Cancer and Alzheimer's disease: intracellular pH scales the metabolic disorders

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REVIEW ARTICLE

Cancer and Alzheimer's disease: intracellular pH scales the metabolic disorders

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Abstract Alzheimer's disease (AD) and cancer have much in common than previously recognized. These pathologies share common risk factors (inflammation and aging), with similar epidemiological and biochemical features such as impaired mitochondria. Metabolic reprogramming occurs during aging and inflammation. We assume that inflammation is directly responsible of the Warburg effect in cancer cells, with a decreased oxidative phosphorylation and a compensatory highthroughput glycolysis (HTG). Similarly, the Warburg effect in cancer is thought to support an alkaline intracellular pH (pHi), a key component of unrelenting cell growth. In the brain, inflammation results in increased secretion of lactate by astrocytes. The increased uptake of lactic acid by neurons results in the inverse Warburg effect, such as seen in AD. The neuronal activity is dampened by a fall of pHi. Pronounced cytosol acidification results in decreased mitochondrial energy yield as well as apoptotic cell death. The link between AD and cancer is reinforced by the fact that treatment aiming at restoring the mitochondrial activity have been experimentally shown to be effective in both diseases. Low carb diet, lipoic acid, and/or methylene blue could then appear promising in both sets of these clinically diverse diseases.

Keywords Alzheimer · Cancer · pHi · Mitochondria · Pyruvate dehydrogenase · Lipoic acid · Methylene blue

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Introduction

The past few decades have seen very limited success in the fight against both cancer and Alzheimer's disease (AD). In both cases, the therapy paradigm has been focused on genomic abnormalities. However, evidences in literature favor reviewing the current prevailing medical dogmas for a paradigm shift.

Cancer and neurodegenerative diseases such as AD are widely considered as two different sets of diseases with different prognosis, sites of origin, patterns of spread, and treatment. Cancer and AD can be seen at

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both end of a biological pattern. In cancer, there is unrelenting cell division. In AD, there is prominent apoptotic cell death. Cancer and AD are different entities, but they share multiple common epidemiological and biological features (Reitz et al. 2011; Adami et al. 2008; Levy Nogueira et al. 2015). Both AD and cancer are now considered as metabolic diseases (Seyfried et al. 2010; Craft 2009).

Literature reports an inverse correlation between cancer and AD (Demetrius et al. 2013; Tabarés-Seisdedos et al. 2013; Sánchez-Valle et al. 2017). The prevalence of AD is correlated with a decreased incidence of cancer (Tabarés-Seisdedos et al. 2013; Driver et al. 2012). Similarly, a occurrence of cancer is associated with a reduced incidence of Alzheimer (Sánchez-Valle et al. 2017).

In this review we conclude that diverging clinical features and mutual exclusion practices may hide an underlying common feature of cancer and AD. In short, alkaline pHi is associated with impaired mitochondrial activity and unrelenting growth in cancer (da Veiga Moreira et al. 2016). In AD the main fuel for neurons is lactic acid. Mitochondrial failure may be the consequence of lactic acid accumulation which results in acidic intracellular pH, synaptic dysfunction, amyloid deposition and ultimately apoptosis. The difference in pHi may explain why patients with AD are less likely to develop cancer.

Similar epidemiological patterns for cancer and AD

In both cancer and AD, there is a small (< 10%) but informative proportion of the patients who have inheritable genetically transmissible risk factors (Levy Nogueira et al. 2015; Garber et al. 2005; Rocchi et al. 2003). More than 40 different genes are known to be involved in cancer. For example, BCRA1 and BCRA2 carriers are at a very risk not only for breast cancer but also for ovarian cancer and sarcoma (Levy Nogueira et al. 2015). This risk is high enough (80%) as to warrant prophylactic surgery (Adami et al. 2008). Differently to more common sporadic cancer, these tumors arise in young patients most commonly before the age of 50. In parallel to the context, cases of the AD are familial forms of autosomal-dominant inheritance, which usually have an onset before the age of 60 (Blennow et al. 2006). Most of autosomal-dominant familial AD can be attributed to mutations in one of three genes: those encoding amyloid precursor protein (APP) and presenilin 1 and 2 (Waring et al. 2008; Selkoe 1999). Most cases of AD do not exhibit autosomal-dominant inheritance and thus are termed sporadic AD.

These genetic features are rare and should not let us miss the mainstream. Most cases of AD and cancer are sporadic in nature. These sporadic diseases are strongly age-related (Demetrius et al. 2013). Cancer and AD share two major risk factors: age and sex. Two-thirds of cancer arise after the age of 70 (Reitz et al. 2011; Adami et al. 2008). Such as for cancer, advancing in age is a primary risk factor for AD. Every five years after the age of 65, the risk of acquiring AD approximately doubles, increasing from 3 to as much as 69 per thousand person-years (Bermejo-Pareja et al. 2008). The second major risk factor is inflammation.

Inflammation is also a common risk factor for cancer and AD (Reitz et al. 2011; Adami et al. 2008). In 1863, Virchow hypothesized that the origin of cancer was at sites of chronic inflammation (Balkwill et al. 2001) and overall inflammation (such as bronchitis, burn or hepatitis, etc.) showed to increase the risk of cancer (Balkwill et al. 2001; Sun et al. 2012; Ringehan et al. 2017; Caplin et al. 1975).

Carcinogenesis is a demonstration of the carcinogenicity of inflammation (James et al. 1997). The physical characteristics of the implant, rather than its chemical composition, is the critical determinants of tumor development. For example, chemically inert implant can only induce cancer if their shape is abrasive and inflammatory. The micrometer-scale surface morphology of the implant determines the nature of the subsequent cellular responses, which may predispose to tumor development (James et al. 1997). Asbestos is chemically inert but is a powerful carcinogen (Uguen et al. 2017).

Similarly, inflammation is a known risk factor for AD (Levy Nogueira et al. 2015). Exposure to traumatic brain injury and to stroke are core risk factors that predisposes an individual to sporadic neurodegenerative diseases (Levy Nogueira et al. 2018). Brain inflammation induced by repeated trauma increases brain levels of hallmark proteins associated with neurodegeneration such as amyloid β 1–42, observed in AD, total tau, and α-synuclein, observed in Parkinson disease (PD) (Levy Nogueira et al. 2018).

AD and cancer: a drastic difference in intracellular pH

Limitless replicative potential and apoptotic cell death can be viewed as the opposite ends of a biological spectrum. They may have the same primary cause.

To perform their normal physiological functions, it is essential that cells maintain the intracellular pH (pHi) within the physiological range. Intracellular enzyme activity, cytoskeleton component integration, and cellular growth and differentiation rates are all closely associated with the pHi (Christen et al. 1983).

In the early 1920's Otto Warburg did demonstrate a unique feature of cancer cells, namely an increased uptake of glucose and secretion of lactic acid by cancer cells, even in the presence of oxygen (Schwartz et al. 2017a, b; Alfarouk et al. 2014; Warburg 1956). This aerobic fermentation is the signature of most if not all cancers. Warburg also noticed a concomitant decreased number of mitochondria as well as of their activity level (Warburg 1956).

The Warburg effect have been proposed as a consequence of a decreased oxidative phosphorylation (Figs. 1, 2 and 3) (Warburg 1956; Schwartz et al. 2017a, b; da Veiga Moreira et al. 2016). Da Veiga Moreira et al. reported that pHi of tumor cells oscillates between 7.2 and 7.5, while in normal cells it oscillates between 6.8 and 7.3. Alkaline pHi triggers DNA decompaction and replication as well as cell division (Aerts et al. 1985; da Veiga Moreira et al. 2015). Unrelenting cell growth results in increased pressure, metastasis immune system activation (Schwartz et al. 2017a, b).

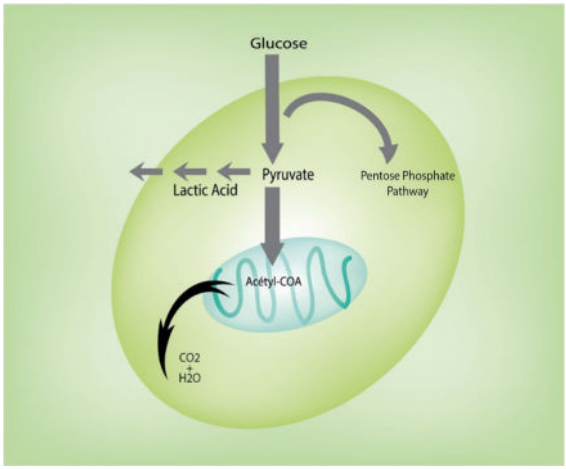

Fig. 1 Metabolism of a normal cell. Glucose is mostly degraded into pyruvate which is mainly degraded into carbonic gas and water by mitochondrial oxidative phosphorylation for ATP production

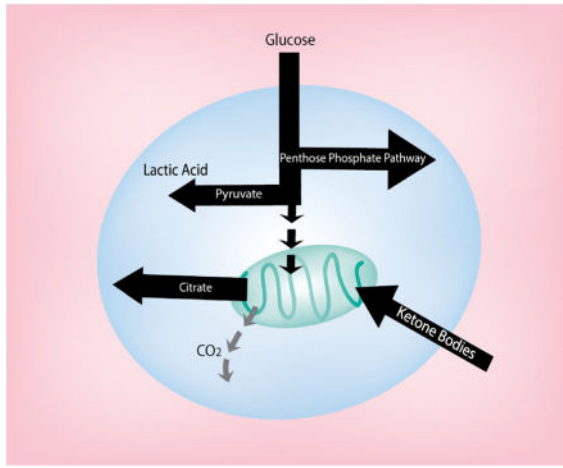

Fig. 2 Metabolism of a cancer cell. Because of decreased PDH activity there is a shift toward the anabolic pentose phosphate pathway and excretion of lactic acid resulting in extracellular acidosis. There is an increase convertion of citrate to cytosolic acetyl-CoA for lipid synthesis. Decreased mitochondrial respiration jointed with lactic acid extrusion probably causing intracellular alkalosis

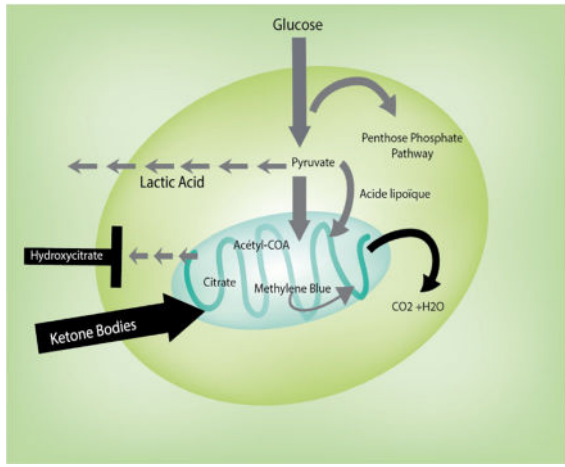

Fig. 3 Metabolism of a cancer cell treated with a metabolic cocktail (hydroxycitrate, lipoic acid, methylene blue) to enhance mitochondria respiration. Treatment with lipoic acid results in the activation of the PDH. Treatment with hydroxicitrate targets the conversion of citrate to acetyl-CoA. Methylene blue improves the mitochondria electron transfer during oxidative phosphorylation

Opposite to cancer, the pHi has been reported to be acidic in AD neurons (Fang et al. 2010; Xiong et al. 2008). The exact value of the pHi in AD does not appear to have been measured. During brain ischemia, pHi falls to 6.5 or below (Rehncrona 1985). A fall in pHi decreases neuronal activity (Sinning et al. 2013). The acidic pHi plays a crucial role in the hallmarks of the AD such as cell death (apoptosis) (Perry et al. 1980), amyloid plaques deposition (Ghalebani et al. 2012), as well as tau phosphorylation (Fig. 4) (Basurto-Islas et al. 2013). AD-associated enzymes have altered activities under acidic condition (Harguindey et al. 2017; Boron 2004; Paris et al. 1984). Pouysségur et al. (1986) showed that even under growth factor stimulation, fibroblasts could not enter S phase and divide when the intracellular pH is maintained below 7.2 (Fig. 5) (Paris et al. 1984).

Mitochondrial dysfunction as primary hallmark of cancer and AD

Transferring mitochondria from AD subjects to cell lines depleted of endogenous mitochondrial DNA (mtDNA) creates cytoplasmic hybrid (cybrid) cell lines that recapitulate specific biochemical, molecular, and histologic AD features (Swerdlow et al. 2017). The reason of the dysregulation of intracellular pH (pHi) is debated. Most authors focus on ion channels (Fang et al. 2010; Xiong et al. 2008; Paris et al. 1984; Blass et al. 2000), but it is mostly probable that the main reason relies on mitochondria dysfunction. Mitochondria feed on the substrate from the cytoplasm and in return provide energy to the eukaryote cell.

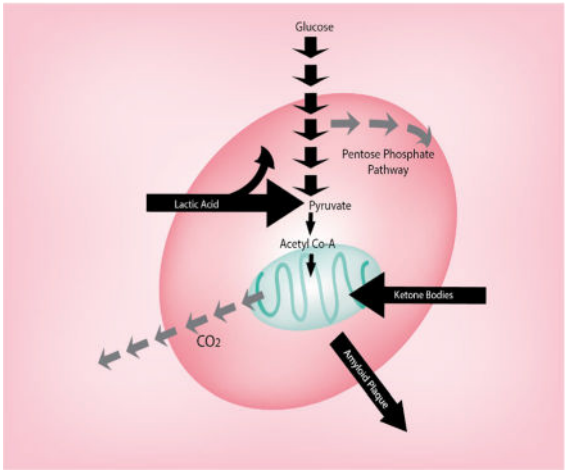

Fig. 4 Metabolism of a neuron with Alzheimer's disease. Because of decreased PDH activity there is a bottleneck at the level of the pyruvate resulting in acidosis (decreased catabolism of lactic acid) and decreased mitochondria respiration. The cell turns to alternative fuel like ketone bodies joined with amyloid plaques deposition

Cancer and AD metabolic phenotypes and show mitochondrial impairment where a sharp drop in the energy yield of the cells are reported, and in both case, there is a depletion in the ATP level (da Veiga Moreira et al. 2016; Blass et al. 2000; Driver et al. 2012).

Pyruvate dehydrogenase (PDH) is a complex set of subunits, converting pyruvate into acetyl-CoA. This complex enzyme connects the glycolysis, which takes place in the cytoplasm, to the mitochondria, where the Krebs cycle takes place. The activity of the PDH is decreased in both cancer and AD (Perry et al. 1980; López-Lázaro 2008). In AD, the decreased synthesis of acetyl-CoA results in deficit of acetylcholine (Perry et al. 1980). Lipoic acid is a cofactor of the second subunit of that complex. Lipoic acid has been suggested to improve the clinical features of AD (Hager et al. 2007; Shinto et al. 2014). Similarly, a combination of lipoic acid and hydroxycitrate (which targets the ATP citrate lyase) has been shown to slow tumor growth in mice whatever the site of primary cells injection. Preliminary clinical results are also encouraging (Schwartz et al. 2010, 2013).

It's known that menopausal transition plays a role on the prevalence of AD cases in women compared to men. A recent study showed that menopausal group of women had highest levels of estrogen-dependent memory lost and amyloid plaque deposition (Mosconi et al. 2018). Studies also report changes in brain consumption of glucose upon menopausal transition. For that, hormone therapy has been proposed as potential modulator of brain bioenergetics to enhance mitochondrial activity and maintenance of cognitive function for reduced risk of Alzheimer's disease (Rettberg et al. 2014). Ratnakumar et al. (2019) carried out post-mortem genome sequencing of women AD brain compared to ovariectomized female rhesus macaques subjected to estrogen intake. Interestingly, researchers found that down regulated genes in AD women are those upregulated in estrogen-treated macaque females. Closer to our study, the authors found that some mitochondrial genes parts of the oxidative phosphorylation and tricarboxylic acid pathways are downregulated in AD. Specifically, they

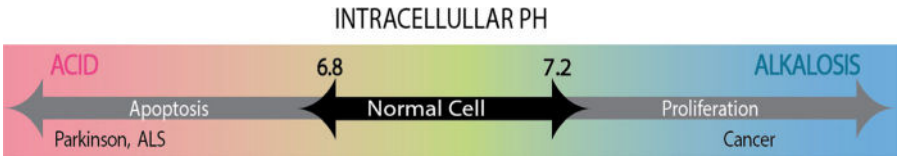

Fig. 5 The intracellular pH (pHi) of a normal cell oscillates between 6.8 and 7.2 from G0 to G2 phase of the cell cycle. In cancer cells, the alkaline pHi is connected to uncontrolled cell proliferation. Neurodegenerative diseases are correlated with acidic pHi and cell death

reported a downregulation of the mitochondrial MACT gene coding for malonyl CoA-acyl carrier protein transacylase involved associated with lipid metabolism and the respiratory electron transfer chain complex I protein. These results support the hypothesis of potential defective mitochondria in AD patients associated with Ab plaques (Zhang et al. 2003). Nevertheless, hormone therapy has shown mixed results at improving cognitive functions (Maki et al. 2012; Osmanovic-Barilar et al. 2016).

Methylene blue, a century-old drug, can receive an electron from NADH in the presence of complex I and donates it to cytochrome c, providing an alternative electron transfer pathway in defective mitochondria (Schwartz et al. 2013, 2014; Yang et al. 2017). In the AD, Methylene blue enhances glucose uptake and regional cerebral blood flow in rats upon acute treatment. Moreover, Methylene blue provides a protective effect in neurons and astrocytes against various insults in vitro, like superoxide production (Poteet et al. 2012), as well as rodent models of AD, PD, and Huntington disease (HD) (Yang et al. 2017). In human, Methylene blue appears effective in the treatment of early-stage AD and memory loss (Panza et al. 2016; Paban et al. 2014; Riha et al. 2005). Methylene blue increases oxygen consumption, which can result in a decrease of aerobic glycolysis in cancer cells and decreased cell proliferation (Wainwright et al. 1997, 1999). Tucker et al. (2018) has detailed the role of MB on neuroprotection and on the improvement of mitochondrial activity in AD-like cell lines and in vivo.

Low carb diet (LCD) bypasses the bottleneck at the level of the PDH and may have beneficial effects on neurodegenerative diseases (Barañano et al. 2008; Sofou et al. 2017; Caplliure-Llopis et al. 2019). Beneficial effects of polyphenols present in some LCD have also been reported (Caplliure-Llopis et al. 2019). These polyphenols are proposed as good antioxidants with key roles in enhancing mitochondria energetics. Therefore, the ketogenic diet appears promising in the treatment of AD (Gonzalez-Lima et al. 2014). However, the application of LCD in cancer patients must be clearly investigated, notably by the capacity of normal cells to supply ketone bodies, the main precursor of acetyl-CoA for lipogenesis in cancer cells (Israel et al. 2020). We propose that LCD provides energy-rich lipids bodies to cancer, which may result in high-throughput glycolysis to sustain anabolic pentose phosphate pathway and amino acids synthesis since glucose is no longer needed for lipid synthesis (Jin et al. 2019; Epstein et al. 2017).

The intracellular acidosis in AD results from lactic acid accumulation (Ortega et al. 2009; Schwartz et al. 2017a, b; Lauwers 1978). The mitochondria extrude proton ions in order to synthesize ATP. A decreased pHi gradient between the cytoplasm and the mitochondria has a profound impact on the energy yield of the mitochondria, and cytoplasmic acidosis results in decreased energy yield (Christen et al. 1983; Rial et al. 1999).

Inflammation causes increased lactate secretion

Inflammation paves the way toward carcinogenesis. Inflammation is characterized by tumor, dolor, rubor, and color as stated by Galen 2000 years ago. Inflammation can be caused by factors as diverse as heat, freezing temperature, trauma or multiple chemicals. Vascular leakage is a common feature of inflammation (Schwartz et al. 2009a, b; Cotran et al. 1964; Roviezzo et al. 2005). It can be caused by direct damage, resulting from a foreign body, burn or necrosis. This partial digestion of the protein will release larger amount of osmolites, further increasing the extracellular osmolarity (Schwartz et al. 2009a, b; Abolhassani et al. 2008).

Increased extracellular osmolarity results in increased cytokines secretion (Abolhassani et al.

2008). Exposure to cytokines has a profound effect on the metabolic profile of the target cells. In dendritic cells, lipopolysaccharide promotes the Warburg effect (Hsu et al. 2008; Palsson-McDermott et al. 2013). Inflammatory immune cells, when activated, display much the same metabolic profile as a glycolytic tumor cell (Palsson-McDermott et al. 2013). This involves a shift in metabolism away from oxidative phosphorylation towards anabolism. The result of this change in macrophages is to provide metabolic intermediates for the biosynthesis of immune and inflammatory proteins. Also, a rise in tricarboxylic acid cycle intermediates results in lipid biosynthesis (Palsson-McDermott et al. 2013).

In inflammation such as infection or trauma, there is increased secretion of lactate resulting in increased serum and urine level of lactate (Kumar et al. 2006; Nguyen et al. 2010; Marcoux et al. 2008).

Increased lactate secretion may trigger initiation of AD

Recent studies have shown a close intertwined metabolism between astrocytes and neurons. In physiological conditions, glucose is metabolized to lactate by astrocytes and microglial cells to a lesser extent, and the lactate is released into the extracellular milieu (Magistretti et al. 2018; Walz et al. 1988; Descalzi et al. 2019). Researchers have highlighted the existence of a physiological gradient of lactate between astrocytes and neurons (Mächler et al. 2016). The authors reported a higher level of lactate in astrocytes as well as a net flow of lactate to neurons. Thus, neurons use lactate as a substrate for mitochondrial energy production by oxidative phosphorylation (Pellerin et al. 2007). As reported above for dendric cells, inflammatory stresses also affect the glials-neurons symbiotic-like relationships in lactate managements. Astrocytes exposed "in vitro" to inflammation secrete larger quantities of lactate (Iglesias et al. 2017; Fuller et al. 2010). In human, during brain inflammation, there is lactic acid secretion in the CSF (Lauwers 1978). This increased secretion of lactate is also present in neurodegenerative diseases as it can be measured in the spinal fluid (Sonntag et al. 2017; Koroshetz et al. 1997). In addition, it has been shown that the gene coding for the enzyme lactate dehydrogenase, which allows the conversion of pyruvate to lactate during glycolysis, is overexpressed in mice showing signs of aging (Ross et al. 2010; Rossignol et al. 2003). In addition, the authors showed that the mitochondrial activity of cells in aging tissues is largely attenuated (Ross et al. 2010). Therefore, these studies have made possible rationalizing mechanisms potentially at the origin of minors neurodegenerative diseases, possibly by the cytosolic acidification of neurons due to a non-metabolizable overconsumption of lactate, is hypothesized here and denominated as the reverse Warburg effect (Demetrius et al. 2014).

Studies have shown that "resting" microglia adapt their glucose uptake upon inflammatory stimuli (Wang et al. 2019; Orihuela et al. 2016). This is referred as microglia activation, which occurs when "resting" microglial macrophases encounter local inflammation and perform cellular debris cleaning and maintenance of the central nervous system (CNS). Microglial cell activation is associated to a metabolic switch from OXPHOS to aerobic glycolysis (Orihuela et al. 2016; Afridi et al. 2020). Uncontrolled microglia activation dissipates the metabolic perturbation by reprogramming to astrocytes showing Warburg-like phenotype, probably the main causes of the enhanced neurotoxicity in AD and in other neurodegenerative disease (Cartier et al. 2014; Afridi et al. 2020).

The most probable mechanism leading to neurotoxicity and the manifestation of the first phenotypic signs of AD is the increased lactate uptake and reduced mitochondrial activity resulting in pronounced cytoplasmic acidification (Erlichman et al. 2008) and probably cell death (Zhou et al. 2010; Cole et al. 2008). Neurons poorly oxidize lactic acid, which accumulates in the brain and favoring amyloid beta (Aβ) plaque deposition (Redjems-Bennani et al. 1998; Liguori et al. 2015; Xiang et al. 2010; Yates et al. 1990). Interestingly, microglial cell and neuron in vitro co-cultures show increased neurons death in presence of Aβ plaques (Giulian et al. 1996).

Similarly to astrocytes/microglial cells in AD, cancer-associated fibroblasts in tumor stroma tend to activate glycolysis and secrete lactate, which leads to a reverse Warburg effect, feeding cancer cells with lactate (Yoshida 2015).

Shift to alternative energy sources

As mitochondria are (at least partially) disconnected from the glycolytic pathway, the cell must also count on alternative energy sources.

In cancer, there is an increased uptake of glucose with enhanced HTG, which provides cancer cells with two ATP molecules per molecule of glucose. Pyruvate, which cannot be converted into acetyl-CoA, is converted and secreted as lactic acid in the extracellular space. This is a clear manifestation of the Warburg effect (Swerdlow et al. 2017).

In AD, there is a generalized shift from glycolytic energy production toward the use of alternative fuel, such as ketone bodies (Yao et al. 2009, 2010). This is evidenced by a 45% reduction in cerebral glucose utilization in AD patients, which is concurrent to a decrease in the expression of glycolytic enzymes coupled to a decrease in the activity of the PDH complex and of the respiratory complex IV cytochrome c oxidase. "Patients with incipient AD exhibit a utilization ratio of 2:1 glucose to alternative fuel, whereas comparably aged controls exhibit a ratio of 29:1, whereas young controls exclusively use glucose as with a ratio of 100:0 ratio" (Yao et al. 2009; Hoyer 1991). These are markers of decreased mitochondrial bioenergetics and of early-onset Alzheimer disease.

White matter degeneration is also a pathological hallmark of neurodegenerative diseases including Alzheimer's disease. One can thus propose that a decline in mitochondrial respiration and pronounced lipid oxidation trigger mitochondrial hydrogen peroxide production and cytosolic phospholipase-A2 sphingomyelinase pathway activation. Indeed, an increase in fatty acids and mitochondrial fatty acid metabolism machinery was concurrent to a rise in brain ketone bodies and a decline in plasma ketone bodies. "catabolism of myelin lipids to generate ketone bodies can be viewed as a systems level adaptive response to address brain fuel and energy demand" reported Yao et al. (2010). As brain cells shift to alternative sources, there is a decrease in the glucose uptake such as seen in Positron Emitting Tomography (Iaccarino et al. 2017).

Recent literature has led to a strong interest in ketone bodies for the possible management of patients with mild cognitive impairments or as a preventive approach. It was first used in the treatment of epilepsy by mean of prolonged fasting or by ketogenic diet (KD) and supplementation of β-hydroxybutyrate, a medium-chain triglyceride (Stafstrom and Rho 2004). These diets could have potential benefits on AD patients by reducing local inflammation accompanying high-throughoutput glycolysis in glial cells and extinguishing mitochondrial ROS accumulation in neurons. As highly encouraging these approaches can be for the management of AD patients (Taylor et al. 2019; Brandt et al. 2019), they can also have a negative effect on cancer patients because the ketone bodies catabolism pathway is widely used by cancer cells as well, notably via the Succinyl-CoA:3-ketoacid-coenzyme A transferase (SCOT) enzyme (Israël and Schwartz 2020; Yao et al. 2010). However, further research needs to be conducted to determine the benefits of these complementary therapies.

Conclusion

Literature thus suggest that AD and cancer have more in common than previously acknowledged. Showing similar epidemiological patterns (age and inflammation), they may also share a common biochemical explanation, i.e. a decreased mitochondria horsepower. The different clinical features may be the simple consequence of the different cell fuel. In cancer cells the major nutrient is glucose for nucleotide and amino acid production, glutamine for amino acids and nitrogen donor, ketone bodies for lipids and membrane synthesis. In Alzheimer disease, lactic acid excreted by astrocytes is reported as a major fuel for neurons. We assume that in cancer cells, the dysfunctional mitochondria may be a relative consequence of a prolonged intracellular alkalinization promoting cell proliferation. Conversely, in Alzheimer disease, the intracellular acidification, probably a consequence of lactic acid consumption, may be involved in mitochondrial dysfunction and neurons apoptosis.

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Compliance with ethical standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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