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REVIEW ARTICLE

Alzheimer's as a metabolic disease

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Abstract Empirical evidence indicates that impaired mitochondrial energy metabolism is the defining characteristic of almost all cases of Alzheimer's disease (AD). Evidence is reviewed supporting the general hypothesis that the up-regulation of OxPhos activity, a metabolic response to mitochondrial dysregulation, drives the cascade of events leading to AD. This mode of metabolic alteration, called the Inverse Warburg effect, is postulated as an essential compensatory mechanism of energy production to maintain the viability of impaired neuronal cells. This article appeals to the inverse comorbidity of cancer and AD to show that the amyloid hypothesis, a genetic and neuron-centric model of the origin of sporadic forms of AD, is not consistent with epidemiological data concerning the age-incidence rates of AD. A view of Alzheimer's as a metabolic disease—a condition consistent with mitochondrial dysregulation and the Inverse Warburg effect, will entail a radically new approach to diagnostic and therapeutic strategies.

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized histopathologically by neuronal loss, and clinically by progressive deficits in memory, impairment of cognitive function, and changes in behavior and personality. The principal biochemical signature of the disease is the presence of extracellular deposits of the peptide beta amyloid as senile plaques and intracellular neurofibrillary tangles in subcortical regions of the brain. This neurodegenerate disorder affects more than 40 million people worldwide. A small fraction of AD cases are hereditary. These cases include an early onset form, attributable to mutations in three genes, the amyloid precursor protein (APP), presenilin 1 and presenilin 2, and a late onset form, associated with the apolipoprotein E gene (APOE). The large majority of AD cases, however, are sporadic and age-related, with an age of onset about 70 years.

Familial and sporadic AD

The dominant paradigm which drives efforts to understand the origin and progression of sporadic

forms of the disease is the amyloid cascade hypothesis. This model assumes that the early onset form and the sporadic form of the disease have the same etiology. Accordingly, AD is primarily a disease of amyloidosis, that is an imbalance in the production and clearance of beta amyloid, a proteolytic degradation product of the APP. The model postulates that amyloidosis, and the concomitant imbalance of amyloid production and clearance, is due to missense mutations in one of three genes APP, presenilin 1, presenilin 2 (Selkoe 1991, 2011; Hardy and Selkoe 2002; Hardy 2009).

The amyloid hypothesis is based on a genetic, neuron-centric characterization of age-related neurodegenerative diseases. The model invokes the assumption that neuronal loss, a histopathological hallmark of AD, is completely determined by the toxicity of senile plaques and tangles, the biochemical signatures of the disease. This assumption ignores the fact that neuronal dynamics is highly contingent on brain energy metabolism, a process which involves both neurons and astrocytes (Pellerin and Magistretti 2004). Both cell types utilize glucose as an energy source. In neurons, the predominant mode of energy production is by oxidative phosphorylation, whereas in astrocytes, energy production is by means of glycolysis. The lactate which is produced anaerobically by astrocytes provides an additional source of energy for neurons under conditions when the OxPhos activity in neurons is impaired.

A recent model of the origin of AD which aims to accommodate this neuron-astrocytic interaction assumes that the early and late onset forms of the disease have distinct etiologies (Demetrius and Simon 2012). According to this model, the early onset form can be understood in terms of a neuron-centric perspective. However, in the case of the sporadic form, the model implicates mitochondria, the energy producing organelles, as the critical elements in the development of the disease. According to this neuroenergetic perspective, the *primary* cause of the sporadic form of AD is the imbalance of the fusion and fission of the mitochondria in neuronal cells. This imbalance is induced by mitochondrial dysregulation, the metabolic analogue of the nuclear genomic mutations proposed in the amyloid cascade hypothesis.

This neuroenergetic model of the sporadic form of AD considers the interaction between neurons and astrocytes as one of the critical factors which determine the origin of the disease and its progression. This model emphasizes the energy supply and demand of cells, and contends that the imbalance in the fusion and fission of mitochondria in neuronal cells—a metabolic hallmark of AD—is the result of the up-regulation of OxPhos activity in the electron transport chain. This mode of metabolic alteration is a compensatory response to the impairment in energy metabolism induced by mitochondrial dysregulation.

The term Inverse Warburg effect which we have introduced to describe the up-regulation of OxPhos activity, derives its rationale from Otto Warburg's studies of metabolic reprogramming in tumor cells. Based on metabolic data collected from animal and human tumor samples, Warburg (1931) proposed that irreversible damage to respiration was the primary cause of cancer. According to this argument, the up-regulation in glycolysis observed in tumor cells is a compensatory mechanism of energy production to maintain the viability of impaired cells—a process now called the Warburg effect.

Oxidative phosphorylation and glycolysis are two complementary mechanisms of energy production in cells. The term Inverse Warburg effect is thus the logical connotation of the shift in OxPhos activity in AD.

Inverse comorbidity and the metabolic paradigm

The amyloid cascade hypothesis remains a very influential model in the study of AD, in spite of the conflict of its predictions with empirical data (see Pimplikar 2009), and the failure of various clinical trials based on the central tenets of the hypothesis (see Palmer 2011).

The prototypic status of the model derives from the fact that it is strongly embedded within the genomic paradigm that currently drives the study of most age-related human diseases. According to this paradigm, diseases such as cancer, and neurological disorders such as AD, Parkinson's disease (PD), Huntington's disease (HD) and (ALS) are primarily the result of genomic instability. This generic concept, which pertains to increased mutability of the nuclear genes, was considered an essential characteristic for manifesting the various hallmarks of these various disorders.

The distinction between early and late onset forms of the diseases which emerged through epidemiological studies has caused a reevaluation of this genomic

instability hypothesis. It is now generally acknowledged that the early and late onset form of these diseases may have different etiologies. The biochemical argument that underlies this notion, in the case of solid tumors, is described in a recent review of the origin of cancer (Seyfried and Shelton 2010). The early onset forms of most cancers do have a genetic basis and are initiated by nuclear gene mutations or chromosomal abnormality. However, the sporadic or late onset forms are often initiated by mitochondrial dysregulation. The cancer phenotype, according to the Warburg model, is caused by the up-regulation of glycolysis, a process of metabolic reprogramming to compensate for the diminished energy production due to mitochondrial dysfunction (Seyfried and Shelton 2010; Shaw 2006; Vander Heiden et al. 2009).

This reassessment of the genomic paradigm in cancer research has recently impinged on the study of neurological disorders. Epidemiological and various clinical studies have indicated an inverse relation between cancer and certain neurodegenerative diseases, in particular AD and PD (Roe et al. 2010; Driver et al. 2012; Plun-Favreau et al. 2010). These diseases were discovered to be longitudinally associated with a reduced risk of cancer, and a history of cancer was associated with a reduced risk of these disorders. This condition, called inverse comorbidity (Tabarés-Seisdedos and Rubenstein 2013), suggests a common mechanism linking both diseases. More precisely, it suggests, in particular, that the sporadic forms of AD may share with cancer certain common biochemical features. We will appeal to this inverse comorbidity condition to contrast the validity of the amyloid cascade hypothesis, and the neuroenergetic hypothesis as models of the origin of AD. We will show that, while the phenomenon of inverse comorbidity can be explained within the context of mitochondrial dysregulation and the Inverse Warburg effect, it is inconsistent with the amyloid cascade model.

This new finding, when integrated with the inconsistent predictions of the amyloid hypothesis, provides compelling reasons to abandon the amyloid model as the primary cause of sporadic forms of AD. Our analysis furthermore provides support for the proposition that metabolic dysregulation and the Inverse Warburg effect are the primary cause of the disorder, and indicates that Alzheimer's is primarily a metabolic disease.

Origin of Alzheimer's disease

The clinical manifestations of AD are cognitive deficit and episodic memory loss with progression over a protracted time course, culminating in dementia and debility.

A minority of AD patients have a familial form of the disease. This form is usually characterized by Mendelian inheritance in an autosomal dominant manner. The large majority of AD cases—the late onset form of the disease, has no consistent mode of inheritance. These cases are strongly influenced by variants of the APOE gene. These variants influence the susceptibility to the disease by decreasing the age of onset. However, the primary risk factor for the disease is the age of the individual (Tanzi 2012).

The amyloid cascade tenet, and the neuroenergetic hypothesis—a general term we have introduced to characterize the cascade of metabolic events initiated by mitochondrial dysregulation and the Inverse Warburg effect—are competing models of the origin of sporadic forms of AD. Both models recognize the primacy of mutations in the APP gene and the secretases in determining the *familial* or early onset form of the disease. The assumptions of the models regarding the origin of the *sporadic* form of AD are based on fundamentally different associations of the disease with age.

Amyloid hypothesis

The amyloid hypothesis holds that the link of the disease with age simply reflects a more prolonged exposure of the neurons to the senile plaques and neurofibrillary tangles generated by abnormal processing of APP. The model thus contends that the early onset and the late onset forms of the disease have the same cause, namely, mutations in the APP genes and the presenilin genes.

Accordingly, the sporadic form of AD can be characterized in terms of genomic instability. The extracellular plaques and intracellular tangles are biochemical abnormalities generated by a genetically induced imbalance in beta amyloid production and clearance. These biochemically defects will ultimately disrupt synaptic function and result in neuronal loss and the clinical hallmarks of AD.

The cascade of events described in Fig. 1 is consistent with studies of the familial form of the

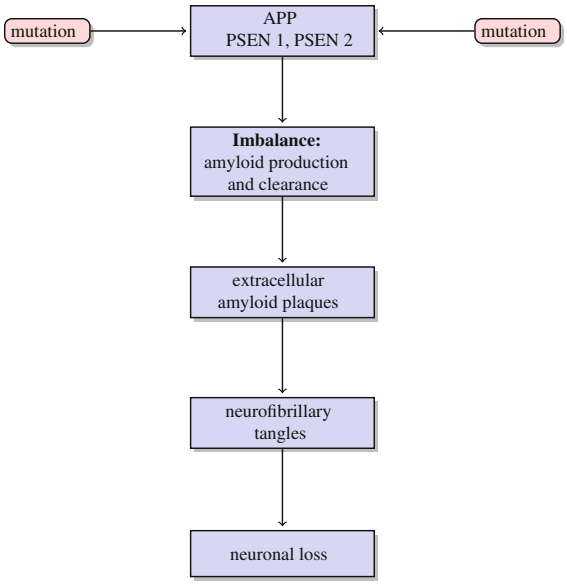

Fig. 1 Amyloid cascade hypothesis: transition towards AD

disease. In these cases the age of onset ranges between 35 and 65 years with a mean age of incidence of about 50 years. The age-distribution of these early onset forms of AD is generally described by a bell-shaped curve (Hendrie 1998; Fratiglioni et al. 1999; Swerdlow 2007). This distribution is consistent with the observation that familial forms of the disease follow a Mendelian inheritance pattern.

The neuroenergetic hypothesis and the Inverse Warburg effect

The neuroenergetic hypothesis holds that the association of the disease with age reflects degenerative changes in the metabolic machinery of both neurons and astrocytes. These changes at the molecular level are characterized by an increase in molecular disorder within the metabolic machinery of mitochondrial neurons and the energy producing networks in the astrocytes. These events will induce an increase in *thermodynamic entropy*, a measure of the extent to which energy is dispersed or distributed among the molecular components of the cells, and a concomitant decrease in *evolutionary entropy*, a measure of the rate at which energy is appropriated from the external environment and distributed among the cellular components (Demetrius 2004).

Now, the activity of complex biomolecules, such as DNA, proteins and RNA are determined by the

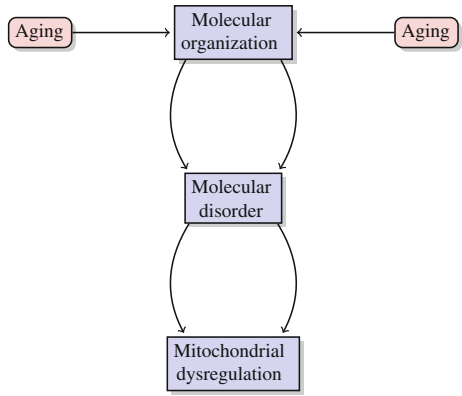

Fig. 2 The transition from molecular organization to mitochondrial dysregulation due to aging

stability of their three dimensional folded structures. The thermodynamic instability of these molecular aggregates entails that their structure and activity cannot be maintained indefinitely. Thermodynamic instability generates molecular disorder and a decrease in molecular fidelity. The impact of these effects on the complex biomolecules will be conformational alterations and covalent modifications in structure. In the case of proteins, the loss of molecular fidelity will result in protein misfolding and amyloid formation. In the context of this model, senile plaques and neurofibrillary tangles are natural consequences of the aging process (Cornwell and Westermark 1980).

The structural molecular changes, the dispersal of energy, and the decline in metabolic efficiency which the process of aging induces, will ultimately result in a state of mitochondrial dysregulation. This pertains to a decrease in the capacity of cells to maintain levels of ATP production necessary to ensure neuronal functioning and viability. The transition from a state of molecular organization to mitochondrial dysregulation due to aging and a concomitant decrease in evolutionary entropy is described in Fig. 2.

Metabolic alteration and the transition to neuronal loss

Neurons are highly specialized cells whose function is to maintain connections with other neurons for the lifetime of the organism. They use an enormous amount of energy to process information, and rely almost exclusively on oxidative phosphorylation to meet energy needs. Our model posits that AD is ultimately a

consequence of a compensatory alteration in brain energy metabolism in response to diminished energy production in damaged neurons. Here we describe the steps by which the response to this energy "crisis" leads to neurodegeneration and eventually cell death.

(a) Upregulation of OxPhos. As neurons are unable to use glycolysis to help meet energy needs, they respond by upregulating OxPhos. This metabolic reprogramming event (*the Inverse Warburg effect*) is the key step toward eventual neuronal loss. Empirical support for this effect is described in Zhu et al. (2006), Reddy (2004), and Nagy et al. (1997). Up-regulation of OxPhos leads to a transition from normal aging, defined by mild accumulation of amyloid plaques and impairment of synaptic function, to pathological aging, characterized by severe and diffuse accumulation of senile plaques and neuronal loss. This occurs by way of increased production of reactive oxygen species (ROS).

(b) Oxidative Stress. ROS are in a more reactive state than molecular oxygen. These molecules have a cell signaling role. However, in large concentrations they can have a deleterious effect on DNA, RNA and proteins. Mitochondria generate most of the endogenous ROS. The production of ROS is increased when the electron carriers in the initial steps of the electron transport chain (ETC) harbor excess electrons, a condition which may arise from the upregulation of OxPhos activity. The term oxidative stress refers to an imbalance between the generation and detoxification of ROS. Oxidative stress can therefore be considered an immediate and inevitable product of the Inverse Warburg effect. Neurons are particularly susceptible to free radicals as they have lower levels of antioxidant enzymes than other cell types.

(c) DNA Damage. Oxidative stress and the resulting free radical damage to DNA and cellular proteins are known to be key events that occur very early in AD pathogenesis (Nunomura et al. 2001). Oxidative stress causes damage to DNA bases as well as strand breaks. If unrepaired, they can lead to derangements ln basic cellular functions and eventually cell death. A careful review and repair of DNA occur each time a cell cycles. As terminally differentiated cells, neurons do not have the benefit of cell cycle repair mechanisms. Thus the neuron limits itself to repairing only the DNA it uses, and accumulates a large amount of mutations in other areas. While the neuron has DNA repair machinery, it is inferior to that found in cycling cells. This makes the neuron more susceptible to apoptosis from DNA damage (Kruman 2004).

(d) Cell cycle activation. Under normal conditions neurons never enter the cell cycle, and once mature, no longer have the capacity to complete mitosis. However, there is clear evidence of aberrant cell cycle entry in AD. It is unclear what prompts this highly abnormal response, but oxidative stress and DNA damage are potent mitogens. The "two-hit" hypothesis of AD holds that oxidative stress and abnormal mitotic signaling are the key factors leading to abnormal cell cycle entry and ultimately to neuronal loss (Zhu et al. 2007). Others have proposed that neurons enter the cell cycle in order to activate the cellular DNA repair response, as a final attempt to cope with overwhelming DNA damage (Kruman 2004). Affected neurons express cyclins and cyclin-dependent kinases and many other characteristics of cycling cells, but in a dysfunctional and uncoordinated way. The cell cycle stalls soon after DNA synthesis is complete, and the mitochondrial proliferation characteristic of S phase leads to further oxidative damage.

(e) Neuronal loss. In normal mitosis, progression through the cell cycle is controlled by checkpoints. If DNA damage is detected, the cycle will be arrested and an attempt at repair made. If repair is not successful, apoptotic pathways will be triggered. However, it seems that neurons can remain in a state of stalled mitosis for some time, despite their burden of DNA damage. This is likely because their apoptotic machinery is also uncoordinated and dysfunctional. Eventually, though, apoptosis occurs in the face of overwhelming DNA damage.

The sequence of events which lead to cell cycle dysregulation as a result of mitochondrial dysregulation and the Inverse Warburg effect is illustrated in Fig. 3. The transition from cell cycle activation to neuronal loss is described in Fig. 4.

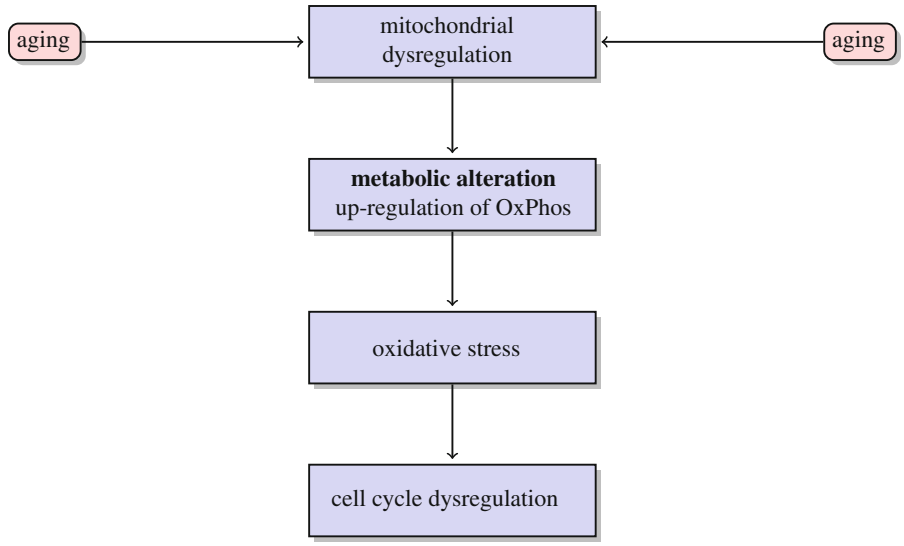

Fig. 3 The transition from mitochondrial dysfunction to cell cycle dysregulation

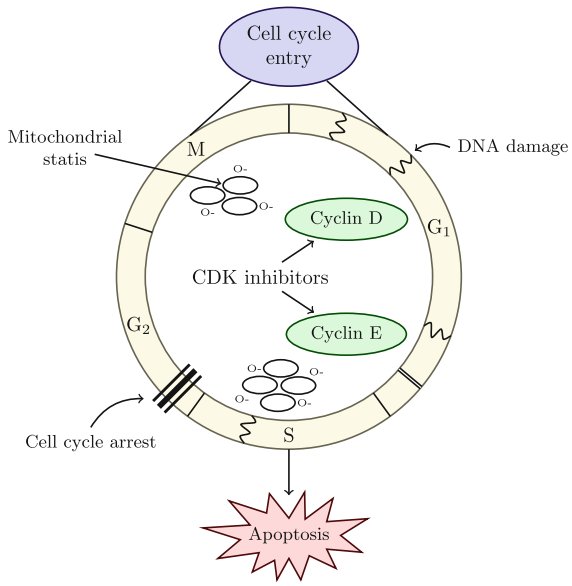

Fig. 4 The transition from cell cycle dysregulation to neuronal loss

Alzheimer's disease: genetic and metabolic perspectives

The amyloid cascade hypothesis and the neuroenergetic process—mitochondrial dysregulation and the Inverse Warburg effect—are two contrasting models of the origin of sporadic forms of AD. The first is a genetic model which postulates that the primary cause of AD is the imbalance in the production and clearance of beta amyloid. The second is a metabolic model which posits that the primary cause of AD is the imbalance in the fusion and fission of intact and damaged mitochondrial neurons. We will now contrast the properties of the two models and then appeal to the inverse comorbidity of cancer and AD to provide support for the claim that the sporadic form of AD is a metabolic disease determined by the processes of mitochondrial dysregulation and the Inverse Warburg effect.

The amyloid hypothesis and the neuroenergetic model: a contrast

The amyloid hypothesis is a genetic and neuron-centric model that considers AD to be determined by processes intrinsic to the genetic network that regulates the biochemical events within neurons. According to the amyloid hypothesis, the critical parameters are the neuritic plaques and the neurofibrillary tangles that arise from mutations and aberrant processing of the APP. Neuronal loss and dementia are the result of the toxicity of the beta amyloid moiety.

The neuroenergetic hypothesis, defined by mitochondrial dysregulation and the Inverse Warburg effect, is a metabolic and neuron–astrocytic model that considers AD to be determined by events intrinsic to the metabolic network that defines neuron–

Table 1 Contrast between amyloid hypothesis and the neuroenergetic model

Properties	Amyloid cascade hypothesis	Neuroenergetic hypothesis and the Inverse Warburg effect
Mechanism	Genetic mutation	Mitochondrial dysregulation and the Inverse Warburg effect
Process	Imbalance in amyloid production and clearance	Imbalance in intact and damaged mitochondria
Neuronal loss	Toxicity of beta amyloid	Diminished energy production

astrocytic interaction. Energy metabolism in the brain involves both astrocytes and neurons. Both cell types utilize glucose as an energy source. In astrocytes, the glucose is metabolized anaerobically to lactate which is released into the extracellular milieu. In neurons, the predominant mode of energy production is oxidative phosphorylation. Neurons are unable to up-regulate glycolysis due to the lack of activity of the glycolysis promoting enzymes. Hence when neurons are subject to mitochondrial dysregulation, the associated increased demand for energy requires the up-regulation of OxPhos activity—the Inverse Warburg effect.

The critical parameters in the context of this neuroenergetic model are the distribution of intact and damaged mitochondria that arise primarily from the diminished energy production induced by the aging process. Neuronal loss is due to apoptosis induced by oxidative stress and cell cycle dysregulation.

The principal features of the two models are contrasted in Table 1. Amyloid plaques are fragmented proteins which are implicated in both the amyloid cascade model and the neuroenergetic model. These biochemical abnormalities, however, derive from different physiological processes and are involved in AD pathogenesis in quite distinct ways.

In the context of the amyloid cascade hypothesis, the beta amyloids are the *primary* cause of AD. These substances are the result of aberrant processing of the APP gene due to mutations in the APP and the secretase genes as postulated in (Hardy and Selkoe 2002). Neuronal loss and dementia are the result of synaptic impairment induced by the beta amyloids. The model predicts that reducing the amyloid burden should ameliorate Alzheimer symptoms.

Amyloid plaques derive from a quite different mechanism when considered in the framework of the neuroenergetic hypothesis (Demetrius and Simon 2012). According to this model, beta amyloids are the derivatives of the thermodynamic instability, and the increase in thermodynamic entropy which defines the aging process. The decrease in molecular fidelity, a critical hallmark of the aging process, will result in covalent modifications of APP, and consequently, the conversion of normally soluble forms of the protein into insoluble fibrils.

This model entails that the beta amyloids are secondary derivatives of the aging process. This model predicts that reducing the amyloid burden will not necessarily ameliorate Alzheimer symptoms. According to the neuroenergetic model, the primary cause of AD is the Inverse Warburg effect, and the cascade of metabolic events which this mode of metabolic alteration generates. Hence amyloid plaques may affect the *rate* at which neuronal loss occurs. However, its effect on the incidence of neuronal loss will be minimal.

Inverse comorbidity

The sporadic forms of cancer and AD are age-related disorders. Epidemiological studies have now elucidated certain significant relations between the two diseases. The incidence of both diseases increases exponentially with age. In addition, the incidence of AD and cancer are inversely related, a phenomenon now described as "inverse comorbidity" (Tabarés-Seisdedos and Rubenstein 2013). The decreased risk of AD in cancer survivors (and vice versa) is not primarily due to increased mortality or diagnostic bias, but suggests the possibility of a biological link between the two families of diseases (Driver et al. 2012). This is quite plausible, since as we have seen, cancer and AD share many pathophysiological features, such as abnormal activation of the cell cycle, DNA damage, oxidative stress and inflammation. While these factors lead to limitless replicative potential in the case of cancer cells, the outcome in the case of AD is progressive neuronal death.

Now a necessary and sufficient condition for two age-related diseases to be inversely comorbid are the

following set of biochemical and epidemiological features.

(I) *Biochemical*: The existence of an enzyme or a metabolic pathway in the biochemical network of both diseases which satisfies the following property: If the enzymes or metabolic pathways are subject to regulatory changes in the same direction, then the probability of individuals being diagnosed with the diseases will be inversely related.

(II) *Epidemiological*: The age-specific incidence rates of each disease in the population must have similar statistical distributions.

The sporadic forms of cancer is primarily a metabolic disease (see Seyfried and Shelton 2010). The major hallmarks of sporadic forms of the disease can be linked to impaired mitochondrial functions. In order to maintain viability, tumor cells undergo metabolic reprogramming whereby the tumor cells gradually up-regulate glycolysis using glucose and glutamine as energy substrates. The glycolytic enzyme PFKFB3 is a master regulator of glycolysis. The up-regulation of this enzyme enhances the metabolic reprogramming which will ultimately lead to the cancer phenotype. The incidence of cancer also increases exponentially with age.

We will now invoke the conditions for the inverse comorbidity of age-related diseases to show that the Inverse Warburg effect provides a bioenergetic explanation of the inverse comorbidity of cancer and AD. However, the amyloid cascade hypothesis is inconsistent with this epidemiological fact.

(a) The neuroenergetic model and the Inverse Warburg effect
According to the neuroenergetic hypothesis, the critical event in the origin of AD is the Inverse Warburg effect. This mode of metabolic alteration is associated with a decrease in the activity of the enzyme PFKB3. This enzymatic regulation, as described in (Demetrius and Simon 2013), is one of the primary events that initiates a cascade of biochemical processes leading to cell cycle dysregulation and neuronal death.
The Inverse Warburg effect also implies that the risk of AD will increase exponentially with age. This property is an immediate consequence of the assumption that age, in this model, reflects the progressive decrease in the functioning of the metabolic machinery in the neuronal cells. The Inverse Warburg effect thus furnishes a mechanism for the origin of AD which is consistent with Inverse Comorbidity of cancer and AD.

(b) The amyloid cascade hypothesis
According to the amyloid cascade model, the association of the disease with age characterizes the prolonged exposure of the neurons to the senile plaques generated by abnormal APP processing. Hence the sporadic forms of the disease will be a result of genomic instability. The age-distribution of these cases will be bell-shaped, a characteristic of most age-related diseases which are driven primarily by genomic instability. However, the age-distribution in sporadic forms is exponential.
Accordingly, when AD is considered in terms of the amyloid cascade model, the statistical distribution of the age-specific incidence rates will *not* be similar to the incidence rates observed in sporadic forms of cancer. This is inconsistent with the inverse comorbidity of cancer and AD.

Conclusion

The amyloid hypothesis and the neuroenergetic hypothesis with the Inverse Warburg effect represent two distinct models for the origin and development of sporadic forms of AD. This review of the biochemical and epidemiological data suggests that though the amyloid hypothesis may be pertinent in providing diagnostic and therapeutic strategies for the familial forms of AD, it has fundamental limitations in studies of the sporadic forms of AD. Our analysis provides support for the claim that the sporadic form of AD is a metabolic disease, whose origin is explained by metabolic dysregulation and the Inverse Warburg effect.

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Conflict of interest The authors declare that they have no conflict of interest.

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