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Review

Methylglyoxal-derived stress: An emerging biological factor involved in the onset and progression of cancer

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ABSTRACT

Cancer is a disease characterised by uncontrolled growth and proliferation of cells. Tumours primarily show a higher rate of glucose uptake for lactate production even in the presence of functional mitochondria. An important metabolic consequence is intracellular formation of glucose-derived carbonyl reactive species such as methylglyoxal (MG). It has become clear that MG is the most potent glycation agent in our body, leading to alterations of proteins and DNA, and cellular dysfunction. In recent years, emerging evidence indicates that MG plays a role in the development of cancer. This review will examine studies regarding the effects of MG on cancer onset and progression and discuss their controversies. Finally, the utilisation of inhibitors and MG scavengers will be addressed in the context of MG-mediated stress blockade for cancer therapy.

1. Introduction

Cancer is a disease characterised by uncontrolled growth and proliferation of abnormal cells. The favoured use of glycolysis as the major source of ATP, even in oxygen-rich condition, over mitochondrial respiration by cancer cells was recognised decades ago by the pioneer work of Otto Warburg. Later on, the so-called Warburg effect has been explained further by the need of cancer cells to adopt an anabolic metabolism that will support their elevated biomass demands [1]. An important consequence of an intensified glucose uptake and glycolytic flux is the increase of non-enzymatic glycation reactions in which reducing sugars react spontaneously with amino group in proteins and with DNA [2] to form advanced glycation end products (AGEs). A large body of evidence has accumulated that AGEs are mediators of various complications in aging and age-related diseases including diabetes and cancer [3,4].

It was long assumed that AGEs accumulate exclusively on long-lived extracellular proteins [5]. However, a more rapid intracellular AGE formation on short-lived proteins is believed to be of even more importance *in vivo*. In fact, glucose has a very slow glycation rate, while glucose-derived glycolysis intermediates or intracellular sugars not only form much more glycated proteins, but also do it more rapidly. The glucose-derived dicarbonyl compound methylglyoxal (MG) plays an important role in this fast formation of AGEs [6,7]. It has become clear that MG is the most potent glycation agent, leading to cellular structural alterations and dysfunction [8]. MG is an endogenous product of metabolism that is present in all cells under normal or pathological conditions. To survive, the cells require a high rate of detoxification of MG. Indeed, the increased expression and activity of MG-detoxifying enzyme glyoxalase 1 (GLO1) has been reported under pathophysiological conditions such as in several types of cancer. In this review, we will highlight the importance of MG-mediated stress and the detoxification by GLO1 in the onset and progression of cancer.

2. Methylglyoxal is a major advanced glycation end products precursor

2.1. The formation of methylglyoxal

MG is a small molecule with a molecular weight of 72 Da and contains a ketone group and an aldehyde moiety of which the aldehyde group is more reactive [9]. MG can be formed from various pathways; it modifies amino acids, lipids and DNA and is detoxified by several enzymatic pathways (Fig. 1).

In cells, the majority of MG is formed non-enzymatically from the degradation of glyceraldehyde-3-phosphate (G-3-P) and dihydroxyacetone phosphate (DHAP) [10,11]. Minor sources of MG are derived from the hydrolysis and dephosphorylation of G-3-P and DHAP by triosephosphate isomerase [12], from aminoacetone during catabolism of threonine and from hydroxyacetone in the metabolism of acetone

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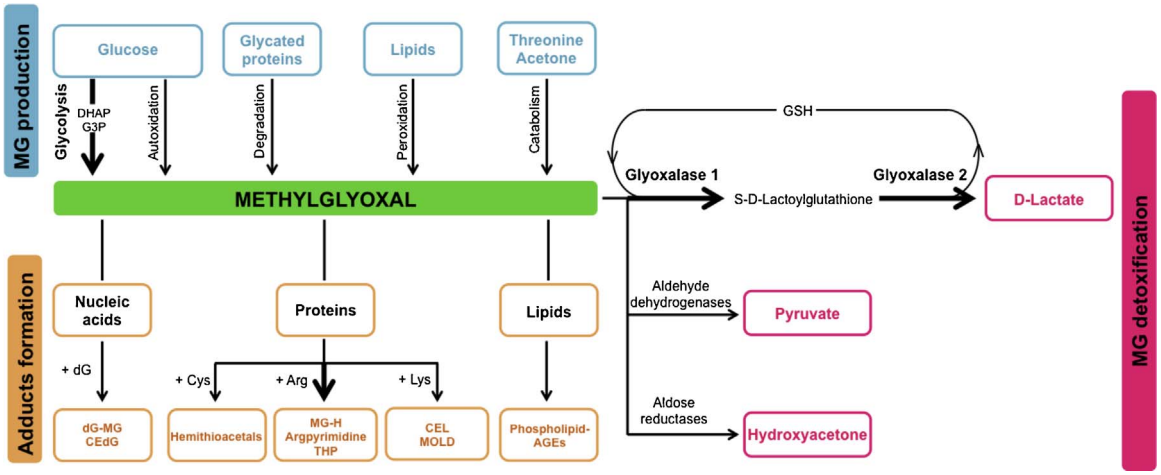

Fig. 1. Formation, detoxification, and glycation of/by methylglyoxal. Methylglyoxal (MG) is mainly formed as a by-product of glycolysis. Other sources are from the catabolism of threonine and acetone and from decomposition of lipid peroxidation reactions. Increased levels of MG can be detoxified predominantly by the glyoxalase (GLO) pathway. During the first step in this pathway a hemithioacetal is formed non-enzymatically by the reaction of MG with GSH. Consequently, the rate limiting enzyme glyoxalase 1 (GLO1), facilitates the formation of S-D-lactoylglutathione. Finally, glyoxalase 2 (GLO2) catalyses the hydrolysis of S-D-lactoylglutathione to D-lactate, thereby reforming GSH. Minor pathways of detoxification of MG are assured by aldose reductases and aldehyde dehydrogenases. If production exceeds its elimination, MG can modify arginine residues to form MG-derived hydroimidazolones (MG-Hs): MG-H1, MG-H2 and MG-H3, next to argpyrimidines and tetrahydropyrimidine (THP). MG also reacts with lysine residues to form CEL and the MG-derived dimer MOLD. MG also induces stable modifications of DNA bases (2′-deoxyguanosine, dG) and on lipids.

[13,14]. MG can also be formed by the decomposition of lipid peroxidation products [15,16] (Fig. 1).

2.2. Modification of proteins by methylglyoxal

It has been reported that MG primarily reacts with arginine residues to form MG-derived hydroimidazolones (MG-Hs): MG-H1, MG-H2 and MG-H3 [17–19] (Fig. 1). In addition to the formation of MG-Hs, the interaction of MG with arginine also leads to argpyrimidine [20] and tetrahydropyrimidine (THP) [21]. MG reacts with lysine residues, although to a much lesser extent in comparison to arginine, to form N_{ε}-(1-carboxyethyl) lysine (CEL) [22], and the MG derived dimer 1,3-di(N_{ε}-lysino)-4-methyl-imidazolium (MOLD) [23] (Fig. 1). MG can also react with one lysine and one arginine to form an adduct called MODIC [24].

The major MG-derived AGE, MG-H1, serves as a ligand for the receptor of AGEs (RAGE), resulting in signal transduction, which could play a role in the development of various health problems [25]. In particular, RAGE signalling has been associated with inflammation and oxidative stress which both contribute to carcinogenesis as recently reviewed by Piperi and collaborators [26].

MG is a key factor in the induction of oxidative stress [27,28]. The major route by which MG generates ROS is by the direct modification of proteins, like mitochondrial membrane proteins [29] and antioxidant enzymes [30]. More specifically for endothelial cells, MG modulates endothelial nitric oxide synthase (eNOS)-associated functions and NADPH oxidase activity [31,32]. Exposure of vascular smooth muscle cells to MG causes oxidative stress [33,34] and decreased hydrogen sulfide levels [35].

An interesting new concept about how MG can influence cell metabolism is by the modification of transcription factors. Yao et al. demonstrated that, in mouse kidney endothelial cells, high glucose causes increased MG modification of the co-repressor mSin3A, which resulted in increased angiopoietin-2 (Ang-2) expression and increased ICAM-I and VCAM-I intercellular adhesion molecules [36]. Another study showed that high MG levels induced by hyperglycemia gave rise to modified p300 transcriptional co-activator, which caused impaired hypoxia induced factor (HIF)-1alpha binding and decreased VEGF expression under hypoxia condition [37].

2.3. Modification of nucleic acids by methylglyoxal

Besides amino acids, MG can also modify nucleic acids (Fig. 1). With the use of ^{32}P-post-labelling technique, the cyclic adducts of MG and 2′-deoxyguanosine have been determined in human lymphocytes and epithelial cells [38]. *In vivo* DNA glycation products have first been described by Pischetsrieder who identified N2-carboxyethyl-2′-deoxyguanosin with an antibody in human urine [39]. Recently, more sensitive assays have been used to screen DNA glycation products and to prove their immunogenicity *in vivo* [40,41]. A recent review by Ashraf and collaborators has summarised the most advanced and emerging techniques for the detection of AGEs [42].

DNA glycation by MG may result in DNA strand breaks [43], nucleotide transversions [44], DNA–DNA crosslinks [45], DNA-protein crosslinks [46], and glycation of the nucleosomal protein histone H2A [47]. Although the biological consequences of MG-derived DNA adducts have not been fully established yet, the non-enzymatic glycation of DNA may have severe implications for various pathological conditions including cancer. A promising field to be explored in this context is autoantibodies formation against both protein [48] and DNA MG adducts. Indeed, MG-modified DNA presents unique epitopes that lead to the generation of circulating auto-antibodies that are detectable in cancer patients [49].

2.4. Methylglyoxal targets in cancer

Proteins susceptible to post-translational modification by MG constitute the MG-dicarbonyl proteome. MG-dicarbonyl proteome includes several proteins such as albumin, haemoglobin, mitochondrial proteins and extracellular matrix proteins, most of which were evidenced in the context of diabetes and aging studies (for review, [50]). In cancer cells, the discovery of endogenous MG modified proteins has been limited to date to the identification of heat shock proteins (Hsps). MG modification on Hsps affected important residues that either altered or enhanced their chaperone functions and stress response activities in cancer cells.

2.4.1. Hsp27 as a MG glycation adduct

Hsp27 is highly expressed in cancer cells and its expression is associated with increased tumourigenicity, metastatic potential and resistance to chemotherapy. The latter is a powerful anti-apoptotic protein counteracting apoptosis at different steps (for review [51]).

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