glycolysis for anti-oxidant and biosynthetic reactions, and may be a contributing factor in neurodegeneration. Alternatively, a decline in NAD^+ levels and sustained HIF-1α activation through loss of SIRT1 activity could promote metabolic reprogramming toward aerobic glycolysis leading to increased risk of cancer in certain tissues while promoting neuronal survival and enhanced memory in the brain. Further experiments are warranted to explore the tissue-specific role of NAD^+/SIRT1/HIF-1α in the development of cancer and neurodegeneration with age.

Mitochondrial dysfunction may also contribute to age-related disorders by promoting the accumulation of nuclear DNA mutations through increased oxidative stress. With age, DNA repair is compromised and mutation rates increase, which may partially explain the increased cancer rates in the elderly (Hoeijmakers 2009). Mutations in genes that encode glucoregulatory enzymes, including those mentioned above, could contribute to a sustained shift in metabolic reprogramming toward or away from aerobic glycolysis. This could lead to an increased risk for developing age-related diseases that are exacerbated by metabolic dysregulation. For example, pre-cancerous cells that contain mutations in oncogenes or tumor suppressor genes, which also efficiently undergo metabolic reprogramming toward a highly glycolytic phenotype, would have a significant competitive advantage against neighbouring cells, leading to tumour formation. In contrast, neurons of a pre-symptomatic AD brain that survive in an environment of high amyloid burden, which subsequently undergo metabolic reprogramming toward OxPhos would lose the survival advantage afforded by aerobic glycolysis and succumb to degeneration. Individuals may also contain polymorphisms in glucoregulatory genes that predispose them toward one metabolic program or the other. This would accelerate the development of age-related diseases and could also partially explain the inverse relationship between cancer and AD in the general population.

Future directions

The role of aerobic glycolysis in cancer is well characterized and documented; however, its role in promoting synaptic plasticity in the adult brain has

only recently emerged. It is still currently unknown if aerobic glycolysis plays a protective role in the adult brain against age-related neurodegeneration or AD. Also, the relative contribution of astrocytic versus neuronal based aerobic glycolysis to synaptic function and neuroprotective mechanisms is still poorly defined. The creation of transgenic mouse models in which metabolism can be directed towards either aerobic glycolysis or OxPhos, within either neurons or astrocytes, would greatly help answer these unresolved questions. As described above, there are several key regulatory proteins that direct the flow of glucose toward or away from glycolysis that could serve as targets for redirecting metabolic programming in experimental animal models. The majority of these regulatory proteins have been extensively studied in the context of cancer, yet their role in the progression of neurodegeneration has yet to be fully elucidated. Moreover, identification of agents which selectively activate these pathways in the CNS could potentially be pursued as therapeutic options for treating neurodegenerative diseases. Orphan nuclear receptors known as the estrogen-related receptors (ERRs) have been shown to interact with the PPARγ coactivator (PGC)-1α, which in turn bind to the promoter and regulate expression of many glycolytic genes and regulators of metabolism (Dublois et al. 2013). Interestingly, studies in breast cancer and hepatocarcinoma cells revealed that ERRα is indispensible for supporting the switch from oxidative to glycolytic metabolism (Dublois et al. 2013). It remains to be determined if selective ERRα expression or activation in the brain if sufficient to activate aerobic glycolysis and elicit neuroprotective effects.

Considering that age is the greatest risk factor for cancer and neurodegeneration, future work with animal models should be conducted with a focus on age-dependent alterations in metabolism in order to uncover its relative contribution to the origin of human diseases. The functionality of most biological molecules, such as DNA and protein, is dependent on the ability to maintain a precise three dimensional structure. The capacity of cells to convert substrates into metabolites depends on the molecular fidelity of biochemical reactions. The instability of the three dimensional folded structures and decline in molecular fidelity is the result of an increase in the thermodynamic entropy of biological molecules (Hayflick 2007). This increase in thermodynamic entropy entails an increase in molecular disorder. The loss of molecular fidelity which results, will induce a decrease in evolutionary entropy of the metabolic network and a concomitant decline in the efficiency of the metabolic processes; events that likely underlie the origin of several age-dependent diseases, including sporadic AD. The exact molecular mechanisms that contribute to the progressive loss of aerobic glycolysis and elevation of OxPhos in the adult brain remain to be fully characterized. Epidemiological studies could determine if polymorphisms in metabolic regulatory genes correlate with the onset of AD in the general population. This will help identify candidate proteins that become deregulated with age, or the proteins that are the most influential in contributing to pathogenesis of age-related diseases. Dissecting these pathways will help determine how metabolism is regulated in the adult brain and may provide insight into ways of maintaining the balance between aerobic glycolysis and OxPhos to promote synaptic plasticity and prevent neurodegeneration with age.

Concluding remarks

It is now apparent that cancer and neurodegenerative disorders likely share a common underlying cellular mechanism that becomes deregulated throughout the course of aging. A progressive shift towards predominately OxPhos within neurons with age may render these cell types more susceptible to toxin insult. In contrast, a shift towards aerobic glycolysis in certain mitotic cells that have undergone a transformation event, may endow these cells with a more aggressive cancer phenotype. Aerobic glycolysis has recently emerged as a key player in neuronal development, synaptic plasticity, and cognitive function. However, age-dependent selective processes may favour a decrease in aerobic glycolysis and a concomitant elevation of OxPhos in CNS neurons to meet the metabolic requirements of these cells. The cellular compartmentalization of aerobic glycolysis and OxPhos in astrocytes and neurons respectively needs to be taken into consideration when developing strategies to maintain metabolic homeostasis in the adult brain and prevent cognitive decline and AD progression with age. Aerobic glycolysis is an attractive mechanism for developing therapeutic interventions because it is regulated by several different mechanisms at multiple

steps, which translates to numerous potential therapeutic targets. However, the mechanisms by which cellular metabolism becomes deregulated through the course of aging is still largely unknown. This is especially true in the context of the human brain. Further investigation of metabolic dysfunction in the brain over the course of aging is warranted, which could lead to lifestyle or therapeutic interventions to ensure optimal metabolic homeostasis and cerebral function.

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