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Review

Synthesis and metabolism of methylglyoxal, S-D-lactoylglutathione and D-lactate in cancer and Alzheimer's disease. Exploring the crossroad of eternal youth and premature aging

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ABSTRACT

Both cancer and Alzheimer's disease (AD) are emerging as metabolic diseases in which aberrant/dysregulated glucose metabolism and bioenergetics occur, and play a key role in disease progression. Interestingly, an enhancement of glucose uptake, glycolysis and pentose phosphate pathway occurs in both cancer cells and amyloid-β-resistant neurons in the early phase of AD. However, this metabolic shift has its adverse effects. One of them is the increase in methylglyoxal production, a physiological cytotoxic by-product of glucose catabolism. Methylglyoxal is mainly detoxified via cytosolic glyoxalase route comprising glyoxalase 1 and glyoxalase 2 with the production of S-D-lactoylglutathione and D-lactate as intermediate and end-product, respectively. Due to the existence of mitochondrial carriers and intramitochondrial glyoxalase 2 and D-lactate dehydrogenase, the transport and metabolism of both S-D-lactoylglutathione and D-lactate in mitochondria can contribute to methylglyoxal elimination, cellular antioxidant power and energy production. In this review, it is supposed that the different ability of cancer cells and AD neurons to metabolize methylglyoxal, S-D-lactoylglutathione and D-lactate scores cell fate, therefore being at the very crossroad of the "eternal youth" of cancer and the "premature death" of AD neurons. Understanding of these processes would help to elaborate novel metabolism-based therapies for cancer and AD treatment.

1. Introduction

Aging of any organism is a process involving changes at cellular, tissue and organ levels (Desai et al., 2010). Different theories of aging have been worked out, which all have their validity and can simply be classified as program theories (e.g. biological clock theory, limited number of proliferation theory), error theories (e.g. disease theory, cross-linking theory, free radical theory) or the combination of those (Semsei, 2000). One of the most evidence-supported theories is the "mitochondrial theory of aging" according to which reactive oxygen species (ROS) normally produced by the mitochondrial electron transport chain, can cause an age-related accumulation of mtDNA mutations/deletions leading to progressive mitochondrial damage and dysfunction. This in turn exacerbates mitochondrial ROS production causing cellular oxidative stress and creating a vicious cycle (Dai et al., 2014). The mitochondrial dysfunction and increased oxidative stress are also traits typical of some age-related neurologic diseases such as Alzheimer's disease (AD) and Parkinson's disease (Pope et al., 2008; Prasad et al., 1999, 2002). Probably to compensate for reduced ATP production, the mitochondrial impairment can cause a metabolic shift toward increased glucose uptake and glycolysis (Currais, 2015), features shared between AD neurons and cancer cells. Additionally, mitochondrial dysfunction, glycolysis activation and oxidative stress can derive from the progressive age-related decline in proteolytic activity that can lead to the accumulation of altered protein species (Hipkiss, 2017).

Methylglyoxal (MG) is a cytotoxic and mutagenic by-product of glucose, as well as lipid and amino acid metabolism, able to induce the formation of stable harmful adducts, oxidative stress and cell death (Thornalley, 1995, 1998; Kalapos, 2008a). An excess of MG formation deriving from increased glycolysis, can on the one hand cause further mitochondrial impairment, ROS production and an increase of oxidative stress, and on the other hand lead to the formation of advanced glycation end products (AGEs) due to MG reaction with proteins, DNA

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and other biomolecules (Kalapos et al., 2010; Rabbani et al., 2016a; Hipkiss, 2017). AGEs are associated with the aging process and age-related diseases (cardiovascular complications of diabetes, neurodegenerative diseases, connective tissue disorders) (Desai et al., 2010; Angeloni et al., 2014).

For energy production, neurons rely on mitochondrial oxidative phosphorylation (OXPHOS), using glucose, L-lactate (L-LAC), ketone bodies, pyruvate, glutamate and glutamine as oxidizable energy substrates (Bélanger et al., 2011a; Schubert, 2005). On the contrary, glycolysis is thought to be maintained low by the particularly low levels of the enzyme 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) generating fructose-2,6-bisphosphate, a potent activator of the key glycolytic enzyme phosphofructokinase (Atlante et al., 2017). However, in normal adult brain approximately 10–12% of the total glucose consumed is in excess of oxygen consumption (Goyal et al., 2014). This excess of adult brain glucose consumption, referred to as "aerobic glycolysis", occurs mainly in certain regions (medial frontal gyrus, precuneus and posterior cingulate cortex) and reflects developmental processes that persist throughout lifespan supporting synaptic and neurite formation and turnover (neoteny) (Goyal et al., 2014). Therefore, it can be hypothesized that brain aerobic glycolysis has a similar role to that seen in cancer cells (Warburg effect), with glucose mainly fueling the branching pathways of glycolysis, such as the pentose phosphate (PP) pathway, supporting both cellular biosynthetic pathways and antioxidant capacities (de Bari and Atlante, 2018). The brain areas with the highest levels of aerobic glycolysis in adulthood are those that have the highest susceptibility to AD development (Demetrius and Driver, 2015). One possible explanation of this can be the limited capacity of neurons of AD patients to detoxify MG (Bélanger et al., 2011b). A parallelism between the metabolism of neurons during the early phase of AD and cancer cells has been recently proposed (Atlante et al., 2017). It was shown that certain nerve cell populations became resistant to amyloid-beta (Aβ) peptide toxicity in the initial phase of AD by increasing glucose uptake and utilization. This is probably the way to sustain energy production and the biosynthesis of macromolecules in response to the mitochondrial impairment and synaptic degeneration due to Aβ peptide and tau hyperphosphorylation or fragmentation (Atlante et al., 2017). Conversely, aerobic glycolysis identifies regions of AD brain most vulnerable to Aβ deposition in the progression of the pathology (Vlassenko et al., 2010), supporting the idea that the increase in neuronal glycolytic flux ultimately exacerbates AD associated pathophysiological processes (Atlante et al., 2017).

In the light of the above considerations, it is feasible that both AD neurons and cancer cells are concerned with the cytotoxicity associated to MG overproduction resulting from increased glucose catabolism. MG-dependent protein modifications and their chemical toxicity have emerged as major causes of neuronal dysfunction and are both linked unequivocally to the primary traits of AD (Aβ plaques and neurofibrillary tangles) (Angeloni et al., 2014), clearly reflecting a deficit in MG detoxification in AD. On the contrary, cancers have a potentiated glyoxalase system (GSy) (Rulli et al., 2001), by which MG is mainly eliminated. This explains why the potentiation of the GSy is emerging as a valid tool for AD treatment (More et al., 2013), whereas its inhibition represents an effective strategy in anticancer therapy (Thornalley and Rabbani, 2011; Geng et al., 2014).

MG formation and degradation pathways in cells are well understood and advanced knowledge of the structure and function of enzymes that degrade MG in the cell is available (Mannervik, 2008; Honek, 2015). Similarly, the mechanisms through which MG exerts its pathological effects are well established (Angeloni et al., 2014; Maessen et al., 2015). On the contrary, the metabolic fate and possible roles of the compounds deriving from MG detoxification through GSy, S-D-lactoylglutathione (SLG) and D-lactate (D-LAC), are scarcely investigated under both physiological and pathological conditions. Yet, mitochondria can metabolize both compounds due to the existence of the mitochondrial enzymes glyoxalase 2 (GLO2) (Armeni et al., 2014) and D-lactate dehydrogenase (D-LDH) (Rojo et al., 1998; de Bari et al., 2002; Flick and Konieczny, 2002) suggesting that aberrant mitochondrial function through impaired product subtraction could influence MG disposal. Furthermore, the mitochondrial transport and metabolism of SLG and D-LAC might significantly contribute to whole energy metabolism, antioxidant power, posttranslational protein regulation and production of biosynthetic precursors necessary for macromolecule synthesis. Consistently, it is increasingly evident that the role of the conversion of MG into D-LAC by the GSy goes beyond the simple detoxification.

In order to be able to learn more about the processes associated to normal aging and potentially harmful to cells, it may be important to compare those pathological conditions such as AD and cancer in which the above-mentioned mechanisms also exist but differ markedly. These two pathological conditions are characterized by a very different ability to cope with MG formation and to metabolize SLG and D-LAC, this finally deciding two opposite cell destinies: the "eternal youth" of cancer and "premature death" of AD neurons. The aim of the present review is to encourage a more in-depth study of these still poorly investigated metabolic pathways. This could be of great importance for a better understanding and treatment not only of cancer and AD, but also of all those conditions in which the remodeling of metabolism has a relevant role, such as aging and age-related diseases, diabetes and the metabolic syndrome.

2. Synthesis and metabolism of methylglyoxal, S-D-lactoylglutathione and D-lactate

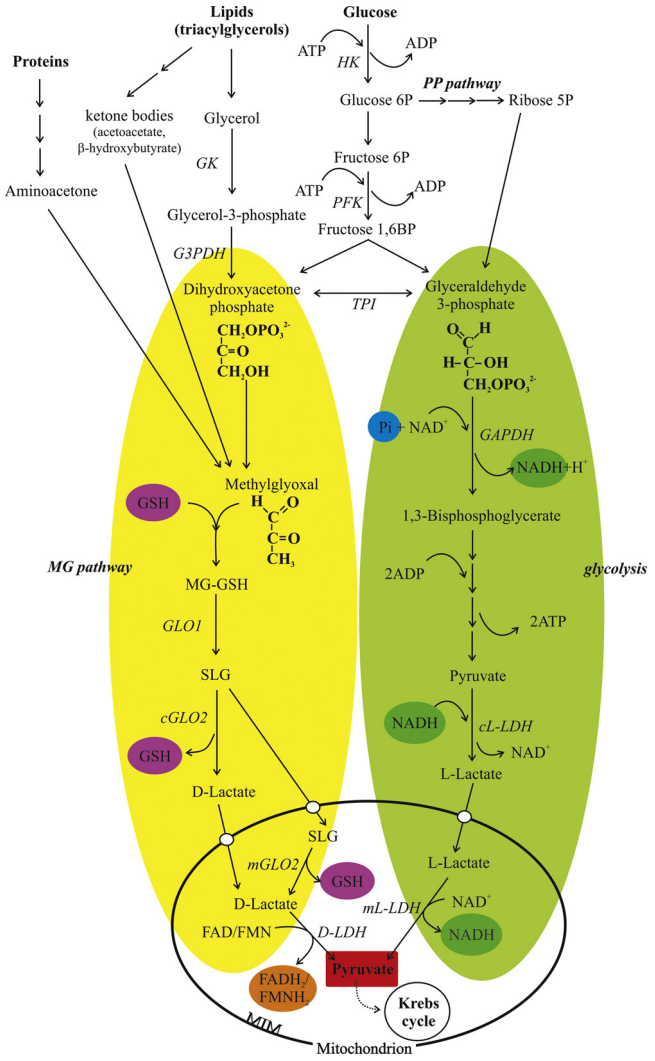
2.1. Methylglyoxal

2.1.1. Methylglyoxal synthesis

In mammals, MG is produced mainly as a by-product of glycolysis, *via* the enzymatic and non-enzymatic conversion of the triosephosphates (TPs), dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (G3P) (Angeloni et al., 2014). In particular, as in *E. coli*, the synthesis of MG might require low phosphate and high DHAP levels (Hopper and Cooper, 1971), a situation that most frequently occurs when glucose flux exceeds the potential for cell growth, or under pathological conditions leading to abnormal TP accumulation. It is estimated that 0.1–0.4% of the TPs accounts for MG production in human red blood cells (Thornalley, 1988; Kalapos, 2008b). Thus, the unavoidable formation of MG normally represents a very minor fate of TPs, even if it finally leads to a significant daily MG production (120 μM/day, based on the rate of D-LAC formation in red blood cells) (see Thornalley, 1995).

Additionally, MG can derive from protein metabolism - through the formation of aminoacetone - and from lipids, by the reactions catalysed by glycerol kinase (in kidney and liver) and glycerol-3-phosphate dehydrogenase that connect glycolysis with lipid metabolism (Kalapos, 2013) (Scheme 1). Not only glycerol and MG production are interconnected (Kalapos, 1999), but it was also shown that glycerol is even more efficient than glucose as a source of D-LAC deriving from MG metabolism, in rat liver (Kondoh et al., 1994). This suggests that, besides glycolysis, lipolysis could be an additional significant source of MG in the cell. Finally, MG can derive from lipid peroxidation or from the oxidation of ketone bodies which is low except where ketone bodies are increased as in diabetic ketoacidosis, prolonged fasting or low carbohydrate diet (Rabbani et al., 2016b; Angeloni et al., 2014).

Plasma MG and MG formed inside the cell may have very different derivations. Under normal conditions, plasma MG scarcely derives from cell export or cell injury and has not yet been shown to come significantly from the diet, but it is formed directly in the plasma mainly via the interaction between glucose and proteins (Kalapos, 2013). There is also a positive correlation between plasma ketone body (β-hydroxybutyrate) levels and plasma MG. However, under pathological conditions the rate of MG formation inside cells may exceed that of its



Scheme 1. Methylglyoxal production and metabolism through the methylglyoxal pathway.
The main pathways leading to MG production are schematically represented. The cytosolic and mitochondrial steps of the MG pathway are also reported. The MG pathway can be considered a by-pass of glycolysis, since both pathways can lead to pyruvate formation deriving from the mitochondrial oxidation of D-LAC and L-LAC, respectively. Both pathways can fuel the Krebs cycle and produce reduced cofactors ($FADH_2$/$FMNH_2$ and NADH, respectively) inside mitochondria, thus accounting for ATP production via OXPHOS. The possible role of the MG pathway in GSH transfer from cytosol to mitochondria is also highlighted. Abbreviations: Fructose 6 P, Fructose 6-phosphate; Fructose 1,6BP, Fructose 1,6-bisphosphate; G3PDH, glycerol-3-phosphate dehydrogenase; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GK, glycerol kinase; GLO1, glyoxalase 1; cGLO2, cytosolic glyoxalase 2; mGLO2, mitochondrial glyoxalase 2; Glucose 6 P, glucose 6-phosphate; GSH, reduced glutathione; HK, hexokinase; SLG, S-D-lactoylglutathione; cL-LDH, cytosolic L-lactate dehydrogenase; mL-LDH, mitochondrial L-lactate dehydrogenase; MG-GSH, methylglyoxal-glutathione hemithioacetal; MG pathway, methylglyoxal pathway; MIM, mitochondrial inner membrane; PFK, phosphofructokinase; PP pathway, pentose phosphate pathway; Ribose 5P, ribose 5-phosphate; SLG, S-D-lactoylglutathione; TPI, triosephosphate isomerase.

elimination leading to MG and SLG outflow from damaged cells (mainly red blood cells) thus contributing to plasma MG and SLG concentration (Kalapos, 2011, 2013). In diabetes, MG and SLG concentrations increase in erythrocytes in response to hyperglycaemia (Thornalley et al., 1989). Moreover, glyoxalase activity, which increases during maturation, declines from mature to old red blood cells (McLellan and Thornalley, 1989). Therefore, an erythrocyte-dependent age-related increase of MG distribution throughout the body might occur during normal aging and be exacerbated under conditions of diabetes or high glycaemic-index diet (Hipkiss, 2017).

2.1.2. Methylglyoxal cytotoxicity

If MG can have important signaling functions at low concentration (Akhand et al., 2001; Du et al., 2001; Yamawaki et al., 2008; Chang et al., 2011; Jia et al., 2012), at higher concentration it is detrimental for the cell due to its ability to readily react with proteins, nucleotides (DNA and RNA) and basic phospholipids in a non-enzymatic process known as glycation, forming stable cytotoxic adducts, called AGEs. Usually, a low rate of formation of MG coupled with an efficient degradation by GSy does not allow accumulation of MG adducts, taking place mostly with chronic elevation in MG concentration. The formation of nucleotide AGEs is associated with nuclear condensation (Roberts et al., 2003), DNA strand breaks and mutagenesis (Rahman et al., 1990; Kalapos, 1999). Protein glycation by MG occurs at lysine and arginine residues (Lo et al., 1994) and can lead to misfolded/dysfunctional proteins or protein cross-linking that can result in the formation of abnormal protein aggregates. The formation of AGEs can cause either the inactivation of antioxidant enzymes or the activation of prooxidant enzymes, thus increasing cell oxidative stress. Moreover, AGEs can determine mitochondrial dysfunction causing an increased production of mitochondrial ROS (Rabbani and Thornalley, 2008) and have been also implicated in cell detachment from the extracellular matrix and anoikis (Angeloni et al., 2014; Rabbani and Thornalley, 2015). AGEs can bind the multi-functional receptor of AGEs (RAGE) which senses a variety of signaling molecules, triggering the production of ROS and apoptosis (Schleicher and Friess, 2007; Sparvero et al., 2009).

Finally, increased MG levels can cause cell energy depletion by targeting both glycolytic and mitochondrial targets (Biswas et al., 1997; de Arriba et al., 2007), and induce cell apoptosis (Okado et al., 1996). In particular, the deleterious effects of MG have been observed in the form of increased ATP depletion, and ROS and L-LAC production in neuronal cells (de Arriba et al., 2007). MG-dependent oxidative stress and AGEs formation increase in ageing and are closely related to the pathogenesis of several diseases, including diabetes, hypertension and neurodegenerative diseases (Ramasamy et al., 2005; Angeloni et al., 2014; Chang and Wu, 2006). In the triosephosphate isomerase (TPI) deficiency syndrome, the deficient TPI activity causes DHAP level increase (see Scheme 1). Consequently, MG overproduction from DHAP occurs, leading to AGEs formation and oxidative and nitrosative stress, this likely contributing to the neurodegeneration associated to the syndrome (Ahmed et al., 2003; Oláh et al., 2005). In diabetes, MG accumulates both intracellularly and in the plasma, due to hyperglycemic conditions (Matafome et al., 2013; Kalapos, 2013). Consequently, MG causes several clinical complications of diabetes like inflammation, nephropathy and vascular damage (Nakayama et al., 2008; Maessen et al., 2015). Another complication of diabetes is often neuronal dysfunction and an increased risk for AD, due to elevated blood sugar levels associated to insulin resistance, leading to high levels of AGEs.

2.1.3. Exogenous sources of methylglyoxal and AGEs

MG and AGEs can not only have a metabolic origin, being formed inside cells, but also derive from exogenous sources, *i.e.* protein glycation in the gut and diet (Hipkiss, 2018). Though MG freely crosses cell membranes, the capacity of ingested MG to cross the gut wall and cause cell toxicity is not proven yet; nevertheless, the associations among nutrition, protein AGEs (glycotoxins), aging, AD and other neurological diseases are well established and documented (Cai et al., 2014; Uribarri et al., 2015; Abate et al., 2017; Hipkiss, 2018). Dietary AGEs can certainly contribute to the body pool of AGEs, thereby increasing oxidative stress and inflammation, two processes that play a major role in aging and in the causation of chronic diseases. Dietary glycotoxins, the content of which can increase due to not-healthy food cooking methods,

can accumulate over time in the body, representing a potential risk factor for AD (Abate et al., 2017). Recently, the effect of dietary glycated proteins on memory has also been reported in elderly humans (West et al., 2014). As far as cancer is concerned, it has been shown that circulating AGEs deriving from AGEs-rich diet can inhibit lung tumor growth *in vitro* and *in vivo* (Bartling et al., 2011). Moreover, pronyllysine, an AGE found in bread crust, has chemopreventive efficacy in rat colon carcinogenesis by acting as an antioxidant (Panneer Selvam et al., 2008). To sum up, both endogenous and exogenous sources of MG and AGEs could contribute to a progressive raise in tissue levels of both MG and AGEs that on one hand can have a detrimental effect mainly on "long-lived" cells like nerve and brain cells (Abate et al., 2017) and on the other hand can exert anticancer effects. This implies that dietary modification may perhaps play a role in delaying AD onset, as well as in contrasting the progression of certain cancers.

2.1.4. Methylglyoxal scavenging

As far as MG elimination is concerned, plasma MG is mainly expelled via renal clearance. Intracellularly, MG elimination can take place in several ways among which GSy in the presence of adequate reduced glutathione (GSH) levels, aldose reductase, a NADPH-dependent enzyme converting MG to acetol (the contribution of which may overcome that of the GSy when GSH concentration is subnormal), and non-enzymatic MG interaction with cellular components (Kalapos, 2013). Although GSy is an efficient pathway for MG metabolism under normal conditions, *in vivo* experiments carried out with [^{14}C]MG at physiological concentration proved that it is not completely eliminated but can irreversibly modify some plasma proteins which are then bound, internalised and degraded by monocytes. Therefore, MG-dependent modification of proteins could be a signal for protein clearance (Thornalley, 1995).

The rapid elimination of MG is of vital importance for cells, especially in cells displaying high glycolytic activity and high MG production, such as rapidly proliferating cells during development (Amicarelli et al., 1998). MG detoxification takes place mainly through the MG pathway consisting of two enzymes called GLO1 (EC 4.4.1.5) and GLO2 (EC 3.1.2.6). These enzymes catalyze the conversion of MG to D-LAC (Thornalley, 1990; Kalapos, 1999; Mannervik, 2008), in the presence of catalytic amounts of GSH (Scheme 1). The availability of GSH is essential for MG elimination, since the first step of the MG pathway is the non-enzymatic condensation of MG with GSH, forming a methylglyoxal-glutathione hemithioacetal (MG-GSH), which is converted into SLG by GLO1 (Mannervik and Ridderström, 1993). It was reported that, under normal conditions, the ratio of MG-GSH hemithioacetal:free MG is 57:1 at pH 7.2 and 37 °C in erythrocytes, this making GLO1 the most active enzyme in MG elimination compared to aldose reductase and aldehyde dehydrogenase that can metabolise MG, too (Rae et al., 1990; Thornalley, 1995). SLG is hydrolysed by GLO2 with the production of D-LAC and the release of GSH. Furthermore, a mitochondrial D-LDH exists in mammals, which converts D-LAC into pyruvate that can be readily reduced into L-LAC (de Bari et al., 2018). Therefore, the MG pathway can be considered an alternative to glycolysis under certain conditions (Cooper, 1984) (Scheme 1).

GLO1 bridges energy metabolism, especially glycolysis, to the potential impairment of cell growth and viability by MG. Being a key enzyme in the anti-glycation defense, it is evolutionally conserved and present in eukaryotes, plants and bacteria. In general, immature, proliferating tissues display a relatively high GLO1 and low GLO2 activity, whereas differentiated, mature tissues show just the opposite activities (Thornalley, 1990). This underlies the importance of MG elimination by GLO1 in metabolically active cells. GLO1 expression level is negatively regulated by HIF1α in hypoxia (Zhang et al., 2012). Therefore, by accelerating glycolysis concomitant with increased MG formation and by decreasing GLO1 expression, hypoxia may induce dicarbonyl stress through MG level increase.

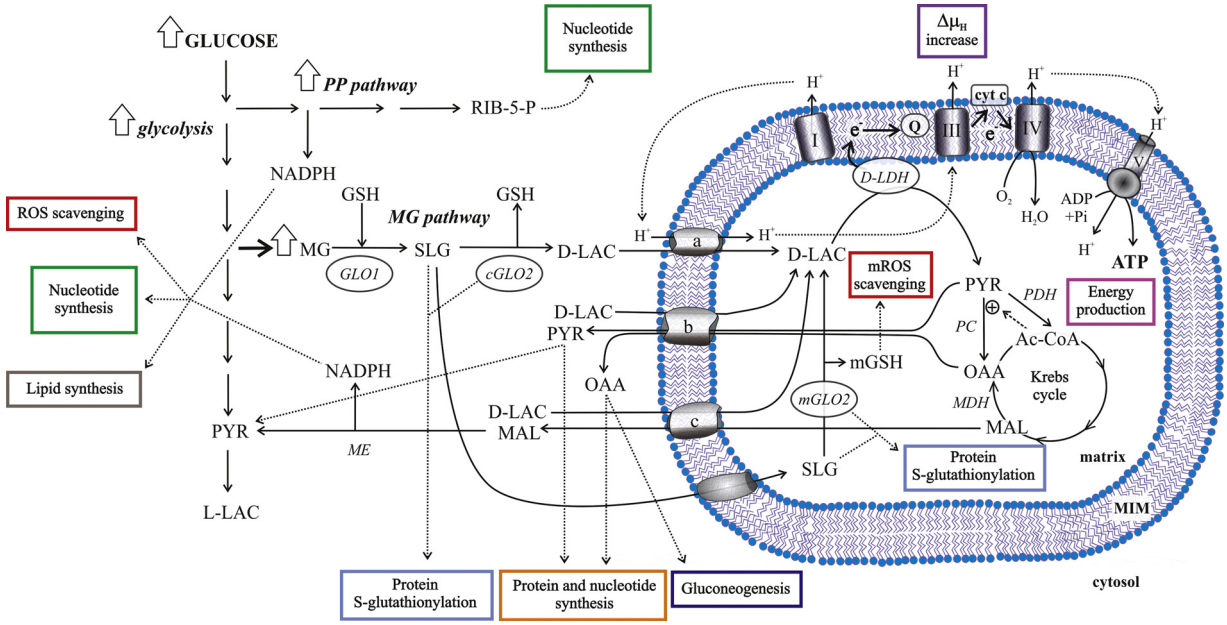
It is believed that GLO1 is related to healthy aging (Xue et al., 2011). GLO1 overexpression proved to enhance lifespan and prevent mitochondrial protein modification and ROS production in *C. elegans* (Morcos et al., 2008). A decline of GLO1 activity was found in old human red blood cells (McLellan and Thornalley, 1989) and during the senescence of human fibroblasts (Ahmed et al., 2010). Interestingly, this profile of GLO1 activity was documented in AD brains depending on the stage of disease (Kuhla et al., 2007). The decrease of GLO1 activity was corroborated in aging human lens, kidney and brain, too (Kuhla et al., 2007; Mailankot et al., 2009; Inagi, 2014). In animals, a similar decline with age was documented (Piec et al., 2005; Fleming et al., 2013). Since MG can cause mitochondrial dysfunction and loss of integrity in neuronal cells (de Arriba et al., 2007), a significant age-related decline of GLO1 activity could contribute to the mitochondrial impairment associated to neuronal aging, as confirmed by the protective effect on mitochondria of GLO1 upregulation in *C. elegans* (Morcos et al., 2008). In humans, higher levels of MG in serum of elderly individuals showed an association with a faster rate of cognitive decline (Beeri et al., 2011). Cognitive decline frequently accomplishes chronic metabolic diseases that are considered as risk factors for AD (Pugazhenthi et al., 2017). At the same time, several overlapping mechanisms, including oxidative and carbonyl stress, mitochondrial dysfunction, inflammation are observed in these disorders and aging, as well (Semsei, 2000; Desai et al., 2010; Pugazhenthi et al., 2017).

2.2. S-D-lactoylglutathione

Similarly to MG, SLG can act as an antiproliferative factor (Edwards et al., 1993; Thornalley, 1995), affects histamine release by leukocytes and microtubule assembly, and its blood level increases in diabetes (see refs in: Talesa et al., 1989). Therefore, GLO1 and GLO2 cooperate to detoxify both MG and SLG by their conversion into the safe final product D-LAC. However, the role of GLO2 and SLG metabolism in cancer and AD has been almost neglected.

2.2.1. Cytosolic GLO2, S-D-lactoylglutathione and the regulation of protein function

SLG is produced by GLO1 exclusively in the cytosol (Martins et al., 2001). Since GLO1 reaction takes place at a much higher rate, GLO2 reaction determines the rate at which MG-GSH is finally converted to D-LAC and GSH is recovered. Therefore, GLO2 accounts for the maintenance of cellular redox state and controls carbonyl stress. Thus, GLO2 is supposed to be involved in the pathogenesis of cancer, diabetes and AD. Unlike exclusively cytosolic GLO1, GLO2 is localized in both cytosolic and mitochondrial compartments, encoded in humans by a single Glo2 gene through alternate translational start sites (Xu and Chen, 2006). GLO2 was purified from rat liver mitochondria (RLM) and two separate pools of that were found, one located in the intermembrane space and the other in the mitochondrial matrix (Talesa et al., 1989). The former isoform resembled the cytosolic GLO2 form, having an identical mobility in SDS electrophoresis and a positive cross-reaction with antibodies to cytosolic GLO2, while different mobility and immunoreactivity were reported for the latter. However, since cytosolic GLO2 can bind to membranes (Scirè et al., 2000), the contamination of isolated RLM with cytosolic GLO2 cannot be ruled out, questioning the existence of GLO2 in the mitochondrial intermembrane space. It was shown that the cytosolic GLO2 might be more effective than the mitochondrial one in protecting cells from MG-induced apoptosis (Xu and Chen, 2006). It was also reported that, using its substrate SLG, GLO2 can promote the S-glutathionylation of proteins of different origin and cellular compartmentalization, *in vitro*, among which malate dehydrogenase, actin and glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Thus, GLO2 and SLG could play an important regulatory role by protein post-translational modification (Cianfruglia et al., 2014; Ercolani et al., 2016; Galeazzi et al., 2018). Besides modulating protein function, this oxidative modification might have a protective role towards cysteine residues, avoiding more dangerous irreversible



Scheme 2. Possible metabolic advantages coming from increased glucose utilization and methylglyoxal formation and metabolism.
The white-filled arrows indicate the enhancement of glucose uptake, glycolysis, pentose phosphate (PP) pathway and methylglyoxal (MG) formation, common features of cancer cells and Aβ-resistant neuronal populations in Alzheimer's disease. The metabolic advantages that might come from this metabolic shift, as well as from increased MG metabolism, are illustrated. Abbreviations: Ac-CoA, acetyl CoA; D-LAC, D-lactate; D-LDH, D-lactate dehydrogenase; e^-, electrons; GLO1, glyoxalase 1; cGLO2, cytosolic glyoxalase 2; mGLO2, mitochondrial glyoxalase 2; mGSH, mitochondrial GSH; L-LAC, L-lactate; MAL, malate; MDH, malate dehydrogenase; ME, malic enzyme; MIM, mitochondrial inner membrane; OAA, oxaloacetate; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase complex; PYR, pyruvate; RIB-5-P, ribose-5-phosphate; ROS, reactive oxygen species; SLG, S-D-lactoylglutathione; ΔμH, proton electrochemical gradient. Respiratory chain complexes: **I**, NADH dehydrogenase (complex I); **III**, coenzyme Q – cytochrome c reductase (complex III), **IV**, cytochrome c oxidase (complex IV), **V**, ATP synthase (complex V); **Q**, coenzyme Q; **cyt c**, cytochrome c. Mitochondrial carriers: **a**, D-lactate/H^+ symporter; **b**, D-lactate/oxoacid (PYR or OAA) antiporter; **c**, D-lactate/malate antiporter.

modifications (Souza and Radi, 1998; Newman et al., 2007). To revers protein S-glutathionylation, GSH is required; therefore the correlation between S-glutathionylation of cytoskeletal proteins and the aberrant polymerization of S-glutathionylated tau protein in AD, in which low GSH levels occur, is not a surprise (Xiong et al., 2011). Moreover, increased S-glutathionylation of the glycolytic enzymes GAPDH and α-enolase, leading to a significant enzymatic activity decline, was reported in AD inferior parietal lobules and hippocampus (Newman et al., 2007). This might alter glycolysis with the accumulation of MG precursors and increased MG formation. Furthermore, S-glutathionylation and inhibition of GLO1 occurs by SLG under conditions of GLO2 activity reduction (see Thornalley and Rabbani, 2011). SLG is also toxic if it leaks out of cells and is metabolised by γ-glutamyl transferase and dipeptidase with the formation of N-lactoylcysteine, an inhibitor of pyrimidine synthesis (Edwards et al., 1996).

2.2.2. S-D-lactoylglutathione, mitochondria and cellular antioxidant power

The existence of the mitochondrial transport and metabolism of SLG suggests that mitochondria may play an additional, still not investigated role in the regulation of cytosolic processes and in cell survival (Armeni et al., 2014). Subtraction of SLG from the cytosol favors both MG elimination and GSH transfer into mitochondria. The activity of the cytosolic and the mitochondrial GLO2 isoforms may be reciprocally regulated since both bind to negatively charged liposomes, but this binding exerts noncompetitive inhibition only on cytosolic GLO2 activity (Scirè et al., 2000). Thus, an enrichment of cell membranes in negatively charged phospholipids could cause an increase in the cytosolic level of SLG influencing the regulation of cytosolic protein function via S-glutathionylation and favoring the mitochondrial transport and hydrolysis of SLG, thus increasing GSH supply to mitochondria (Scirè et al., 2000).

Being the rate of GLO1 reaction 3–5 fold higher than that of GLO2 (Racker, 1951; Thornalley and Bellavite, 1987), SLG may be considered a trap for GSH under conditions in which GSH is not limiting the rate of GLO1 reaction. SLG may be a means to exchange GSH among subcellular compartments, *e.g.* cytoplasm and mitochondria, or even among cells. In this latter case, an example may be given by neurons and astrocytes: indeed, if both neurons and astrocytes can synthesize GSH, only astrocytes are able to export it. In the extracellular phase GSH can be degraded and the constitutive amino acids (glutamate, cysteine and glycine) are taken up by neurons for GSH synthesis in the cytosol (Xiong et al., 2011). However, the possibility that SLG can also be exchanged between the two cell types as a GSH source has not been investigated yet.

On the other hand, the combined activity of SLG mitochondrial translocators and mitochondrial GLO2 may facilitate GSH uptake by mitochondria from the cytosol (Jassem et al., 1996). GSH plays an important role as both antioxidant and cofactor for many enzymes involved in redox and detoxification reactions. It is synthesized exclusively in the cytosol and then distributed to different cell compartments, including the mitochondrial matrix where its concentration equals that of the cytosol (for refs see Ribas et al., 2014). The mitochondrial GSH (mGSH) pool plays several important roles in cell survival and a decrease in mGSH levels can make the cell more susceptible to apoptotic death (Ribas et al., 2014). Indeed, mitochondria are the main source of cellular free radicals under both physiological and pathological conditions, particularly in neurodegenerative diseases and AD (Valenti et al., 2014). mGSH has an important function in protecting mitochondrial DNA, proteins and membranes from the oxidative damage, thus maintaining mitochondrial function.

The mitochondrial carriers that allow cytosolic GSH to cross the mitochondrial inner membrane (MIM) are poorly characterized. Three potential candidates for the transport of cytosolic GSH into mitochondria have been identified, namely oxoglutarate carrier (Marí et al.,

2009), dicarboxylate carrier, and tricarboxylate carrier (Ribas et al., 2014). As noted, the intramitochondrial hydrolysis of cytosolic SLG may represent an additional mechanism for the maintenance of mGSH pool. Since SLG, similarly to GSH, is exclusively synthesized in the cytosol, and is not membrane permeable, it must cross the MIM in a carrier-mediated manner. This was first demonstrated in RLM by the use of radiolabeled compounds (Armeni et al., 2014). The transport processes of SLG and GSH were characterized by two different kinetics, indicating two separate transport systems for these two compounds. SLG transport was not dependent on either ATP or mitochondrial membrane potential. Moreover, the incubation of RLM with SLG caused oxygen consumption, mGSH level increase and mitochondrial membrane potential generation, likely due to SLG hydrolysis inside mitochondria and subsequent D-LAC oxidation by D-LDH (Scheme 2).

Inside mitochondria, SLG may be involved in the S-glutathionylation of certain mitochondrial proteins (malate dehydrogenase, cytochrome b, complex I of the respiratory chain) (Armeni et al., 2014; Gill et al., 2018). S-glutathionylation of proteins in mitochondria is highly sensitive to local changes in the redox state, specifically through fluctuations in GSH/GSSG ratio. Therefore, this process may be important for the adaptation of mitochondrial function to changes in overall cell redox state (see Mailloux et al., 2014). Hence, both the mitochondrial transport of SLG and the activity of the mitochondrial GLO2, as well as their regulation, are certainly important not only to sustain the antioxidant capacity of mitochondria, but also in the regulation of specific mitochondrial functions. It can be hypothesized that, under normal conditions, the cytosolic GLO2 would keep SLG concentration in the cytosol at very low levels and its mitochondrial import would be negligible, whereas in situations in which a higher supply of mGSH is necessary, the inhibition of cytosolic GLO2 might occur, this favoring cytosolic SLG accumulation and its uptake and hydrolysis by mitochondria (Scirè et al., 2000). The temporary binding of cytosolic GLO2 to negatively charged membrane phospholipids inhibits its activity. Therefore, it seems likely that the changes in membrane phospholipid composition, which can be influenced by dietary fatty acid intake (Field et al., 1990; Gimenez et al., 2011), as well as by aging (Kalén et al., 1989; Tamburini et al., 2004), might be fundamental for the control of cellular oxidative stress and viability.

2.3. D-lactate

D-LAC and L-LAC are optical isomers of lactic acid, both naturally occurring in human tissues where D-LAC is present at micromolar concentrations and represents about 1% of L-LAC (Racker, 1951). The two compounds have different origins, since L-LAC derives from carbohydrate catabolism through glycolysis or from amino acids, through transaminations forming pyruvate, whereas D-LAC derives from both carbohydrate and lipid metabolism through MG formation (Scheme 1) (Kondoh et al., 1994). Another source of D-LAC in humans is its production by intestinal bacteria (see Adeva-Andany et al., 2014).

Intravenously infused D-LAC is efficiently taken up and metabolized in healthy men (Oh et al., 1985), indicating a role for this metabolite in cell metabolism. D-LAC can penetrate the central nervous system by simple diffusion. As suggested by D-LAC concentration in cerebrospinal fluid, which is equal to that in the blood, brain should have the same ability of other tissues to metabolize D-LAC (Uribarri et al., 1998). D-LAC blood concentration increases several-fold after running and the D-LAC content of plasma, liver, and skeletal muscle is markedly increased in diabetic and starved rats, whereas it decreases in aging (Kawase et al., 1995; Ewaschuk et al., 2005; Kondoh et al., 1992a, b; Chou et al., 2015). Interestingly, the urinary level of D-LAC is significantly higher in diabetic patients than in healthy subjects, so that it has been proposed as a new risk marker for diabetes (Chou et al., 2015). The high urinary and blood D-LAC levels in diabetes (Scheijen et al., 2012), pathology associated to an increased risk for AD, may be indicative of a reduced capacity of D-LAC metabolism in these pathologies. Unfortunately, for AD nothing is known on blood and urinary level of D-LAC, nor on its metabolism.

2.3.1. D-lactate formation and oxidation. The mitochondrial D-lactate dehydrogenase

D-LAC is produced from SLG either in the cytosol or inside mitochondria, due to the existence of GLO2 in both compartments. D-LAC is then oxidized to pyruvate by the mitochondrial D-LDH (see refs in: Thornalley, 1995; de Bari et al., 2002). The enzymes catalysing L- and D-LAC oxidations are isomer-specific and evolutionarily not related (Taguchi and Ohta, 1991; Kochhar et al., 1992). L-LAC can be oxidized both in the cytosol and inside mitochondria due to the existence of cytosolic and mitochondrial L-LDH (Passarella et al., 2008) and a putative mitochondrial L-lactate oxidase (de Bari et al., 2010). D-LAC metabolism takes only place in mitochondria by D-LDH. Mammalian D-LDH is a FAD/FMN-dependent enzyme located at the inner side of the MIM and able to oxidize D-LAC to pyruvate in the mitochondrial matrix giving reducing equivalents deriving from D-LAC oxidation to coenzyme Q and then to complex III of the respiratory chain (de Bari et al., 2002) (Scheme 2). The addition of D-LAC to isolated RLM increased mitochondrial oxygen consumption, membrane potential and ATP production via OXPHOS (de Bari et al., 2002) (Scheme 2). Thus, D-LAC oxidation may contribute to cell energy production and mitochondrial function *in vivo*. The existence and mitochondrial localization of the enzyme was also shown in several human and mouse tissues by immunofluorescence and by the isolation of cDNAs encoding homologs of D-LDHs found in lower organisms (Flick and Konieczny, 2002). The human D-LDH gene (GeneID:197257) has been finally mapped to human chromosome 16 (Flick and Konieczny, 2002) and missense variants of this gene leading to massive D-LAC excretion and increased plasma concentration has been recently reported in two patients with aberrant neurological phenotype (Monroe et al., 2019).

2.3.2. D-lactate transport across the MIM

Due to the mitochondrial localization of D-LDH, cytosolic D-LAC must cross the MIM. It enters RLM via three separate mitochondrial carriers, the D-LAC/H^+ symporter which causes net carbon uptake in a proton-compensated manner, the D-LAC/oxoacid antiporter which exchanges externally added D-LAC with either pyruvate or oxaloacetate, and the D-LAC/malate antiporter which exchanges D-LAC with malate (de Bari et al., 2002). Therefore, mitochondria can take advantage of the electrochemical proton gradient to take up cytosolic D-LAC and oxidize it into pyruvate, from which acetyl-CoA, oxaloacetate and malate can be formed via the pyruvate dehydrogenase, pyruvate carboxylase and malate dehydrogenase reaction, respectively. These metabolites can then either leave mitochondria in exchange with further D-LAC, or fuel the Krebs cycle in the matrix (Scheme 2).

In the cytosol, oxaloacetate and malate released from mitochondria can be used to fuel biosynthetic pathways such as gluconeogenesis, in liver and kidney, or protein and nucleotide biosynthesis. Consistently, a previous study showed that D-LAC oxidation to CO_2 and D-LAC-dependent gluconeogenesis occur in bovine tissues (Harmon et al., 1984; Brandt et al., 1984). Moreover, as malate can be oxidized in the cytosol by malic enzyme to form pyruvate and NADPH, the mitochondrial D-LAC oxidation by D-LDH and transport across the MIM in exchange with malate could contribute to ROS scavenging and fatty acid synthesis in the cytosol (Scheme 2). Consistently, D-LDH was recently shown to be the most important enzyme of MG pathway, followed by GLO1, in providing oxidative stress tolerance in both E. coli and yeast (Jain et al., 2018).

Another interesting finding was that the transport of D-LAC across the MIM was rate-limiting in the oxidation of D-LAC, raising that the rate of cytosolic D-LAC oxidation inside mitochondria is regulated by its mitochondrial uptake rate (de Bari et al., 2002). The regulation of the mitochondrial transport of D-LAC would directly influence in this way its removal from cytosol, thus contributing to the prevention of MG and

SLG accumulation. A similar mechanism can be hypothesized for the mitochondrial transport and metabolism of cytosolic SLG, too.

3. Methylglyoxal, the glyoxalase system and D-lactate metabolism in cancer and Alzheimer's disease

Increased MG level can exacerbate oxidative stress, impair both glycolysis and mitochondrial function, and induce cell apoptosis under non-physiological conditions associated to either impaired GSy (Kuhla et al., 2006), increased oxidative stress due to low GSH levels (Vander Jagt et al., 2001), aberrant triose phosphate metabolism causing DHAP accumulation (Thornalley et al., 2001; Ahmed et al., 2003), or impaired SLG or D-LAC transport and metabolism. Several of these conditions take place in AD pathogenesis, but not in cancers.

3.1. Methylglyoxal pathway and D-lactate metabolism in cancer metabolic reprogramming

In response to a pathologic increase in glucose uptake rate, cancer cells show a peculiar enhancement of glycolysis and L-LAC production even in the presence of oxygen, named Warburg effect (de Bari et al., 2018). The pentose phosphate (PP) pathway is also potentiated in cancer, thus supporting macromolecule synthesis and the maintenance of a high NADPH/$NADP^+$ ratio for the control of oxidative stress. This way cancer metabolic reprogramming overall allows cancer cells to obtain higher ATP production and conditions favourable for cell proliferation and redox state maintenance (de Bari et al., 2018). Increased aerobic glycolysis causes an augmented production of MG in cancer. However, no increase in MG level, but rather its decrease, occurs in pathological specimens compared to controls (Antognelli et al., 2006) due to increased expression and higher activity of GSy (Rulli et al., 2001; Antognelli and Talesa, 2018), another specific hallmark of reprogrammed cancer cells preventing MG-induced cell damage and apoptosis (Thornalley, 1998; Thornalley et al., 2010; Thornalley and Rabbani, 2011). At present, an extensive research has concerned only GLO1 whereas much less is known on GLO2 in cancers. Increased GLO1 expression level and activity correlate with cancer progression and innate and acquired (*i.e.* induced by conventional anti-cancer drugs) drug resistance in most cancers (Antognelli et al., 2006, 2007; Chiavarina et al., 2017). For this reason, targeting GLO1 activity represents an efficient anticancer strategy (Thornalley and Rabbani, 2011). Also, the polyphenol curcumin, known for its anti-inflammatory and anti-tumor activity, or the potent anticancer molecule 3-bromopyruvate, have been found to inhibit human GLO1 (Santel et al., 2008; Valenti et al., 2015). GLO1 activity is generally higher in cancer, whereas GLO2 activity is often markedly decreased in comparison to normal cells (Antognelli et al., 2006; Thornalley, 1990). However, in studies carried out on GLO2 activity in tumors no distinction was made between the cytosolic and the mitochondrial isoforms, and the mitochondrial metabolism of SLG was not investigated, either. Therefore, a modest speculation may be appropriate here. If the decrease in total GLO2 activity in cancer reflects a decrease in the activity of the cytosolic isoform only, this would increase the cytosolic level of SLG favoring its import and metabolism by mitochondria, thus supporting the mGSH pool and D-LAC production in the matrix. This would explain why the peculiar GLO2 reduction gives metabolic, biosynthetic and antioxidant advantages to cancer cells.

The mitochondrial D-LDH has been even less studied than GLO2 in cancer. The mitochondrial oxidation of both L- and D-LAC was found enhanced in cultured human androgen-insensitive prostate cancer cells (PC-3), compared to immortalized, non-tumorigenic prostate cells (PNT1A) (de Bari et al., 2010, 2013; de Bari and Atlante, 2018). D-LDH of human prostate cells is a flavoprotein linked to the inner side of the MIM and able to give the reducing equivalents deriving from D-LAC oxidation to the respiratory chain in a manner very similar to succinate dehydrogenase. Interestingly, both the activity and protein level of D-LDH, as well as mitochondrial oxygen consumption and $\Delta\Psi$ generation rates consequent to the mitochondrial oxidation of D-LAC, were higher in PC-3 than in PNT1A cells (de Bari et al., 2002). The transport of D-LAC across the MIM was not studied in detail, but the experimental data suggested that D-LAC enters prostate cancer mitochondria via at least two carriers, a D-LAC/H^+ symporter and a D-LAC/malate antiporter, in good agreement with earlier findings (de Bari et al., 2002). D-LAC addition caused malate efflux from the matrix at a higher rate in PC-3 than in PNT1A mitochondria (de Bari et al., 2013). Thus, D-LAC-dependent energy production, ROS scavenging and macromolecule synthesis might be potentiated in prostate cancer due to enhanced D-LAC uptake and oxidation by mitochondria. Recently, an inverse correlation between D-LDH expression level and overall survival has been found in patients with clear cell renal carcinoma (Wang et al., 2018), but the underlying mechanism remains to be explored.

3.2. Alzheimer's disease from a metabolic point of view

AD is characterized by an altered processing of specific proteins, mitochondrial dysfunction, abnormal protein aggregation, inflammation, degeneration of synapses and apoptosis. Hallmarks of AD brains are the presence of extracellular and intracellular neuritic plaques resulting from the accumulation of β-amyloid (Aβ) peptides, and the intracellular accumulation of neurofibrillary tangles mainly containing hyperphosphorylated tau protein (Querfurth and LaFerla, 2010; Correia et al., 2012). According to the "amyloid cascade hypothesis", the Aβ initiates the pathological alterations of tau metabolism, which in turn triggers neuronal apoptosis causing the neuronal loss and cognitive deficiency typical of AD (Barage and Sonawane, 2015). However, the occurrence of substantial Aβ deposition in elderly patients with normal cognition, the uncertain nature of Aβ, and the failure of Aβ-centered therapeutic trials suggest that Aβ cannot be the primary or the only cause of AD (Pimplikar, 2009; Atlante et al., 2017). AD is increasingly considered a metabolic disease linked to a progressive perturbation/deregulation of neuronal glucose utilization and bioenergetics (Atlante et al., 2017). According to the "mitochondrial cascade hypothesis" proposed by Swerdlow and Khan (Swerdlow and Khan, 2004; Swerdlow et al., 2014), age-related changes in mitochondrial function cause changes in Aβ homeostasis and increased Aβ production, leading to its accumulation. Thus, in this hypothesis, Aβ can be considered a consequence rather than the cause of AD or other age-related diseases (Swerdlow et al., 2014). It can also be hypothesized that only when both energy metabolism perturbation and Aβ deposition occur and go beyond a certain threshold, AD symptoms become evident. The impairment of mitochondria - also targets and sites of accumulation of Aβ aggregates - seems to occur before the appearance of Aβ plaques (Manczak et al., 2006) and is a typical trait of age-related diseases in which it can induce several metabolic alterations such as the decrease of cellular antioxidant capacity resulting in increased oxidative stress (Lin and Beal, 2006; Alikhani et al., 2009; Cardoso et al., 2017). Therefore, in AD, the early impairment of the mitochondrial transport and metabolism of SLG and/or D-LAC is feasible, with possible consequences on MG elimination and on mitochondrial and cellular antioxidant capacity, enhancing AD progression. Moreover, Aβ aggregates can induce the nitrotyrosination and inactivation of TPI, one of the most affected enzymes in AD, thus favoring DHAP accumulation and MG overproduction leading to neuronal death (Tajes et al., 2014). GAPDH activity is also significantly reduced in AD patients and animal models compared to controls (Mazzola and Sirover, 2001; Shalova et al., 2007), probably due to either the reduced capacity of AD brain to respond to insulin and insulin-like growth factor (IGF) stimulation (de la Monte, 2012; Atlante et al., 2017), or MG-dependent glycation (Davidson et al., 2002). The bottleneck of glycolysis generated by the decrease in GAPDH activity in AD slows down glucose utilization causing a significant deficit in energy production and favouring the MG bypass of glycolysis (Scheme 1). However, if the detoxification of MG

and/or the metabolism of its products are defective in AD neurons, MG could accumulate becoming cytotoxic and further inhibiting GAPDH by glycation. This protein modification can also favour both the formation of GAPDH aggregates enhancing Aβ amyloidogenesis (Itakura et al., 2015), and GAPDH translocation to the nucleus during apoptosis (Muronetz et al., 2017). Furthermore, MG can indirectly induce/exacerbate the hyperphosphorylation of tau protein, probably through the enhancement of kinase activities and the reduction of phosphatase level (Angeloni et al., 2014).

Consistently with a situation of progressive impairment of MG, SLG and D-LAC metabolism, AGEs levels are high in the brain of AD patients and the percentage of AGE-positive neurons and astroglia increases with the progression of the disease (Angeloni et al., 2014). AGEs accumulate in the cerebrospinal fluid of AD patients and have been found associated to both neuritic plaques and neurofibrillary tangles, causing protein cross-linking and making the protein aggregates insoluble and resistant to proteases and, then, more toxic. Both AGEs and MG can increase the intracellular level of ROS, through the increase of NADPH oxidase activity, the inactivation of antioxidant enzymes (GSH peroxidase and superoxide dismutase) and the impairment of mitochondria, thus increasing mROS production (Angeloni et al., 2014). In turn, the increase in oxidative stress affects several cell components and signaling pathways, leading to cell dysfunction and apoptosis (Angeloni et al., 2014). It should be noted that the brain is particularly susceptible to oxidative stress due to its high energy demand, high oxygen consumption, large amounts of peroxidizable polyunsaturated fatty acids, and low levels of antioxidant enzymes (Andersen, 2004).

Since the linkage between MG cytotoxicity and AD is evident, GLO1 was investigated in AD and its expression level was found to increase in the early stage, but to decrease below normal levels in the middle and late stages of AD, events correlating with a marked increase in AGE accumulation with time (Kuhla et al., 2007). However, no significant change in the specific enzyme activity of GLO1 was detected in AD stages, compared to healthy controls (Kuhla et al., 2007). Since a glycolytic activation takes place in certain neuronal populations of brain in the early phase of AD, a consequent overproduction MG might occur and induce the mentioned initial GLO1 expression enhancement (Rabbani et al., 2016b).

Differently from GLO1, both the cytosolic and the mitochondrial isoform of GLO2 have been scarcely studied in AD. However, an important role for GLO2 counteracting MG toxicity in neurons has emerged. It was shown that the overexpression of the cytosolic Glo2 inhibited MG-induced cell death, whereas knockdown of Glo2 enhanced it (Xu and Chen, 2006). Glo2 knockdown sensitized cells to DNA damage-induced apoptosis in a p53-dependent manner and a novel link between p53 family and Glo2 was revealed. In this picture, Glo2 emerges as a pro-survival factor of the p53 family, thus playing a critical role in the pathogenesis of various human diseases including cancer and neurodegenerative diseases. In turn, MG can induce the autophagic degradation of GLO2 and thioredoxin (Trx1) in immortalized mouse hippocampal HT22 nerve cells, in an AMPK-dependent manner (Dafre et al., 2017). A protective effect of transduced Tat-GLO2 from MG-induced neuronal cell death was also shown in HT-22 neurons and, *in vivo*, in an animal model of ischemia (Shin et al., 2014). In particular, the co-treatment with transduced Tat-GLO1 and Tat-GLO2 proteins had a greater neuroprotective effect than the treatment with individual Tat-GLO proteins. Moreover, transduced Tat-GLO proteins reduced MG-induced oxidative stress, DNA damage and the activation levels of caspase-3, MAPKs, p38 and JNK, thus efficiently protecting neurons against cell death caused by MG.

The mitochondrial metabolism of SLG can account for the maintenance of adequate mGSH levels. Since mGSH is necessary for the protection of mitochondrial DNA, proteins and membranes, its depletion may occur upstream of mitochondrial dysfunction and oxidative stress in neurons, acting as a trigger for pathological mechanisms (Merad-Boudia et al., 1998; Marí et al., 2009). Consistently, mGSH appears to specifically support both glial and neuronal cell viability and its selective reduction was shown to cause ROS production increase and cell death, whereas the depletion of the cytosolic GSH pool did not elicit the same deleterious effects (Wüllner et al., 1999). Therefore, neuronal loss may be a consequence of the mGSH depletion. Mitochondrial dysfunction and oxidative stress occur early in AD brain, before the onset of pathologic plaques and tangles accumulation (Calingasan et al., 1999; Lin and Beal, 2006). The oxidative stress of AD has been correlated with the impairment of GSH transport from cytosol into mitochondria, due to a cholesterol enrichment of the MIM. However, cancer cells exhibit a similar increase in mitochondrial membrane cholesterol content, but still maintain normal mGSH levels conferring them protection against mitochondrial membrane permeabilization and cell death (for refs see Ribas et al., 2014). Therefore, it is suggested that a still unknown mechanism exists controlling mGSH levels, impaired in AD but not in cancer, probably based on the traffic of parental molecules that generate GSH once inside the mitochondrial matrix (Ribas et al., 2014). In invasive cancer cells, the impairment of GSH uptake by mitochondria is emerging as an important tool to induce cell death mechanisms (Samudio et al., 2005; Traverso et al., 2013). A better understanding of SLG traffic between cytosol and mitochondria, and of the activity of the mitochondrial GLO2 and D-LDH could therefore open the way for novel therapeutic strategies in both cancer and AD treatment.

4. The Warburg effect in AD neurons and cancer cells. The common way to the crossroad of life and death

In normal brain, astrocytes and neurons differ in their metabolisms (Bélanger et al., 2011b). Astrocytes are more glycolytic than neurons and show an optimal capacity to cope with high levels of MG due to a particularly efficient GSy, based on higher expression level and enzyme activity of glyoxalases and a higher level of GSH (Schurr and Gozal, 2015). Neurons rely on mitochondrial OXPHOS to fulfill the high energy demand associated to neurotransmission. Due to their poor capacity to replenish the GSH pool, neurons show a high susceptibility to MG level increase, which rapidly causes oxidative stress and leads to neuronal apoptosis (Kikuchi et al., 1999; Di Loreto et al., 2008; Chen et al., 2010). Therefore, any increase in neuronal glycolysis and/or decrease in GSy efficiency or GSH pool easily leads to MG-associated cytotoxicity in neurons, thus contributing to the onset of neurodegenerative disorders. According to the “astrocyte-neurons lactate shuttle (ANLS)” hypothesis (Pellerin and Magistretti, 1994), astrocytes protect and feed neurons by producing and exporting L-LAC, which is taken up and oxidized by neurons to satisfy their high energy requirements. This cooperation is induced by glutamate secretion from neurons upon their activation (Pellerin and Magistretti, 1994), avoiding glycolysis increase in neurons and consequent MG formation (Bélanger et al., 2011b). However, glucose transporters (mostly GLUT3) are present in neuronal cell membrane, are abundant in synaptic membrane and their number increases at the cell surface during neuronal activation, as confirmed by glucose uptake increase (Currais, 2015). Hence, it is likely that glucose importantly supports neuronal function under physiological conditions by fueling in particular the PP pathway to sustain both the reductive biosynthesis and glutathione reduction for ROS detoxification (Currais, 2015). Glyceraldehyde 3-phosphate (G3P) can be produced from the PP pathway substrates, thus re-entering glycolysis downstream of the phosphofructokinase reaction, the glycolytic step under-regulated in neurons (Scheme 1). Since G3P can be converted into DHAP by the TPI, defects in the GAPDH reaction causing G3P level increase and/or in the metabolism of MG formed from DHAP, would lead to MG elevation at toxic concentrations, causing neuronal damage and death. This would occur particularly during neuronal activation when glucose uptake increases, or in those brain areas that maintain high levels of glucose consumption in adulthood and are highly susceptible to AD development (Demetrius and Driver, 2015).

Increased aerobic glycolysis defined as amount of glucose use apart from that entering OXPHOS, is emerging as a trait of certain neuronal cell populations in the mild, initial phase of AD (Soucek et al., 2003; Atlante et al., 2017) and in brains of patients with sporadic AD (see Currais, 2015). This phenomenon is typical of proliferating cells and very similar to cancer metabolic reprogramming known as Warburg effect. Consistently, a significant increase in L-LAC concentration occurs in the cerebrospinal fluid of AD compared to healthy patients (Liguori et al., 2015), probably indicative of increased glycolysis overriding mitochondrial capacity to oxidize L-LAC (de Bari et al., 2018).

The neuronal populations showing high glucose uptake and utilization capacity are becoming attractive due to their peculiar resistance to Aβ-induced cytotoxicity and apoptosis (Atlante et al., 2017). AD brain shows increased activities of enzymes of both glycolysis and PP pathway, compared to age-matched controls (Soucek et al., 2003). It has been proposed that this neuronal Warburg effect in the early phase of AD, may occur in response to the initial impairment of mitochondria caused by intracellular protein aggregates (Currais, 2015), or as a consequence of Aβ-dependent activation of the transcription factor HIF-1, that increases both glycolysis and the PP pathway (Soucek et al., 2003). Interestingly, short-term exposure of cortical neurons and clonal nerve cell lines to sublethal concentrations of Aβ caused a significant increase in glucose uptake, glycolytic flux and PP pathway and higher NADPH levels and resistance to prooxidants in these cells (Soucek et al., 2003). Thus, since Aβ plaque density is not highly correlated with nerve cell loss or cognitive decline (Terry, 2000), a possible early function of Aβ in normal aging could be neuroprotection. Interestingly, L-LAC can act as a signaling molecule and its elevation due to enhanced glycolysis can induce mitochondrial mass increase (de Bari and Atlante, 2018). Therefore, the enhancement of glucose uptake, glycolytic flux and PP pathway in Aβ-resistant neurons might serve to improve the defective mitochondrial function, while increasing both macromolecule biosynthesis and cell antioxidant capacities against oxidative stress generated by impaired mitochondria (Scheme 2). Consistently, Aβ-resistant neurons show a significant reduction of ROS level (Soucek et al., 2003). On the other hand, Glo1 expression is increased in early and middle stages of AD, probably induced by dicarbonyl stress (Rabbani et al., 2016b) reflecting the glycolysis-associated MG level increase. However, noteworthy is that GLO1 is a very active enzyme, hence any increase or decrease in GLO1 expression and activity do not necessarily lead to a higher or lower MG elimination rate as its activity is strictly limited by both cytosolic GSH availability (Creighton et al., 1988), GLO2 activity and probably also by the mitochondrial uptake and metabolism of SLG and D-LAC. A preclinical study on the therapeutic efficacy of ψ-GSH, a synthetic cofactor of GLO1, proved to mitigate the development of mnemonic impairment and to drastically reduce both oxidative stress and amyloid β deposition indicators, in a transgenic mouse model (APP/PS1) predisposed to AD (More et al., 2013). This suggests that GSH availability and its consequent influence upon GLO1 activity are the primary causes of neuronal dysfunction and loss in AD.

Differently from cancer cells, in Aβ-resistant neurons the Warburg effect is destined to decrease during AD progression (see Atlante et al., 2017) as shown by the decrease in L-LAC production in moderate-severe AD (Liguori et al., 2015). The initial adaptive advantage given by potentiated glucose utilization is likely overridden later by an upcoming cytotoxic condition that exacerbates the pathophysiological processes associated to AD (Dargusch and Schubert, 2002; Atlante et al., 2017). This represents the very crossroad of cancer and AD, *i.e.* of cell life and death. It is supposed that the activation of neuronal glycolysis switches from a helpful process to a suicide one when acquired or innate defects in either of the following processes occur: MG conversion into SLG by GLO1, SLG conversion into D-LAC by the cytosolic GLO2, mitochondrial transport of SLG and/or D-LAC across the MIM, mitochondrial metabolism of SLG and/or D-LAC by the mitochondrial GLO2 and D-LDH, occurring solely or in combination. All these conditions may lead to the pathological persistence of high cytosolic levels of MG or SLG, as well as to other still unknown deleterious effects, that can induce the appearance and progressive worsening of AD symptomatology. Since cancer cells actively grow and proliferate by adopting a metabolic strategy similar to that of Aβ-resistant neurons in the early phase of AD, the above supposed presence of acquired or innate defects in MG, SLG and/or D-LAC metabolism, finally causing cell death are forbidden to occur in cancer. This would explain why AD occurrence correlates to a reduced risk of cancer development and *vice versa* (Demetrius and Simon, 2012, 2013). Indeed, MG, SLG and D-LAC metabolism are likely not defective, but rather potentiated in cancer. A major contribute to this metabolic difference between cancer and AD may arise from mitochondria that are functional in most cancers, while typically impaired in age-related diseases. If the mitochondrial impairment in AD is the cause or the effect of AD increased oxidative stress, remains to be elucidated.

5. Conclusions

During the normal aging process, protein aggregates accumulate forming senile plaques and neurofibrillary tangles. Although these aggregates can target certain cell components among which mitochondria causing deleterious effects, they are not the primary cause of dementia (Terry, 2000).

Since mitochondrial dysfunction is able to lead to Aβ accumulation, in order to arrest both the development and progression of AD the restoration of the mitochondrial function and cell bioenergetics is likely required (Swerdlow et al., 2014). The exposure to initial, subtoxic amounts of Aβ, probably via HIF-1 activation, can induce a metabolic adaptation in neurons, but not in glial cells, by increasing their ability to take up glucose and catabolize it through glycolysis and the PP pathway (Soucek et al., 2003). This metabolic shift potentiates neuronal ability to scavenge ROS, mainly produced by impaired mitochondria, and to produce biosynthetic precursors to cope with synaptic damage and mitochondrial impairment. A similar metabolic strategy is adopted by cancer cells, probably in response to the pathological increase in glucose uptake, and allows these cells to grow and proliferate (de Bari and Atlante, 2018). On this basis, and considering the inverse correlation existing between cancer and AD onset, here we hypothesize that cancer could represent a kind of “control” to have indications, by comparison, on why the shared protective metabolic shift is destined to fail in neurons of those individuals in which AD will occur. From this comparison, it emerges that oxidative and dicarbonyl stresses occur in AD neurons, but not in cancer, likely due to the increase to cytotoxic values of glycolysis-derived MG level in AD neurons. This is confirmed by the ameliorative effects obtained in animal models of AD by mTOR inhibition by rapamycin, which suppresses glycolysis (Cai et al., 2012; Chiarini et al., 2019). It should, however, be noted that ageing and diet can also lead to the increase in MG and AGEs levels, therefore likely contributing to the reaching of a threshold of MG/AGEs level beyond which AD onset might occur due to defect(s) in MG metabolism, as well as in that of SLG and D-LAC. This metabolic defect(s) could be upstream the onset and exacerbation of AD. Indeed, contrarily to neurons, cancer cells appear to have a potentiated ability to metabolize all these compounds, thus obtaining important metabolic and proliferative advantages (Scheme 2).

By converting MG derived from triosephosphates into pyruvate, through the sequence of GLO1, GLO2 and D-LDH reactions, the MG pathway bypasses glycolysis. Through the formation and mitochondrial transport and metabolism of SLG and D-LAC, the MG pathway can play important roles, going beyond the mere, although essential, elimination of MG. These likely include the regulation of cytosolic and mitochondrial protein function by S-glutathionylation, D-LAC-dependent energy production via OXPHOS and synthesis and efflux of biosynthetic precursors from mitochondria, the balancing of cytosolic and mitochondrial GSH pools, and the improvement of NADPH production in the cytosol for sustaining cellular antioxidant power (Scheme 2). The

existence of both mitochondrial and cytosolic enzymes in the MG pathway clearly shows that the MG bypass of glycolysis represents a way for cytosol-mitochondria crosstalk. In turn, the efficiency of MG detoxification relies on a correct interplay between cytosolic and mitochondrial pathways. The enhancement of cytosolic pathways in the presence of a perturbation of mitochondrial function, as that occurring in aging, can lead to an aberrant cytosol-mitochondria crosstalk and MG accumulation. The metabolic pathways reviewed here and, in particular, the mitochondrial transport and metabolism of SLG and D-LAC, which could be defective in AD but not in cancer, have been scarcely investigated or never taken into consideration either in neurological pathologies or in cancer. The identification of the defective step(s) of cell metabolism making impossible for cells to respond properly to age-related Aβ deposition and progressive mitochondrial malfunction could certainly be fundamental for the establishment of a novel therapeutic strategy for AD treatment, as well as for delaying normal aging. The same information could be useful to target cancer proliferation. Moreover, since the onset of AD likely occurs when a certain threshold of MG/AGEs level is exceeded, both endogenous and exogenous sources of these compounds might contribute to the reaching of that threshold. For this reason, dietary intervention might contribute to the delay of AD onset.

Competing interest

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