Cancer Letters 390 (2017) 153–159

Contents lists available at ScienceDirect

Cancer Letters

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

Mini-review

Potential of glycative stress targeting for cancer prevention

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ARTICLE INFO

Article history:
Received 10 November 2016
Received in revised form
10 January 2017
Accepted 11 January 2017

Keywords:
Glycative stress
AGEs
Cancer
RAGE
Glyoxalase inhibitors
Dicarbonyl scavengers

ABSTRACT

Glycative stress from endogenous and exogenous advanced glycation end-products (AGEs) has been implicated to cancer development and progression. Dicarbonyl compounds, the main AGE precursors and crosslinked AGE forms may directly react with proteins, lipids and nucleic acids, modify their structure and affect tissue microenvironment. They may also induce elevation of reactive oxygen species (ROS) and enhance cellular oxidative stress, an important regulator of cancer hallmarks. Moreover, the activation of AGE-receptor for AGE (RAGE) signalling pathways mediates inflammation, oxidative stress, autophagy and apoptosis leading to genomic instability and cancer initiation.

Here, we provide evidence on the impact of glycative stress in promoting human tumorigenesis and we discuss the potential application of anti-glycating agents, RAGE and glyoxalase-1 inhibitors in cancer prevention.

Introduction

Over the last decade, cancer therapy targeting the molecular basis of tumours has reduced significantly their progression and recurrence with beneficial impact on patients' survival. However, epidemiological studies indicate certain populations that still suffer disproportionally from cancer incidence and mortality. Moreover, several interrelated lifestyle parameters such as poor diet, lack of exercise, cigarette smoking, obesity and low income have been proposed to affect cancer disparity [1,2]. They can interfere with metabolic pathways and alter the dynamic equilibrium between formation and detoxification processes of metabolic products, thus enhancing their accumulation in human tissues and promoting cell dysfunction and disease onset.

Of particular interest is the increased prevalence of reducing sugars (glucose, fructose) in circulation that induces non-enzymatic glycation of proteins, lipids and nucleic acids. Over time, highly reactive dicarbonyl metabolites are formed that undergo several reaction steps (Maillard Reaction) to generate irreversible crosslinked compounds known as Advanced Glycation Endproducts (AGEs) (Fig. 1) [3].

Abnormal accumulation of dicarbonyl metabolites in the human body may directly induce 'dicarbonyl stress' while glyceraldehyde-derived toxic AGEs (TAGE) generate 'glycative stress' that is associated with cell and tissue dysfunction, leading to progressive ageing, chronic diseases and cancer [4].

The levels of dicarbonyl compounds (Glyoxal, GL and methylglyoxal, MG) in human plasma commonly range between 50 and 150 nM and in mammalian cells between 1 and 4 μM [5]. Any deviations above these values lead to altered protein structure and function, affecting multiple tissues and eventually leading to health impairment [6].

Apart of the imbalance on formation and metabolism of dicarbonyls and AGEs, glycative stress may also occur by high exposure to exogenous AGEs via a typical Western diet with high fat/high sugar content, peptide-enriched commercial beverages and cigarette smoke [7]. High exogenous AGE intake has been associated with elevated circulating and tissue levels, contributing to 30% of accumulated AGEs in human body [7]. Additionally, dietary AGE concentration is increased by cooking methods employing dry heat to improve food flavour and appearance or during the manufacturing process of several commonly consumed, low cost processed foods [7]. In these cases, the glycation process is accelerated and the AGE content is increased up to 10-fold. At the same time, cigarette smoke-derived AGEs can be rapidly absorbed through the lungs and enhance modification of serum proteins or cause DNA mutagenesis [7].

Therefore, the rate of AGE accumulation in our body depends on an imbalance between their endogenous formation during

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http://dx.doi.org/10.1016/j.canlet.2017.01.020
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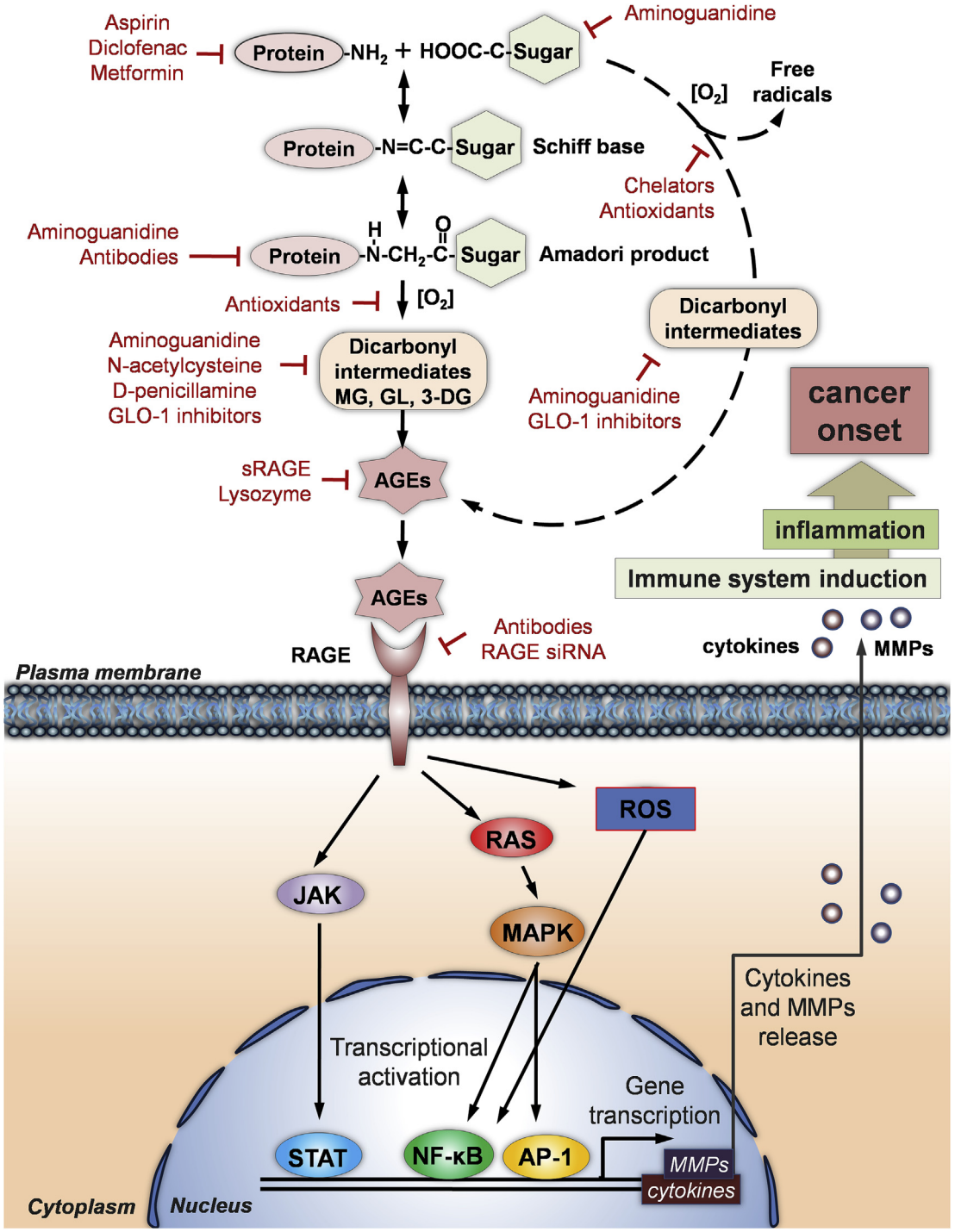

Fig. 1. Mechanism of AGE-mediated induction of cancer onset. Non-enzymatic protein glycation starts extracellularly with an initial reaction of reducing sugars and amino groups of proteins. This leads to formation of a reversible Schiff base that rearranges to Amadori product. Upon time dicarbonyl intermediates are formed that give rise to crosslinked AGE forms. AGEs bind to the specific transmembrane receptor RAGE on the cell surface of various cell types inducing ROS generation and activation of pro-inflammatory and stress-related transcription factors. Increased ROS, cytokine and MMPs release in the extracellular space leads to oxidative stress, immune cell recruitment and induction of inflammatory response, the hallmarks of cancer onset.

carbohydrate metabolism and/or their exogenous intake through nutrition and sedentary lifestyle along with inefficient removal via renal and/or enzymatic clearance. The enzymatic removal of AGE intermediates is mediated by glyoxalase-1 (GLO-1) and -2 (GLO-2) of the natural defence glutathione-dependent glyoxalase system present in most cell types [8].

Biochemical and physiological consequences of glycative stress

During glycative stress, elevated *in situ* glycation rates of proteins, nucleic acids and phospholipids take place. The reaction is primarily directed to arginine residues at the functional sites of

proteins generating hydroimidazole and dihydroxyimidazolidine, the most quantitative and functionally important AGEs in normal conditions.

Modification of arginine residues alters the charge of the side chain guanidine group [9]. Additionally, modification of lysine residues may also result in the formation of two common AGEs, Nε-carboxymethyllysine (CML), Nε-carboxyethyllysine (CEL) [8,9].

Glycated proteins have a reduced half-life, and often loose their substrate activity, being recognised as misfolded and directed to proteasome for proteolysis. Alternatively, they can adapt an altered toxic/damaging function and structure becoming smaller or denser, as in the case of MG-modified LDL [8,10].

These changes have an overall effect in multiple proteins of different cells and tissues since unhydrated dicarbonyls have the ability to escape from the site of formation, diffuse into plasma and permeate to other tissues. A diffusion distance of MG has been estimated to 2–3 cm indicating its ability to gain time in order to reach and inactivate sensitive enzymes and proteins, leading to cell dysfunction [8]. Dehydration is the rate limiting step which is estimated to a ~4 min half-life for MG [8,9].

Tissue effects of AGEs can be both extracellular and intracellular. Serum proteins (such as ApoB) as well as long-lived extracellular matrix proteins (such as collagen, elastin, laminin) represent direct targets of AGEs leading to advanced protein crosslinking and subsequent mechanical alterations [3,8,10]. Circulating AGEs may also directly stimulate intracellular reactive oxygen species (ROS) generation. Additionally, AGEs can bind to specific cell surface receptors in various cell types including the receptor for AGEs (RAGE), scavenger receptor type I, II, 80 K-H phosphoprotein, oligosaccharyl transferase-48 (OST-48) and galectin-3 [11]. RAGE is the only receptor that mediates the intracellular signalling of AGEs while the others possess scavenging and detoxification properties.

RAGE is a multiligand pattern-recognition receptor that apart of AGEs binds to high mobility group box 1 (HMGB1), S100 family proteins, amyloid-β and phosphatidylserine. RAGE engagement by AGEs activates NADPH oxidase, enhancing generation of ROS and induces intracellular signalling that leads to propagation of inflammatory and immune response.

Dysfunctions associated with extracellular and intracellular AGEs include enhanced crosslinking of intra- and extracellular matrix proteins that permanently alters cellular structure and function, increased formation of reactive oxygen species (ROS) and oxidative stress induction, interference with electron transport chain, altered mitochondrial protein function, elevated inflammatory protein expression, mitochondrial pathway-activated apoptosis and anoikis (Fig. 1) [8,12].

The impact of glycative stress in human health is constantly expanding. Endogenous and exogenous AGEs are major pathogenic contributors of metabolic diseases including obesity, diabetes mellitus, advanced ageing, cardiovascular and neurodegenerative disorders [3,7,8,10,12].

Association of glycative stress with cancer

Main biologic consequences of glycative stress include chronic unchecked inflammation and increased oxidative stress which are also underlying factors of cancer onset and tumour growth [13]. Interestingly, circulating AGE levels have been reported as an independent determinant of the inflammatory marker C-reactive protein (CRP) that is linked to systemic diseases and cancer [13]. Furthermore, elevated exogenous AGE levels due to poor diet, tobacco smoke and sedentary lifestyle may contribute to tumour growth due to perpetual activation of immune and inflammatory response (Table 1).

Epidemiological studies provide evidence of an association between biological AGE levels and cancer development [14–16].

High in AGE-content diets such as the Western diet enriched in fat and sugar and processed red meat were shown to increase circulating AGE levels that are associated with pancreatic and prostate cancer [14]. Animal models injected with azoxymethane and receiving Western diet supplemented with 15% linoleic acid in 10% water, exhibited elevated AGEs in their colonic neoplasms [15]. Several studies indicate a positive correlation between AGE levels and the risk of colorectal, liver and pancreatic cancer in smokers [13,16]. Collagen crosslinking and extracellular matrix stiffening is a common finding in several tumours being implicated both in tumour progression and invasion. AGE-modified basement membrane has been associated with metastatic breast cancer and reduced survival of prostate cancer patients [16].

Clinical studies on patients with metabolic and cardiovascular diseases indicate that activation of RAGE by dicarbonyls and AGEs deteriorates malignant lesions suggesting that glycative stress is the link integrating metabolic diseases with cancer development [17]. The underlying pathogenic mechanism involves activation of AGE-RAGE signalling axis that leads to increased ROS generation and induction of inflammatory transcriptional regulators (NF-κB, STAT3, HIF1α). As an outcome, elevated cytokine secretion (IL-1β, IL-6, TNFα), enhanced generation of cell adhesion molecules (VCAM-1, ICAM-1, endothelin-1), vascular endothelial growth factor (VEGF) and reduced endothelial NO synthase (eNOS) expression take place. They mediate recruitment of myeloid and lymphoid immune cells into the tumour microenvironment, induce inflammation and promote angiogenesis (Fig. 1) [17]. This cycle is further fuelled by formation of dicarbonyls/AGEs that possess a direct action in ROS production, leading to a persistent inflammatory milieu that promotes genetic instability, cell proliferation, survival and metastatic potential, contributing to tumour progression [13,17].

Recently, AGE-RAGE signalling was shown to regulate the activity of the important metabolic transcription factor ChREBP (carbohydrate response element binding protein) in liver and colorectal cancer cells by directly promoting their proliferation and providing an explanation of the increased cancer progression in diabetic patients [18].

In established tumours, STAT3 and NF-κB lead to sustained tumour-promoting responses through activation of RAGE, production of prostaglandin E2 and β-catenin that facilitate tumour growth and at the same time enhance matrix metalloproteinases and IL-6 production that favour tumour metastasis [19]. Following this mechanism, AGE-RAGE signalling pathway has been shown to induce tumour formation in pancreatic, colorectal, liver, breast, oral, renal, leukaemia and skin cancer [16,20] by regulating the growth, invasion and angiogenesis of cancer cells (Table 1).

Additionally, AGEs may induce translocation and secretion of HMGB1, another RAGE ligand, leading to activation of RAGE signalling. The synergism of AGEs and HMGB1 in activating RAGE signalling can foster tumour microenvironment. Several *in vivo* and animal studies indicate that RAGE and its ligands are implicated in colorectal tumorigenesis. Blockade of its interaction with HMGB1 reduced the growth and metastases of implanted and spontaneous tumours in susceptible mice while in clinical studies, coexpression of RAGE and HMGB1 induced an aggressive phenotype to colorectal adenomas [21,22].

Most importantly, different AGE types display specific functions in different types of tumours. A study investigating TAGE effects in tumour formation showed elevated proliferation and invasion of human melanoma G361 cells and significant association with liver and oral cancer [16,23]. In athymic mice bearing melanoma cell xenografts, tumour formation was prevented by RAGE neutralizing antibodies indicating the importance of RAGE interaction in the

Table 1
Effects of different AGE types in various cancers.

AGE type	Cancer type	Type of study	Effect	Reference
Methylglyoxal	Gastric	*In vivo*, Wistar rats, thiamine-deficient rats	DNA damage, Increased aberrant colonic crypt foci	[16,27]
Methylglyoxal	Gastrointestinal	*In vivo* and in cancer patients	Hsp27 modification, increased cancer cell survival	[28]
Glyoxal	Liver	*In vivo*, c3H/HeN mice	DNA damage	[30]
Glyoxal	Gastrointestinal	*In vivo*, thiamine-deficient rats	Increased formation of aberrant colonic crypti	[27]
3-Deoxyglucosone	Leukaemia	*In vitro*, U937	Apoptosis	[31]
3-Deoxyglucosone	Liver	*In vitro* Huh-7, HepG2 hepatoma cells	Impairs cell adhesion, migration via regulation of p53	[32]
Glyceraldehyde-BSA (100 μg/ml)	Lung	*In vitro*, A549	Increased invasion, metastasis	[24]
Glyceraldehyde-BSA (1 mg/ml)	Melanoma	*In vitro*, G361	Increased proliferation, invasion	[16,23]
Glyceraldehyde-BSA (1 mg/ml)	Breast	*In vitro*, MCF7	Increased proliferation, RAGE, VEGF	[24]
Glyceraldehyde-BSA (100 μg/ml)	Hepatocellular	*In vitro*, Hep3B/HepG2	Increased angiogenesis, VEGF	[25]
AGE-BSA (500 μg/ml)	Colon	*In vitro*, Colo320	Increased proliferation, invasion, metastasis	[16]
AGE-BSA (200 μg/ml)	Colon	*In vitro*, HCT116	Increased proliferation	[16]
CML-AGE	Colon	*In vivo*, azoxymethane injected rats receiving western diet supplemented with 15% linoleic acid	Increased AGEs in colonic neoplasms	[15]

growth and invasion of melanomas. In addition, TAGE upregulated VEGF and RAGE mRNA levels in the breast cancer cell line MCF7 while it enhanced migration and invasion of A549 lung adenocarcinoma cells though ROS generation and Rac1 activation [24].

In non-B or non-C hepatocellular (NBNC-HCC) patients, high TAGE levels were implicated in NBNC-HCC pathogenesis while a strong positive association of TAGE levels with rectal cancer was revealed in the nested case–control cohort study of European Prospective Investigation into Cancer and Nutrition (EPIC) [25].

Accumulated CML levels have been detected in leiomyosarcomas and colon adenocarcinomas while argpyrimidine was present in breast adenocarcinomas and squamous cell carcinomas of the larynx [26].

Elevated dicarbonyl levels have also been associated with genotoxic effects contributing to cancer development and progression. High MG concentration generates carbonyl stress and elevates ROS and carbonyl species which induce depletion of glutathione (GSH) and DNA damage. Exposure of male Wistar rats to MG in drinking water induced gastric carcinogenesis. In thiamine-deficient rats, MG-induced DNA damage is associated to increased aberrant colonic crypt foci [16,27]. In patients with diabetes and obesity, MG-mediated AGE formation was associated with inflammation, impairment of insulin signalling and enhanced cancer risk [16]. In gastrointestinal cancer, MG has been shown to modify Hsp27 and increase cancer cell survival [28] while in breast cancer MG induces Hsp90 glycation and activates the transcriptional co-activator Yes-associated protein (YAP) that enhances tumour progression [29].

Glyoxal, a major constituent of oxidized oils has been shown to cause liver genotoxicity to c3H/HeN male mice [30], promote chemically-induced gastrointestinal cancer and increase aberrant colonic crypt formation in thiamine-deficient rats [27].

3-deoxyglucosone (3-DG), another dicarbonyl that is abundant in alimentary and high glucose foods, has been reported to induce AGE formation and oxidative stress as well as apoptosis of leukaemia U937 cells [31]. Additionally, in Huh-7 and HepG2 hepatoma cells, 3-DG impairs adhesion and migration via regulation of p53 [32].

Except of their cancer promoting effects, increased AGE levels are inversely associated with lung cancer prognosis [33]. This has been attributed to the differential expression of RAGE in lung tissue with higher levels in normal and lower in neoplastic lung tissue [34]. Contradictory studies also exist regarding increased circulating AGE levels on smokers and their association with cancer risk. High CML levels have been correlated with prostate cancer in smokers [35] while a Finish study on male smokers showed that CML levels were inversely correlated with liver cancer [36] and not with pancreatic cancer. These data indicate the variable biological effects of AGEs among different populations that need to be taken into consideration in future studies.

Anti-glycating agents in cancer prevention

Recent studies indicate that non-enzymatic glycation and the concomitant glycative stress can be efficiently prevented by the use of synthetic and natural inhibitors that prevent or block AGE formation, target RAGE signalling and GLO-1 activity (Table 2).

AGE formation inhibitors

Several synthetic and natural anti-glycating agents are capable to block various stages of AGE formation process by interfering with sugar attachment to proteins, scavenge or trap glycation intermediates and/or inhibit Amadori product formation (Fig. 1).

Initial attachment of glucose or fructose to the amino groups of proteins can be successfully inhibited by anti-inflammatory drugs, such as aspirin and diclofenac. Aspirin acetylates free protein amino groups and blocks further attachment of reducing sugars, while diclofenac makes covalent interactions with proteins, preventing glycation reactions and AGE formation [37]. They both exhibit inhibitory effects over cancer cell proliferation possibly by inhibiting cyclooxygenase 2 and affecting arachidonic acid metabolism.

Metformin, a well-known anti-hyperglycaemic agent also inhibits AGE levels and dicarbonyl formation by interfering with early stages of glycation. It has been demonstrated to reduce cancer risk of lung, ovarian, breast, pancreas, gastrointestinal, and liver cancer [38,39]. Its actions are mediated through AMP-activated protein kinase (AMPK) signalling pathways and involve induction of apoptosis, autophagy as well as aberrations in energy metabolism.

Other synthetic inhibitors have been shown to interfere with late stages of glycation by scavenging reactive dicarbonyls and free radicals, thus preventing Amadori product formation. Among them, aminoguanidine is an AGE inhibitor and MG scavenger that targets nitric oxide synthase (iNOS) (Fig. 1). It shows inhibitory effects on thyroid follicular, breast and hepatocellular carcinoma through modulation of iNOS [40]. *In vivo* studies on pancreatic cancer xenografts bearing mice showed that 2 mg/ml of aminoguanidine in drinking water reduced significantly tumour volume through its effect on cell proliferation and angiogenesis [41].

Antioxidants such as N-acetylcysteine and D-penicillamine have the ability to function as scavengers of MG and interfere with glycation [42]. They induce p53-mediated apoptosis and DNA damage

Table 2
Effects of anti-glycating agents in different cancer types.

Drug	Cancer type	Mechanism of action	Type of study	Reference
Aspirin, Diclofenac	Breast, rhabdomyosarcoma	Acetylates free amino acids, blocks attachment of reducing sugars	*In vitro*, HeLa cell, mammary cell carcinoma, rhabdomyosarcoma and fibroblast cell lines	[37]
Metformin	Lung, ovarian, breast, pancreas, gastrointestinal, liver	Inhibits AGE levels and dicarbonyl formation, interferes with early glycation stages	*In vitro*, *in vivo*	[38,39]
Aminoguanidine	Thyroid follicular, hepatocellular, breast	AGE inhibitor, MG scavenger, targets nitric oxide synthase	*In vitro*, *in vivo*	[40,41]
Aminoguanidine	Pancreatic	Reduced tumour volume by reducing cell proliferation, angiogenesis	*In vivo*, pancreatic cancer xenograft bearing mice	[42]
RAGE siRNA	Breast, hepatocellular, gastric	Reduces cell proliferation, NF-κB expression, PCNA, cyclin D1	*In vitro*	[47–49]
sRAGE	Melanoma	Decreases motility, migration	*In vitro*, A375 cells	[50–52]
Lysozyme	Breast, gastric cancer	Blocks AGE-binding site, reduces proliferation	*In vitro*	[46,53–55]
Anti-RAGE antibodies	Melanoma	Reduced tumour growth, metastasis	*In vivo*, melanoma tumour bearing mice	[46,56–58]
S-p-bromobenzylglutathione diester	Leukaemia	GLO-1 inhibitor, apoptosis	*In vitro*, *in vivo*	[59,60]
Cyclopentyl ester	Adenocarcinoma	GLO-1 inhibitor, apoptosis	*In vivo*	[60]

in cancer cells and they have been proposed as chemopreventive agents.

Natural compounds such as flavonoids, carnosine, curcumin and phenolic acids also interfere with glycation process [43] and scavenge dicarbonyls [44]. Due to their regulatory role over oxidative stress and associated signalling pathways, they have been implicated in cancer prevention. The antioxidant activity of vitamin C has also been associated with anti-glycation properties and potential effects on cancer progression.

Finally, Angiotensin Converting Enzyme (ACE) inhibitors such as benazepril and ramipril have been reported to exhibit anti-glycation effects and reduce cancer progression [45], however through an unknown mechanism.

RAGE signalling inhibitors

As previously described, RAGE expression and signalling has been ultimately linked to carcinogenesis. RAGE exhibits a proliferative impact on cancer cells by increasing cell numbers via regulation of cell cycle proteins such as cyclin D1 and limiting apoptosis via activation of anti-apoptotic, prosurvival and autophagic proteins. It is also implicated in angiogenesis through VEGF upregulation in cancer cells and myeloid-derived suppressor cells activation [46]. Its expression has been associated with the pathogenesis of several cancer types including breast, gastric, colon, pancreatic, prostate cancer and hepatocellular carcinoma [46].

Gene targeting of RAGE is undoubtedly a promising method for therapeutic intervention in cancer aiming to combat complications mediated by RAGE activation (Fig. 1). siRNA targeting of RAGE in breast cancer cell lines was demonstrated to reduce cell proliferation by arresting cells in G1 phase and blocking DNA synthesis. It further reduces the expression of transcription factor NF-κB p65 and cell proliferation markers such as proliferating cell nuclear antigen (PCNA) and cyclin D1 [47]. Similar data were reported for siRNA targeting of RAGE in hepatocellular carcinoma cell lines with inhibition of cell growth [48]. In gastric cancer, RAGE upregulation has been associated with lymph node metastasis. RAGE knockdown was revealed to decrease growth and invasion of cancer cells and to induce cell apoptosis as well as cycle arrest, indicating the potential of RAGE as a therapeutic target for this tumour's aggressiveness [49].

Other therapeutic measures to block RAGE signalling and the associated complications include blocking of RAGE with sRAGE, lysozyme and anti-RAGE antibodies (Fig. 1). sRAGE is the cleaved soluble form of RAGE and exhibits decoy receptor properties against any interactions of RAGE with its ligands. sRAGE was detected in various human tissues, being primarily associated with anti-atherogenic effects. Importantly, high sRAGE levels confer resistance over inflammatory AGE-RAGE signalling pathways. In IL-10-deficient mice, sRAGE administration reduced colonic inflammation [50]. sRAGE was shown to decrease motility, migration and prometastatic activation of A375 melanoma cells, by blocking S100A4-RAGE signalling axis [51]. Furthermore, in a human study of Finnish male smokers, serum levels of sRAGE were found inversely correlated with pancreatic cancer risk [52].

Lysozyme, an enzyme of the innate immune system has the ability to block the AGE-binding site of RAGE and enhance removal and clearance of AGEs. It can also increase their uptake and degradation by macrophages through interference with AGE-RAGE signalling [46]. Recently, application of a stable nanostructured lysozyme in MCF-7 breast cancer cells showed potent anti-proliferative properties (95% cell death within 24 h) through a ROS-based mechanism [53]. In a similar way, lysozyme may reduce proliferation of gastric cancer cell lines [54] and B16-V melanoma cells [55].

Anti-RAGE antibodies block the recognition pattern of the receptor and may interfere with RAGE intracellular signalling. They have been demonstrated to reduce hepatocellular apoptosis [46], prevent upregulation of TGF and peritoneal accumulation of fibronectin in diabetic animals [46]. In melanoma tumours-bearing mice, treatment with anti-RAGE antibodies significantly reduced tumour growth, implicating RAGE in melanoma tumour formation. Furthermore, the efficacy of dacarbazine, an alkylating agent was significantly enhanced after anti-RAGE antibody treatment in decreasing the growth of RAGE overexpressing tumours [56]. Additional animal studies with anti-RAGE antibodies indicate that blockade of RAGE signalling affects both melanoma tumour growth and metastasis formation [57]. Moreover, enhanced AGE-induced

proliferation of MCF-7 cells was completely prevented by anti-RAGE antibodies treatment [58].

GLO-1 inhibitors

GLO-1 is an important enzyme for dicarbonyl metabolism, employing the antioxidant GSH as a cofactor to convert MG to the non-toxic hemithioacetal [4,5]. Due to the high glycolytic rate of tumour, GLO-1 inhibition leads to MG burst and GSH depletion in cancer cells [8,59]. As a result, carbonyl and oxidative stress is established that eventually leads to cell dysfunction and apoptosis or necrosis making the utilization of GLO-1 inhibitors an appealing and effective anticancer strategy (Fig. 1) [59].

Cell permeant GLO-1 inhibitors have been found useful for the treatment of GLO-1-linked multiple drug resistance (MDR) tumours. The first specific inhibitor was S-p-bromobenzylglutathione diester with medium potency and anti-tumour properties in cancer cell lines. The cyclopentyl ester derivative that was subsequently developed, exhibited more potent anti-tumour activity in animal models [59,60]. Natural occurring GLO-1 inhibitors have also been detected including the flavonoids curcumin, quercetin, naringin, myricetin, luteolin, and kaempferol, 18-β-glycyrrhetinic acid, Monacolin K, delphinidin, andrographolide, γ-tocotrienol [16,61]. Curcumin showed stronger inhibitory activity compared to flavonoids and attenuated proliferation of prostate, breast and astrocytoma cells [16]. Andrographolide induced apoptosis of HL-60 cells through GLO-1 and 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibition [62]. Delphinidin among anthocyanidins also exhibited strong inhibitory effects and induced HL-60 apoptosis. The active component of red yeast rice, monacolin K leads to U937 cell apoptosis via MAPK/NF-κB/GLO-1 and Akt/NF-κB/GLO-1 signalling pathways [63].

In human tumours, identification of sensitivity to GLO-1 inhibitors is difficult since a high GLO-1 expression and activity and a high flux of MG formation is required for a cytotoxic response [4,8]. Elevation of GLO-1 expression in tumours may be due to increased gene copy number as observed in breast and small cell lung cancer or increased nuclear factor erythroid 2-related factor 2 (Nrf2) signalling that leads to Nrf2-mediated MDR [4,8,64]. However, studies in different tumours show that gene amplification of *GLO-1* cannot be a reliable marker because it is not consistently functional and does not induce MG flux [4,8]. Further studies to assess GLO-1 inhibitors potency in systems modelling the glyoxalase pathway are required to determine their pharmacological effects.

Concluding remarks

Many studies highlight the central role of advanced glycation end products and their downstream signalling pathways in tumorigenesis. Increased AGE and dicarbonyl levels from endogenous or exogenous sources induce the establishment of oxidative stress along with persistent unchecked inflammation, generating a suitable microenvironment for tumour formation and progression.

In the present paper, we provide evidence that glycative stress plays a critical role in cancer onset and needs to be considered as a possible target for achieving effective prevention. Overall, several anti-glycating agents have been shown to prevent carcinogenesis by reducing dicarbonyl and AGEs formation as well as the concomitant DNA damage. Furthermore, they may delay tumour progression through interference with AGE-RAGE axis and the associated oxidative stress. Among them aspirin, metformin and aminoguanidine achieved significant inhibition of several glycation steps both *in vitro* and *in vivo*. sRAGE and lysozyme were proved effective in inhibiting AGE-RAGE signalling *in vivo* and the S-p-bromobenzylglutathione cyclopentyl diester demonstrated efficient inhibition of GLO-1 and potent anti-tumour activity in preclinical animal models.

However, several limitations arise from current studies that need to be clarified and better investigated in the future. AGEs encompass a heterogeneous group of compounds with diverse properties. Most *in vitro* studies are mainly performed with glycated BSA, a mixture of AGE forms while epidemiological studies mainly investigate the association of CML with cancer risk. AGE compounds possess different biological roles and must be systematically investigated in carcinogenesis.

Special attention must be given to dicarbonyls that play a central role in the progression of glycation reaction and formation of toxic AGEs. Their doses in experimental studies must be carefully studied since low levels can be tumour promoting but higher doses may cause shock in cancer cells. Also, experimental studies on the effects of carbonylation by dicarbonyl intermediates have revealed contradictory results by inducing both promoting and suppressing effects in cancer cells. A well-designed molecular to clinical investigation is highly demanded to determine the functions of dicarbonyls in cancer progression.

Regarding the application of anti-glycating inhibitors in cancer prevention, several drugs exhibited potent anti-cancer effects *in vitro* and *in vivo* but clinical data are currently missing in order to link their anti-cancer properties with their anti-glycating activity and their concomitant biological function.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest to declare.

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