Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Invited review

Methylglyoxal, a potent inducer of AGEs, connects between diabetes and cancer

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ARTICLE INFO

Article history:
Received 24 October 2018
Accepted 4 January 2019
Available online 18 January 2019

ABSTRACT

Diabetes is one of the most frequent diseases throughout the world and its incidence is predicted to exponentially progress in the future. This metabolic disorder is associated with major complications such as neuropathy, retinopathy, atherosclerosis, and diabetic nephropathy, the severity of which correlates with hyperglycemia, suggesting that they are triggered by high glucose condition. Reducing sugars and reactive carbonyl species such as methylglyoxal (MGO) lead to glycation of proteins, lipids and DNA and the gradual accumulation of advanced glycation end products (AGEs) in cells and tissues. While AGEs are clearly implicated in the pathogenesis of diabetes complications, their potential involvement during malignant tumor development, progression and resistance to therapy is an emerging concept. Meta-analysis studies established that patients with diabetes are at higher risk of developing cancer and show a higher mortality rate than cancer patients free of diabetes. In this review, we highlight the potential connection between hyperglycemia-associated AGEs formation on the one hand and the recent evidence of pro-tumoral effects of MGO stress on the other hand. We also discuss the marked interest in anti-glycation compounds in view of their strategic use to treat diabetic complications but also to protect against augmented cancer risk in patients with diabetes.

Contents

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https://doi.org/10.1016/j.diabres.2019.01.002
0168-8227/

1. Introduction

Diabetes prevalence and associated mortality are continuously rising. The International Diabetes Federation recently published global estimates for the prevalence of diabetes over the coming 28 years period [1]. The number of people with diabetes worldwide is predicted to rise from 451 million in 2017 to 693 million by 2045. In 2017, approximately 5 million deaths worldwide were attributable to diabetes in the 20–99 years age range [1]. This new projection alerts us, as much necessary it might be, about the large social, financial and health system burden represented by diabetes across the world. Even more worrying for public health is the link established between diabetes and the other severe and multifactorial chronic disease that is cancer. Indeed, substantial evidence indicates that individuals with diabetes present with an increased risk of developing cancer. Common risk factors for both diabetes and cancer are evident, including age, overweight, obesity, lack of physical activity and poor diet.

Methodological aspects and study designs supporting the association between diabetes and cancer must be carefully examined. Two reviews of a group of experts from the Diabetes

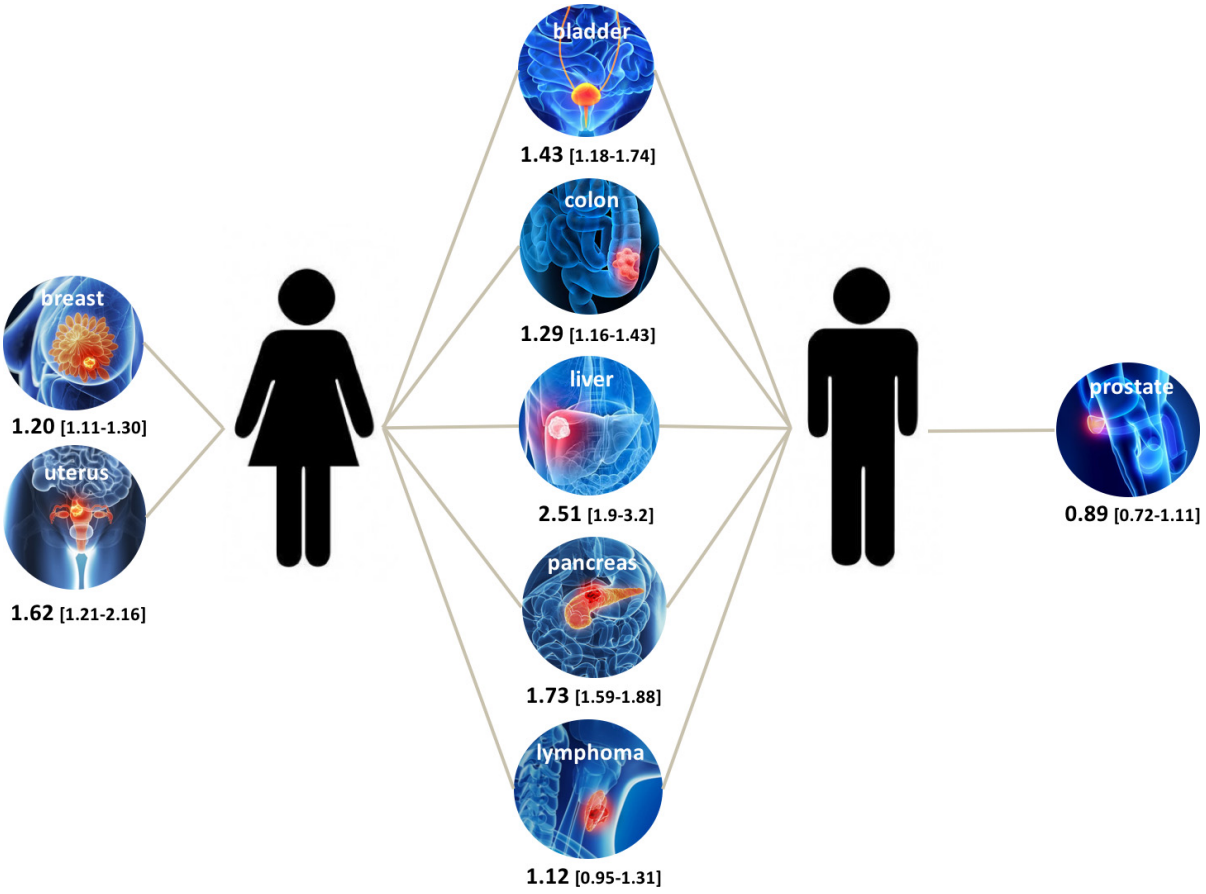

Fig. 1 – Diabetes and tumor risk. Relative risk of association between T2D and representative types of cancer. Numbers indicate relative risk and 95% confidence interval between brackets as reported in *meta*-analyses based on cohort studies and referenced in [99].

and Cancer Research Consortium recapitulate the potential biases, confounders and modifiers to consider when studying cancer incidence [2] and mortality [3] in patients with diabetes. A consensus report by the American Diabetes Association and American Cancer Society concluded that type 2 diabetes (T2D) is convincingly associated with an increased risk for several solid cancers (colorectal, breast, endometrial, liver, pancreatic, and bladder) (Fig. 1), while the evidence appears less conclusive for kidney and esophageal cancer [4]. A recent large cohort prospective study found that T2D was independently associated with a greater risk of renal cell carcinoma in women but not in men [5]. Interestingly, meta-analysis studies consistently reported an inverse relationship between diabetes and prostate cancer [6,7]. It is remarkable that although men with diabetes have a significant lower risk of prostate cancer, they present with a higher mortality from it [8] suggesting that cancer cells develop unique characteristics under diabetic conditions. Indeed, a meta-analysis revealed that newly diagnosed cancer patients with pre-existing diabetes have an increased risk of mortality compared with those without diabetes [9]. Chronic diabetes leads to serious complications each of which may worsen or accelerate the others including microvascular disease, neuropathy, retinopathy, atherosclerosis and diabetic nephropathy.

2. Diabetes-related pathophysiological mechanisms enhance the pathogenesis of cancer

Diabetic disease could be associated with a higher risk of cancer in patients partly because of the many risk factors these diseases have in common such as aging, inappropriate diet, smoking and poor physical activity. Hyperglycemia, hyperinsulinemia and inflammation are three pathophysiological mechanisms that are characteristic of T2D early stages. It is widely accepted that these conditions contribute to essential aspects of neoplastic transformation and cancer progression as can be read in several excellent recent reviews [10,11] (Fig. 2).

- Hyperglycemia primarily supports cancer cells' increased energetic and biosynthetic needs. High glucose circulating levels also trigger direct and indirect mechanisms notably leading to the induction of insulin, growth factors and inflammatory cytokines secretion all of which favor cancer cell proliferation, migration and resistance to apoptosis. The molecular mechanisms underlying hyperglycemia and cancer links will also need to consider further exploration of a phenomenon referred to as "metabolic memory" [12]. Interestingly, studies in animal and cell culture models have evidenced glucose-induced epigenetic changes that endow cancer cells with enhanced growth characteristics even after a return to normoglycemic conditions [13].

- Hyperinsulinemia is considered one of the enabling characteristics of cancer development as insulin exerts its pro-tumoral effects via abnormal stimulation of oncogenic signaling pathways, enhancing growth factor-dependent cell proliferation and/or by directly affecting cell metabolism.

- Low-grade inflammation precedes and predicts diabetes development in middle-age adults [14]. Nowadays, no

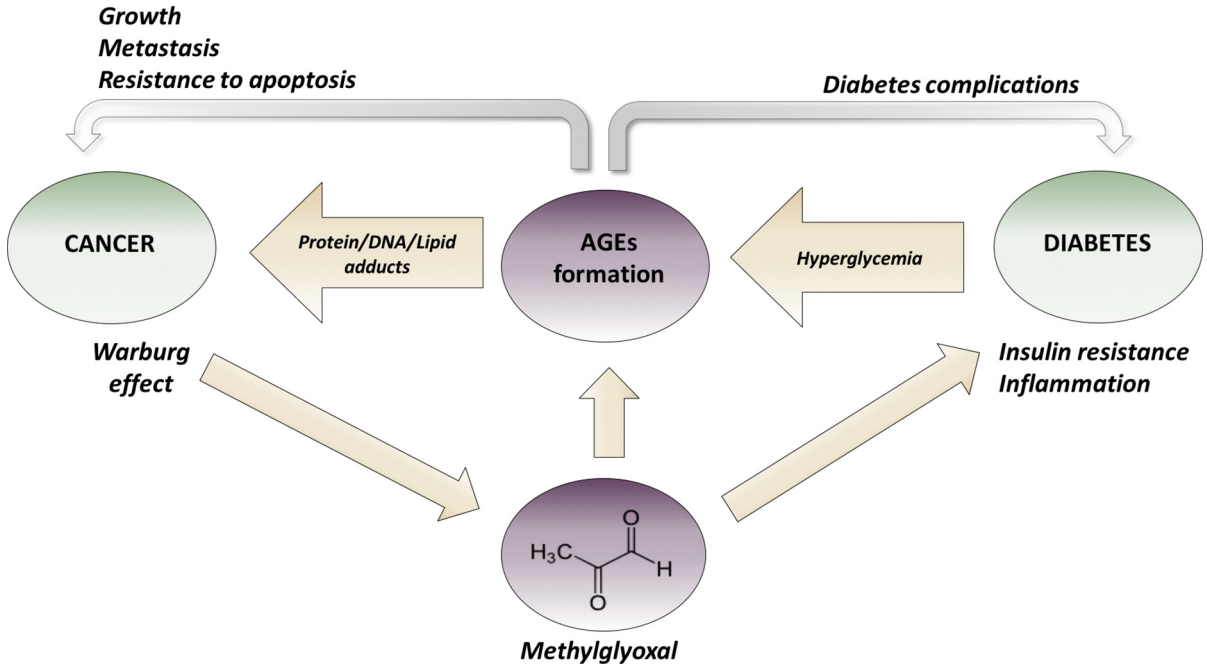

Fig. 2 – Advanced Glycation Endproducts (AGEs) formation as the link between diabetes and cancer where methylglyoxal (MGO), a potent precursor of AGEs, sustains a vicious cycle. Diabetic hyperglycemia favors the formation of MGO and AGEs that will create a favorable environment for growth, metastasis, progression and therapy resistance on the one hand, and to diabetes chronic complications on the other hand.

doubt is left that chronic inflammation contributes to establish a tumor-supportive microenvironment and targeting inflammatory cells and mediators is a strategy to reduce tumoral development, growth and spreading [15,16].

Next, we will essentially focus on hyperglycemia and elaborate on how this fundamental facet of diabetic disease is responsible for the generation of glycative stress that is progressively considered as an important factor to explain cancer predisposition in patients with diabetes (Fig. 2).

3. Diabetic hyperglycemia connects to MGO production and MGO adducts formation

3.1. *Hyperglycemia triggers protein glycation process*

The most obvious hallmark of diabetes is hyperglycemia which can be the consequence of an absolute or relative deficiency of insulin (T1D) or systemic insulin resistance (T2D). Glycation of proteins is a complex series of sequential reactions collectively called the Maillard reaction (that must not be mistaken with glycosylation that is a post-translational modification mediated by enzymes, in which a defined carbohydrate molecule is added to specific residues on a protein). Glycation occurs in all tissues and body fluids, during which reducing sugars such as glucose and fructose react spontaneously with amino residues of proteins, lipids and nucleic acids and lead to the formation of advanced glycation end-products (AGEs) at later stages. Hyperglycemia accelerates the rate of glycation reactions and leads to endogenous accumulation of AGEs. Serum and tissue levels of AGEs are elevated in both type 1 [17] and type 2 [18] diabetes. A very well established early sugar adduct linked to diabetic hyperglycemia is hemoglobin. Since 1976, the monitoring of glycated hemoglobin A1c (HbA1c) blood levels provides a useful way to document glucose metabolism in patients with diabetes [19,20].

3.2. *Reactive carbonyl species*

Reducing sugars not only directly contribute to the formation of AGEs but also lead to the accumulation of highly reactive dicarbonyl molecules (Fig. 3). These molecules called reactive carbonyl species (RCSs) induce a dicarbonyl stress when their detoxification/production is misbalanced, in analogy with reactive oxygen species (ROS) known to be responsible for oxidative stress in cells. RCSs notably comprise glyoxal (GO), methylglyoxal (MGO) and 3-deoxyglucosone (3-DGO) that will contribute to AGEs formation.

A critical property of AGEs is their ability to bind and activate the receptor for advanced glycation end products (RAGE), a signal transduction receptor of the immunoglobulin superfamily [21]. AGE-RAGE system is etiologically involved in inflammatory-linked diseases including diabetes, atherosclerosis and cancer [22,23]. RAGE expression is elevated in various cancer types where it is correlated with poor patient outcome. The targeting of RAGE-ligand signaling has been recently reported to impair breast cancer cell invasion and metastasis [24]. Because of their major impact on diverse pro-

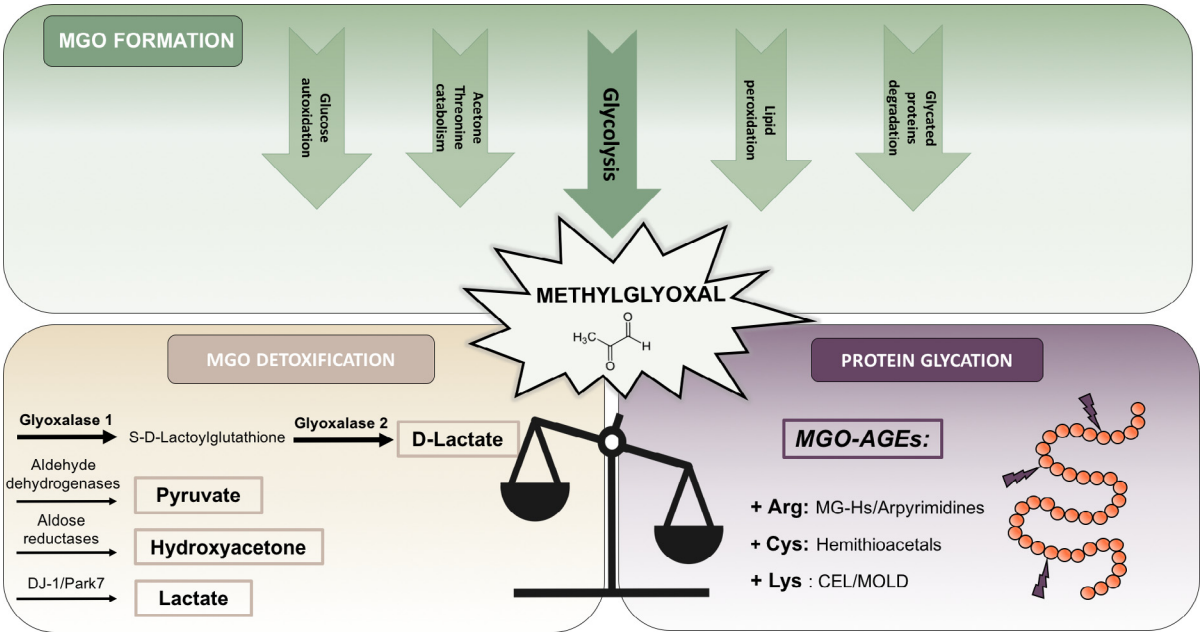

Fig. 3 – Methylglyoxal (MGO) formation, detoxification and protein glycation by MGO. MGO is mostly produced during glycolysis. It can also be produced during glucose autoxidation, catabolism of acetone and threonine, from lipid peroxidation and degradation of glycated proteins. MGO is essentially detoxified by the glyoxalase system. Other minor detoxification pathways include aldehyde dehydrogenases, aldose reductases and DJ-1/Park7 enzymes. The imbalance between MGO production and detoxification increases MGO concentration and the formation of MGO-AGEs among which MG-Hs hydroimidazolones are predominant. Arg: arginine, Cys: cysteine and Lys: lysine.

tein functional properties dealing with extracellular matrix structure, intracellular signaling and enzymatic activity, it is conceivable that more AGEs pro-malignant effects, receptor-independent and dependent, will be discovered in the future.

3.3. MGO formation and detoxification

MGO highly reactive alpha-oxoaldehyde can be formed from various pathways in cells. It is mainly formed as a by-product of glycolysis, following the fifth reaction, through the spontaneous degradation of triose phosphate intermediates, glyceraldehyde-3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP) [25,26]. MGO is also formed by oxidation of acetone, catabolism of threonine and the degradation of glycated proteins [27,28] (Fig. 3). Per day, the production of MGO has been estimated to be around 125 umol/kg cell mass [29].

Reflecting the deleterious impact of MGO on biological systems, all mammalian cells have developed an enzymatic system dedicated to the detoxification of MGO. Glyoxalase 1 (GLO1) and glyoxalase 2 (GLO2) are key enzymes in the anti-glycation defense that catalyze the conversion of MGO to D-lactate, via the intermediate product S-D-lactoylglutathione, in presence of reduced glutathione (GSH) (Fig. 3) [30]. Other minor MGO detoxification systems include aldehyde dehydrogenases (ALDHs) and aldose reductases (ARs) [31] (Fig. 3). More recently, Parkinsonism-associated protein DJ-1/Park7 has been described as a novel glyoxalase able to convert glyoxal and MGO to glycolic and lactic acid, respectively, in the absence of glutathione [32]. DJ-1 proved to be also efficient at deglycating MGO-modified amino-acids and proteins such albumin and GAPDH thus repairing glycation damage in prokaryotic systems [33]. The misbalance between the generation of MGO (with AGEs accumulation) and its detoxification is defined hereafter as MGO dicarbonyl stress.

3.4. MGO adducts as part of the dicarbonyl proteome

MGO is up to 10,000–50,000 folds more active than glucose and is considered as the most potent glycating agent [34]. MGO leads to spontaneous chemical modifications of nucleotides, lipids and proteins. In proteins, MGO can interact irreversibly with the side chain amino group arginine residues leading to the formation of argpyrimidines, hydroimidazolones (MG-H1, MG-H2 and MG-H3) and tetrahydropyrimidines (THP). It also reacts with lysine residues to generate minor MG-derived lysine adducts such as N_{ε}-carboxyethyl-lysine (CEL) (Fig. 3).

It is expected that 1 to 5% of proteins are modified by MGO [35]. As arginine residues are frequently present in the functional domains of proteins, AGEs can generate substantial cellular damage. All proteins susceptible to RCS-mediated glycation modification constitute the “dicarbonyl proteome” [36]. MGO-modified proteins notably include albumin, hemoglobin, type IV collagen, HIF1-alpha co-activator protein P300, and other proteins (Table 1). Interestingly, most of these proteins are reported in the context of diabetes and aging studies. Thornalley and al. reported that MGO-derived AGEs are increased at sites of vascular complications using a diabetic rat model (renal glomeruli, retina and peripheral nerve) and in plasma [37]. Elevated MGO level in plasma and urine of patients with diabetes is currently considered as a common feature in diabetes that has been reported in several studies [38–40].

The identification of MGO protein adducts has been best studied in the pathophysiology of diabetes. We propose that diabetes-related MGO adducts could bear new functional properties that are favorable to cancer pathogenesis and sustain the association between diabetes and cancer conditions [41]. For example, type IV collagen, a vascular basement membrane component, comprises an RGD (arginine-glycine-aspartic acid) motif that is targeted by MGO in endothelial

Table 1 – Methylglyoxal-induced dicarbonyl proteome.

Proteins	Modification sites	Consequences	Refs.
Albumin	Majority Arg-410 Minority Arg-114, 186, 218, 428	Inhibition of esterase activity and protein-ligand interactions	[100,105]
Hemoglobin	Alpha chain: Arg-31, 92, 141; Beta chain: Arg-30 40, 104	Increased oxygen binding	[101]
Type IV collagen	Alpha1 chain: Arg-390; Alpha2 chain: Arg-889, 1452	Decreased integrin binding	[42]
Alpha A-crystallin	Arg-12, 65, 157 and 163	Increased chaperone function	[102]
HIF1-alpha co-activator protein P300	Arg-354	Decreased association with HIF1-alpha	[103]
20S proteasome	Beta chain 2: Arg-85; Beta chain 4: Arg-224, 231; Beta chain 5: Arg-123, 128	Impaired proteasome activity	[104]
HSP27	Arg-75, 79, 89, 94, 127, 136, 140, 188 Lys-123	Prevents cytochrome c-mediated caspase activation and apoptosis	[76,105,74]
HSP90	Arg-46-60-87-299-510-512-647	Decreased ATPase activity	[68]
AKT	Cys-77	Increased AKT activity	[106]
GAPDH	Undetermined	Decreased GAPDH activity	[107]
FASN	Undetermined	Increased FASN activity	[108]
PDGFR	Undetermined	Inhibition of tyrosine kinase activity of PDGFR	[109]

cells cultured under hyperglycemia condition. Thus, MGO triggers endothelial cell detachment, anoikis, and inhibition of angiogenesis that likely contribute to diabetic vascular and renal complications [42,43]. On the cancer side, it is well known that the modifications of the composition, the architecture and/or the stiffness of ECM (of which collagen is the most prevalent structural protein) crucially intervene in the control of the malignant phenotype of the cells that are embedded in it [44].

4. Glycolytic switch in tumors favors MGO stress

4.1. *MGO accumulation in tumors*

Unlike normal cells, cancer cells reprogram their energetic metabolism toward the preferential use of glycolysis over mitochondrial respiration. Best known as the "Warburg effect", this phenomenon is observed even in oxygen-rich condition and in the presence of functional mitochondria. This metabolic switch is characterized by an increased glucose uptake and fermentation to lactate. Even if aerobic glycolysis is an inefficient mean of generating ATP compared with mitochondrial respiration, the fermentation of glucose occurs 10–100 times faster than the complete oxidation of glucose in mitochondria. Glucose carbons are the main building blocks for macromolecules biosynthesis to support cancer cell biosynthetic requirements when they are in microenvironments with limited energy resources [45].

An underestimated consequence of high glycolytic flux in cancer cells is the spontaneous production of MGO. Early work from Van Heisjt and collaborators demonstrated CML and argpyrimidines adducts formation in larynx squamous cell carcinoma, leiomyosarcoma, in breast and colon human adenocarcinoma using immunohistochemistry [46]. Our more recent studies reported a consistent accumulation of MGO adducts in breast and colon cancer tissues, compared to their normal counterparts [47,48].

4.2. *MGO anti-cancer effects*

Considering its potent cytotoxic effects, MGO has been initially tested in preclinical studies as a potential anti-cancer therapy at the end of the 60's. Several studies showed a significant decrease of tumor size after MGO intra-peritoneal or intra-venous injections to tumour-bearing mice [49–51]. The treatment with intra-peritoneal injections of MGO in a sarcoma mouse model further confirmed this beneficial effect of MGO [52]. GLO1 expression and activity were reported to be higher in cancer cells and correlated with tumour progression suggesting an important role of GLO1 in carcinogenesis [53]. GLO1 inhibition with S-p-bromobenzylglutathione cyclopentyl diester (BBGC) was rapidly viewed as a potential anticancer strategy. BBGC treatment induced apoptosis and inhibited the growth of human leukaemia 60 cells in *vitro* [54], and inhibited tumor growth of murine colon adenocarcinoma 15A *in vivo* [55]. Sakamoto and collaborators demonstrated that BBGC selectively induced apoptosis in human lung cancer cells that presented high GLO1 activity, and inhibited the growth of xenografted lung and prostate cancer cells [56]. Other more recent studies have highlighted the capacity of MGO to impair cell viability, invasion and migration of human breast [57] and liver cancer cells [58], and colon cancer tumor growth *in vivo* [59]. More recently, MGO proved to induce cell death of human T98G and U87-MG glioblastoma cells [60]. It is indisputable that MGO induces pro-apoptotic effects in several types of cancer cells through diverse routes including ROS induction [61] and impaired mitochondrial function with cytochrome *C* release [62].

Altogether these studies recapitulating the high toxicity of MGO toward cancer cells propose that MGO stress induction could be of value in the therapeutic management of drug resistant tumors. However, MGO effects are rather non-specific to cancer cells and high toxicity of MGO to normal cells such as neurons [63] and endothelial cells [64] excluded further potential development in human therapy.

4.3. *MGO pro-cancer effects*

While GLO1 is traditionally considered as an oncogene because of its increased expression and amplification in cancer, a genomic study conversely identified GLO1 as a tumor suppressor gene [65]. GLO1 tumor suppressor role is also strongly supported by our studies, which were among the first to highlight the role of MGO in cancer onset and metastasis development. Indeed, during the last years, emerging evidence supported the importance of MGO-mediated stress notably using a GLO1-silencing strategy in cancer progression, as we have recently reviewed in [41]. We have further explained the dual role of MGO (as a pro- and anti-tumoral metabolite) through the demonstration of its "hormetic effect". Hormesis is defined as "a process in which exposure to a low dose of a chemical agent or environmental factor, that is damaging at higher doses, induces an adaptive beneficial effect on the cell or organism" [66]. We showed for the first time that cancer cells display a characteristic biphasic dose response growth curve upon MGO treatment. While low doses of MGO led to AGEs formation and increased tumor growth *in vivo*, high MGO doses decreased tumor growth by inducing apoptosis. Both responses to MGO were significantly reverted by co-treating the cells with carnosine [67].

Our studies also showed that GLO1 silencing using shRNA in MDA-MB231 breast cancer cells showed enhanced growth using *in vivo* models [68]. In breast cancer, the comparison of breast cancer subtypes indicated that triple negative breast tumors and cell lines presented with globally less argpyrimidine adducts than triple positive, HER2- and HER2 + subtypes. More specifically, we observed that triple negative breast tumors showed higher GLO1 activities than triple positives ones. Moreover, when exposed to a chronic treatment of MGO, only triple negative breast cancer cell lines were able to respond by up-regulating GLO1 expression and activity [47]. These data suggest that these aggressive tumors are able to manage efficiently dicarbonyl stress. More recently, we demonstrated a mechanism by which MGO-mediated dicarbonyl stress impacts on breast tumor progression. High endogenous MGO induced nuclear YAP accumulation and activity, a key transcriptional co-activator regulating tumor growth and invasion [68].

In colorectal cancer (CRC), we reported that high stage CRC tumors presented lower GLO1 activity and higher accumulation of argpyrimidine adducts than low stage ones. Inhibition of GLO1 using shRNA favored CRC cell growth *in vivo*, an effect that was reverted by carnosine [48]. Additionally, a recent study indicated that exogenous MGO treatment promoted the growth of CT26 mouse colon cancer isografts [69]. Altogether, these findings establish a functional link between MGO stress and tumor progression.

5. Heat shock proteins as MGO main targets in cancer

Heat shock proteins (HSPs) are a family of molecular chaperones that are produced after exposition to stressful conditions and are classified according to their molecular size. In cancer, highly expressed HSP90, HSP70 and HSP27 have been the most studied. Importantly, these HSPs expression and chaperone activity are correlated with aggressiveness, metastasis, poor outcome and drug resistance and therefore constitute attractive targets in cancer therapy [70]. Interestingly, HSP27 is also present at high level in the serum of patients with diabetes and has been proposed as a biomarker of diabetic neuropathy [71] and nephropathy [72]. MGO-modified HSP27 is detectable in different human cancer types, including lung [73], gastrointestinal tumors [74] and melanoma [75]. MGO modification of HSP27 is involved in its oligomerization, is essential to prevent cytochrome *c*-mediated caspase activation and facilitates the escape of tumor cells from apoptosis [76,73].

We have recently characterized HSP90 as another target of MGO in breast cancer cells [68]. HSP90 plays a critical role in cancer because it stabilizes and activates several client proteins including transcription factors and kinases implicated in signal transduction pathways and adaptive responses to stress in cancer cells [77]. We have demonstrated that MGO-HSP90 is less effective in binding LATS1, a key kinase of the Hippo pathway, thus inactivating this important tumor suppressor pathway in breast cancer cells [68]. These findings point to hyperglycemia as a risk factor for cancer incidence and bring renewed interest in MGO scavengers for cancer treatment.

6. MGO scavengers and MGO-AGEs formation inhibitors

We have extensively described above at what point the formation of MGO-AGEs is crucial in both diabetes and cancer. Therefore, it is not surprising that major efforts have been invested in the discovery of pharmacological approaches to inhibit AGEs formation. Possible strategies include: blocking RAGE expression and interaction with AGEs, reducing serum glucose levels and/or trapping MGO. We will focus on anti-diabetic agents because they may control one or several of these mechanisms that are responsible for diabetes complications. Interestingly, some of these anti-diabetic molecules also bear effective anti-cancer properties. The causal relationship established between MGO stress and cancer being recent, there is only a few studies demonstrating that the blockade of MGO stress could have a beneficial role in preventing cancer initiation and progression. Table 2 recapitulates commonly used anti-diabetic molecules and their impact on cancer. In particular, we develop below the therapeutic potential of three MGO scavenger molecules selected for their proven safety either as a medication (metformin), an endogenous product (carnosine) or a natural extract (curcumin).

6.1. *Metformin*

Metformin is a potent anti-diabetic molecule prescribed for the treatment of T2D and its complications for over 50 years. Interestingly, Metformin has been implicated in modulating the risk of cancer incidence in people with T2D [78]. Preclinical studies reported that metformin affects cancer initiation and progression at least through the systemic reduction of insulin levels and via the induction of energetic stress [79]. More recently, the metastatic risk was decreased with metformin treatment among T2D patients with preexisting cancer [80]. Metformin is actually tested in several recent clinical trials as a monotherapy or in combination with chemotherapy and/or radiotherapy [81]. Both anti-diabetic and anti-tumorigenic effects of metformin have been explained through numerous molecular mechanisms including AMPK-dependent and independent pathways recently reviewed in [82]. Importantly, one of the remarkable proper-

Table 2 – Main anti-diabetic agents demonstrating anti-cancer properties: relationship with MGO and AGEs.

Anti-diabetic agents	Proven anti-cancer effects?	Interference with AGEs formation?	Interaction with MGO?
Aminoguanidine	Yes [110,111]	Yes [112]	Yes [112,113]
Inhibitors of angiotensin converting enzyme (ACEi)	Yes [114]	Yes [113]	No
Pentoxyfilline	Yes [115,116]	Yes [117]	No
Vitamin C	Yes [118]	Yes [119]	No
Vitamin E	Yes [120]	Yes [119]	No
Pyridoxine	Yes [121]	Yes [122]	Yes [113,123]
Aspirin	Yes [124]	Yes [125]	No

ties of metformin as a biguanide is to scavenge MGO [83] and to decrease its plasma levels in T2D patients [84]. Therefore, the proof of metformin anti-tumoral capacity through MGO trapping is timely needed and could represent an innovative hypothesis to be verified in pre-clinical settings.

6.2. *Carnosine*

Carnosine is an endogenous dipeptide synthesized from beta-alanine and histidine that is mainly found in brain and muscle tissues. Carnosine presents protective functions against secondary diabetic complications, including diabetic retinopathy and nephropathy [85]. In a mouse model of advanced obesity-related diabetes, carnosine reduced plasma glucose and HbA1c and attenuated albuminuria and glomerular hypertrophy suggesting that it could be a promising therapeutic treatment for diabetic nephropathy [86]. Moreover, carnosine protected retinal capillary cells in experimental diabetic retinopathy [87]. Next to its numerous biological effects as anti-oxidant, anti-inflammatory, anti-senescence and anti-chelating agent [88], carnosine reacts with MGO and glycated proteins [89,90]. Importantly, carnosine has been shown to exert anti-cancer effects *in vitro* through different molecular mechanisms: (a) decreasing ATP and ROS production [91] and interfering with both glycolysis and mitochondrial respiration [92], (b) inducing cell cycle arrest [91] and (c) inhibiting AKT/mTOR signaling pro-growth pathway [93]. Thanks to its ability to penetrate the blood-brain barrier, carnosine inhibited the migration of aggressive glioblastoma cells [94]. Using an *in vivo* xenograft model of breast cancer, we have demonstrated a potent inhibitory effect of carnosine on tumor growth and lung metastases development [68]. Oncolytic adenoviruses loaded with carnosine have been proposed as a novel anti-tumor strategy tested on murine models of colon and lung cancers [95]. Altogether these studies shed light on carnosine as a promising pan-cancer therapy that is especially relevant given the innocuity of this dipeptide.

6.3. *Curcumin*

Curcumin is a natural product considered as a remedy in Ayurvedic and Chinese traditional medicine. It appears that this polyphenol derived from the plant *Curcuma longa* exhibits plenty of therapeutic effects including antibacterial, anti-inflammatory, antioxidant and anti-proliferative activities. As such, this molecule showed interesting results for the treatment of T2D patients [96]. Interestingly, curcumin and its derivative dimethoxycurcumin are able to trap MGO in a cell-free system as determined using HPLC/MS-MS. Moreover, in human endothelial cells, curcumin decreased MGO intracellular level and inhibited the formation of AGEs. In cancer, curcumin anti-proliferative and anti-metastasis effects notably occurred through the inhibition of NF-κB, Akt pro-survival kinase and epidermal growth factor receptor (EGFR) activity [97]. To date none of the anti-cancer effects reported for curcumin has been ascribed to its MGO scavenger capacity.

7. Conclusions and perspectives

It is well admitted that changes in the levels of reactive metabolic intermediates can result in major alterations of fundamental cellular processes such as signalization pathways and enzymatic activity. In their excellent review, Sullivan and collaborators [98] recapitulated how changes in concentration of these so-called “oncometabolites” impact on cancer cells. Being a by-product of glycolysis, MGO is also an oncometabolite that is unavoidably formed in highly proliferative and metabolically active cancer cells. Hyperglycemia induces high MGO concentration in patients that are inherently more susceptible to diabetic complications. As a consequence, MGO-AGEs formation connects diabetes and cancer and the identification of novel MGO protein targets in either of these conditions will mutually enrich our knowledge about MGO stress in these diseases. Finally, the understanding of MGO effects and MGO-AGEs altered functions will be crucial for improving both diabetes and cancer outcomes as they might be exploited to propose new therapeutic strategies.

Acknowledgements

J.B and E.L are Télévie PhD fellows, M-J.N is a Télévie Post-Doctoral fellow and A.B is a Research Director, all from the National Fund for Scientific Research (NFSR, Belgium). These authors are also supported by the Centre Anti-Cancéreux and Fonds Spéciaux (University of Liège, Belgium).

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