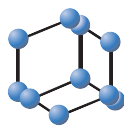


REVIEW ARTICLE

BENTHAM
SCIENCE

Role of Advanced Glycation End Products in Carcinogenesis and their Therapeutic Implications

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Abstract: Aging is one of the biggest risk factors for the major prevalent diseases such as cardiovascular diseases, neurodegeneration and cancer, but due to the complex and multifactorial nature of the aging process, the molecular mechanisms underlying age-related diseases are not yet fully understood. Research has been intensive in the last years aiming to characterize the pathophysiology of aging and develop therapies to fight age-related diseases. In this context advanced glycation end products (AGEs) have received attention. AGEs, when accumulated in tissues, significantly increase the level of inflammation in the body which has long been associated with the development of cancer. Here we discuss the classical settings promoting AGE formation, as well as reduction strategies, occurrence and relevance of AGEs in cancer tissues and the role of AGE-interaction with the receptor for advanced glycation end products (RAGE) in cancer initiation and progression.

Keywords: Advanced glycation end products, cancer, aging, inflammation, RAGE, cardiovascular diseases.

1. INTRODUCTION

Aging is a complex and multifactorial process characterized by a progressive accumulation of damage to an organism over time and is considered as one of the biggest single risk factors for the development of a multitude of diseases such as type-II diabetes [1, 2], neurodegenerative diseases [3, 4], and cancer [5, 6]. Furthermore, it is widely accepted that these age-related diseases result from a combination of various endogenous, genetic, lifestyle, and environmental factors [7-9]. Due to the complex and multifactorial nature of aging, the molecular mechanisms underlying the initiation and progression of age-related diseases are not yet fully understood. Research has been intensive in the last years aiming to characterize the pathophysiology of aging and developing therapies to fight age-related diseases. In this context advanced glycation end products (AGEs) have received attention [10-12]. AGEs are a group of heterogeneous compounds formed via non-enzymatic glycation/glycoxidation of reducing sugars with free amino groups of proteins. Not only proteins but also lipids and nucleic acids exposed to reducing sugars could suffer glycation or glycoxidation reactions. Formation of AGEs occurs exogenously in food, especially by thermal processing, but also endogenously in the body.

In vivo glycation of proteins occurs under physiological conditions and represents a type of post-translational modification taking place slowly but continuously throughout the life span, promoting AGE accumulation during aging. Thus, to some extent the accumulation of AGEs is inevitably linked to aging and age-related accumulation of AGEs was shown to exist in human cartilage, skin collagen and pericardial fluid [13-15]. Increased protein glycation is also associated with the pathogenesis of several age-related and chronic inflammatory diseases such as cardiovascular diseases [13], Alzheimer's disease [16], stroke [17], as well as the general decline in health associated with old age. Under hyperglycemic conditions,

such as that found in diabetes, AGE accumulation is accelerated. Hyperglycemia is known to be responsible for high rates of protein glycation and the gradual build-up of AGEs is furthermore involved in the pathogenesis and development of long-term diabetic complications such as retinopathy, nephropathy, neuropathy, and cardiomyopathy [18].

Protein glycation interferes with normal protein function by disrupting molecular conformation, or altering enzyme or receptor functionality and activity. The effects of AGEs are exerted on the one hand by direct damage to protein structures and extracellular matrix modification, and on the other hand by binding the receptor for advanced glycation end products (RAGE). A multitude of signaling cascades are activated via RAGE causing multiple pathological effects associated with oxidative stress and inflammation [19].

Since it is generally accepted that chronic inflammation, oxidative stress, and cancer are intrinsically linked [20], a potential contribution of AGEs to malignant cell transformation and the development and progression of cancer also seems to be conclusive. In addition, cancer cells are generally characterized by an inclination towards anaerobic metabolism of glucose, a phenotype that was first noted by Otto Warburg, called Warburg effect [21]. To meet the energy requirements and to compensate for this inefficient energy supply, tumors are characterized by an increased glucose uptake and a high rate of glycolysis. Consequently, as a by-product of enhanced glycolytic flux, this could lead to an elevated level of glycation and increased formation of AGEs. In this review, we tried to summarize the current knowledge on AGE formation as well as reduction strategies, occurrence and relevance in cancer tissues, the role of RAGE in cancer initiation and progression and the potential of AGEs as cancer biomarkers.

2. ENDOGENOUS GLYCATION AND EXOGENOUS SOURCES OF AGES/ALES

AGEs are formed endogenously via complex heterogeneous chemical reactions. The underlying mechanism is the so-called Maillard reaction, occurring at different rates depending on tem-

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perature, pH value and the respective sugar reactant. Most commonly, the formation of highly reactive α -dicarbonyls (e.g. 3-deoxyglucosone (3-DG), methylglyoxal (MGO) and glyoxal (GO)) initiates the formation of AGEs [22, 23]. These compounds arise from different pathways including the non-oxidative cleavage of Amadori compounds [24], oxidative fission of the Schiff base (Namiki pathway) [25], hexose autoxidation (Wolff pathway) [26], as by-product of the glycolytic or polyol pathway [27] as well as ketone body catabolism [28], or from lipid oxidation [29]. The latter pathway, in addition, initiates the formation of short chain reactive carbonyl species (RCS), i.e. α,β -unsaturated aldehydes, dialdehydes, keto-aldehydes, and phospholipid-based RCS which react with free amino groups of proteins to form advanced lipoxidation end products (ALEs) or in case of dialdehydes such as glyoxal or keto-aldehydes such as methylglyoxal so-called EAGLEs (either advanced glycation or lipoxidation end products) [22]. AGEs and ALEs precursors are prone to react with nucleophiles; moreover, they readily react with free amino moieties of proteins and peptides as well as nucleic acids and phospholipids. Lysine and arginine residues are the most susceptible glycation sites resulting in covalent modifications and/or cross-linked proteins with irreversibly modified biological activity. In addition, cysteine, tryptophan and histidine residues were shown to be favorable glycation sites [30]. The formed products can be divided into fluorescent and non-fluorescent, as well as cross-linking and non-cross-linking AGEs, with AGEs exhibiting both properties, while others show none of these characteristics. Prominent AGEs discussed to adversely affect the progression of hyperglycemic, inflammatory diseases and cancer are 3-DG derived pyrraline and pentosidine, MGO-derived N^ε-(carboxylethyl)-L-lysine and N^ε-(5-hydro-5-methyl-4-imidazolone-2-yl)-L-ornithine (MG-H1), GO-derived N^ε-(carboxymethyl)-L-lysine (CML) and S-carboxymethylcysteine as well as the cross-linking AGEs glyoxal-lysine dimer (GOLD) and methylglyoxal-lysine dimer (MOLD). It has been shown that the level of these compounds is high in plasma and tissues during aging, in various cancers as well as under hyperglycemic conditions such as diabetes mellitus [31-35]. ALE formation has been shown to be dependent on the oxidative status of individuals and is therefore connected to chronic inflammation and oxidative stress [36]. Furthermore, lipid oxidation might be initiated by glycosylation of phospholipids, indicating that AGE formation can trigger the formation of ALEs [29].

In combination, these pathways might increase the severity of inflammatory diseases, and the initiation and progression of malignant tumors. Up to now the quantification of AGEs in tissues and serum of humans is most commonly assessed by ELISA or immunohistochemical staining [35, 37]. However, some studies used liquid chromatography methods, which have been shown to be more reliable in terms of validity at least in the AGE analytics of food [38, 39]. Human studies show that baseline levels of MGO and GO range from upper nanomolar to lower micromolar, depending on the analytical set-up [40-43]. The discrepancies among the different baseline levels of e.g. MGO concentrations were investigated by Chaplen et al. showing that different analytic approaches give significantly different results [44]. To the best of our knowledge, so far no routine analytical method for serum and tissue levels of AGEs precursors exists. This lack of a reliable and reproducible method is even more pronounced for AGEs and ALEs levels. However, all studies have reported that elevated serum and tissue levels of AGEs and their precursors can be found in patients suffering from hyperglycemia, diabetes mellitus and uremia as well as individuals undergoing peritoneal dialysis [32, 45-48], suggesting that the endogenous pool of AGEs is inherently connected to the health status of an individual.

Besides being endogenously formed, AGEs and ALEs occur as a result of food processing. The dietary burden of AGEs and ALEs contributes to the accumulation of these compounds *in vivo*. Several

studies show that every processed food contains AGEs in a certain amount and that the AGEs content of food relates to the processing conditions [38, 49, 50]. Most commonly AGEs concentrations are determined via monoclonal antibodies e.g. for CML contents [49, 51]. However, when analyzing the same food by means of chromatographic methods significant differences in concentrations are observed [38, 39, 49, 51]. Generally, high temperature processing of food leads to high amounts of AGEs while moderate processing like steam blanching limits the formation of AGEs. Raw products contain only negligible AGEs concentrations. The highest AGE concentrations are found in cereals, bakery products and processed meat. Fruits, vegetables, and high-fat or high moisture food like butter/ oil and yoghurt, respectively, provide the lowest concentrations. The overall daily intake of food-derived AGEs from a conventional diet is estimated to be between 25-75 mg [45]. In addition, smoking was shown to significantly elevate AGEs *in vivo* and should not be neglected when estimating an individual's AGEs burden. Regarding the heterogeneity of the chemical structures of AGEs, absorption rates differ significantly, e.g. Urribarri and co-workers found that about 30% of ingested AGEs accumulate in the human body [46], while Koschinsky *et al.* concluded that up to 10% of food-borne AGEs (mainly CML) might be absorbed and undergo metabolic transition, with only 30% of the ingested AGEs being retrievable in the urine of healthy patients [52, 53]. In contrast, other studies found that 60-80% of food-borne pyrraline and pentosidine were absorbed, with 50-60% of the free consumed AGEs being excreted via the kidney [54, 55]. The urinary excretion rates might further be influenced by the health status of the individual being lowered to less than 5% in patients with diabetes mellitus or renal failure [37, 52]. The formation and accumulation of AGEs and ALEs *in vivo* seem to be inherently connected to lifestyle choices (e.g. diet and smoking), and the individual's oxidative status and metabolism.

3. INFLAMMATION, RAGE AND CANCER

In contrast to several receptors such as scavenger receptors class A and B (SR-Ai, SRAII, CD36 and SR-BI)[19] described to be responsible to detoxify or remove AGEs from circulation or tissues, RAGE is a signal transduction receptor for AGEs, mediating diverse cellular responses. RAGE is a multiligand single transmembrane receptor and a member of the immunoglobulin superfamily of cell surface molecules [56], binding in addition to AGEs several other molecules such as β -amyloid peptides and β -sheet fibrils, high-mobility group box 1 (HMGB1), several members of the S100 protein family, and prions [57]. By binding to the receptor these molecules stimulate signal transduction via a multitude of pathways including Ras-extracellular signal-regulating kinase 1/2 [58], CDC42/Rac [59], p38 mitogen-activating protein kinase [60], NADPH-oxidase [61], and JAK1/2 [62]. Downstream signaling activates members of the STAT (signal transducers and activators of transcription) family [63], AP-1 (activator protein-1) [57] and NF κ B [64], a key target of RAGE signaling. NF κ B is a transcription factor for a large group of genes which is involved in several different pathways, transducing a multitude of pro- or antiapoptotic and inflammatory signals. The activation of NF- κ B induces the expression of adhesion molecules, growth factors (e.g. transforming growth factor- β), and proinflammatory cytokines (such as IL-6 and TNF- α) [65]. In addition, the interaction of AGEs with RAGE activates NADPH oxidase, leading to increased intracellular oxidative stress. This sudden reactive oxygen species (ROS) increase will again activate NF- κ B [61, 66]. Furthermore, it is important to note that RAGE also exhibits a functional NF- κ B binding site and has been shown to be a direct target gene of NF- κ B signaling. Therefore NF- κ B activation increases RAGE expression, creating a positive feedback cycle, able to convert a transient proinflammatory reaction into a chronic pathophysiological state [67, 68]. Thus it is not surprising that the AGE-RAGE interaction is implicated in aging and considered as a major contributor to the initiation, progres-

sion and clinical severity of diseases by triggering oxidative stress and chronic inflammatory responses (Fig. 1). Numerous studies have shown a strong contribution of chronic inflammation to tumor development [69, 70]. The generation of an inflammatory, pro-tumorigenic microenvironment largely depends on the activation of several transcription factors, mainly NF- κ B, regulating the expression of tumor promoting cytokines, but also survival genes such as Bcl-X_L. These soluble factors then recruit and activate immune cells of myeloid and lymphoid origin and trigger signaling pathways leading to the production of a large number of pro-inflammatory mediators in a positive feed-forward manner [53]. In the initial phase, inflammatory mediators such as cytokines and reactive oxygen and nitrogen species (ROS/RNS) derived from infiltrating immune cells induce epigenetic changes in pre-malignant lesions and silence tumor suppressor genes [71]. During tumor promotion, cytokines and chemokines are secreted from immune cells acting as survival and proliferation factors for malignant cells. The onset of angiogenesis is critical for an adequate supply of tumor cells with oxygen, nutrients, growth- and survival factors and the removal of waste products [72]. During progression and metastasis, both tumor and immune cells produce cytokines and chemokines leading to an increase in cell survival, motility, and invasiveness [73]. Through its ability to activate NF- κ B, RAGE signaling and up-regulation provides a critical link between the accumulation of AGEs and cancer, and has been implicated in the development of many cancers [74-78]. The occurrence of AGEs (CML and argpyrimidine) in human tumors was first shown in squamous cell carcinomas of larynx, adenocarcinomas of the breast, adenocarcinomas of the colon, and leiomyosarcomas by immunohistochemical staining, with a great variation between different types of tumors [35]. AGE treatment of immortalized prostate [79] and breast [80] cancer cell lines showed promotion of cell growth, migration and invasion. A comparison of fresh-frozen breast cancer samples and corresponding noncancerous tissue samples indicate a

high expression of the RAGE-encoding gene in cancerous tissues [81]. RAGE expression was up-regulated in high-stage, metastatic, and aggressive breast cancer tumors, suggesting that RAGE may contribute to the malignant potential of tumors. RAGE gene overexpression was also shown in ovarian cancer tissue compared to adjacent noncancerous tissue. A significant association between RAGE expression and tumor size, depth of stromal invasion, lymphovascular invasion and stage of cancer was observed [82]. RAGE is overexpressed in human pancreatic tumors but not in adjacent normal ducts. Furthermore, RAGE is a critical promoter in the transition of premalignant epithelial precursors to invasive pancreatic cancer [83]. Longstanding type II diabetes is an established risk factor for several cancers, especially pancreatic cancer and the mechanistic link might be the accumulation of AGEs, especially under poor glycemic control [84, 85]. In mice prone to pancreatic cancer, exogenous AGE administration (CML) induced RAGE upregulation in pancreatic intraepithelial neoplasias and markedly accelerated progression to invasive pancreatic cancer [86]. Overall, there is accumulating evidence that AGEs, via interaction with RAGE, could play a role in various types of cancer and contribute to tumor development, migration and metastasis. However, further studies are needed to shed more light on the physiological relevance of AGE-RAGE signaling in cancer biology.

4. STRATEGIES FOR AGES REDUCTION

Due to the adverse effects of AGEs and the direct link to a multitude of diseases including cancer, strategies aiming to prevent or reduce AGEs accumulation could provide clear health benefits. Strategies to reduce AGEs/ALEs formation *in vivo* (Fig. 2) include metal chelators and antioxidants able to interfere with oxidative pathways such as Namiki and Wolff pathway as well as radical-based pathways such as lipid oxidation. A diet rich in antioxidants (e.g. polyphenols and α -tocopherol as found in the Mediterranean

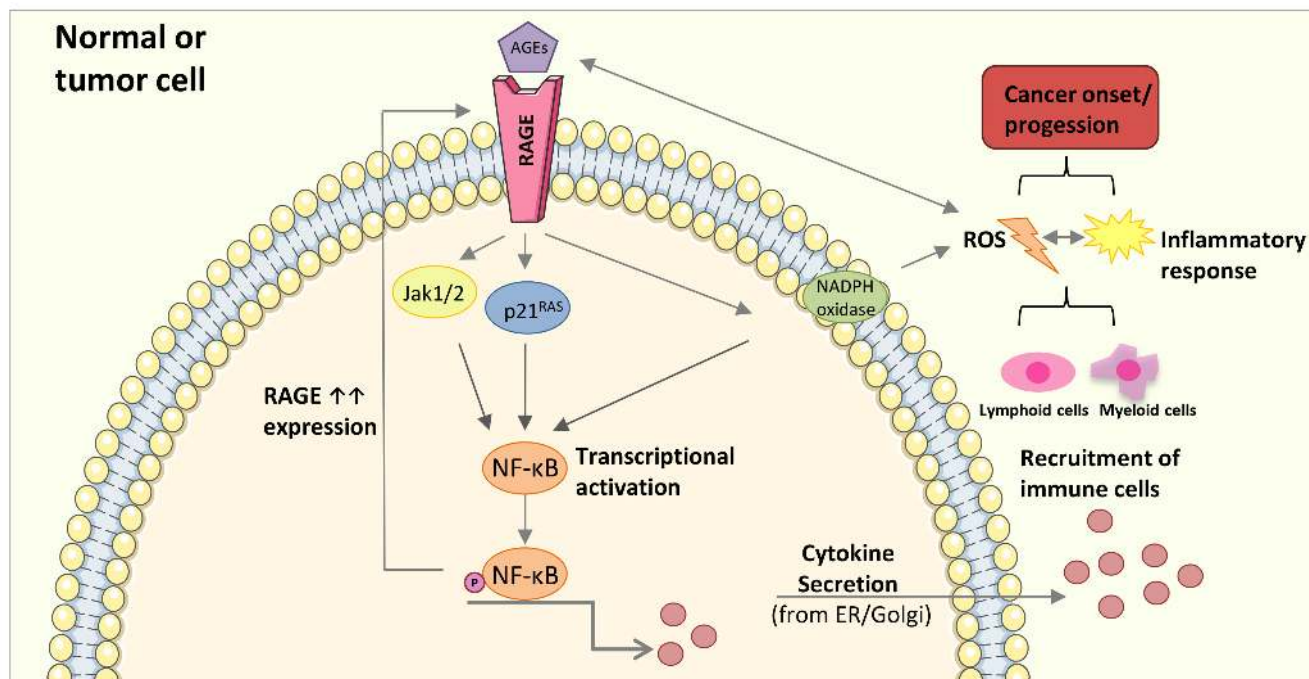


Fig. (1). Simplified AGE-mediated activation of an inflammatory response leading to cancer onset and/or progression. AGE-RAGE interaction triggers the activation of transcription factors transducing inflammatory signals, mainly NF- κ B, leading to an increased cytokine secretion, followed by lymphoid and myeloid immune cells recruitment into the tumor microenvironment, elevated ROS production, and an inflammatory response. NF- κ B activation also increases RAGE expression, creating a positive feedback cycle. In addition, reactive intermediates generated during AGE formation can directly increase ROS production promoting the immune response and the formation of further AGEs creating a chronic inflammatory state. Membrane and RAGE receptor illustration were used from Servier Medical Art under creative commons license 3.0 (<https://smart.servier.com/>).

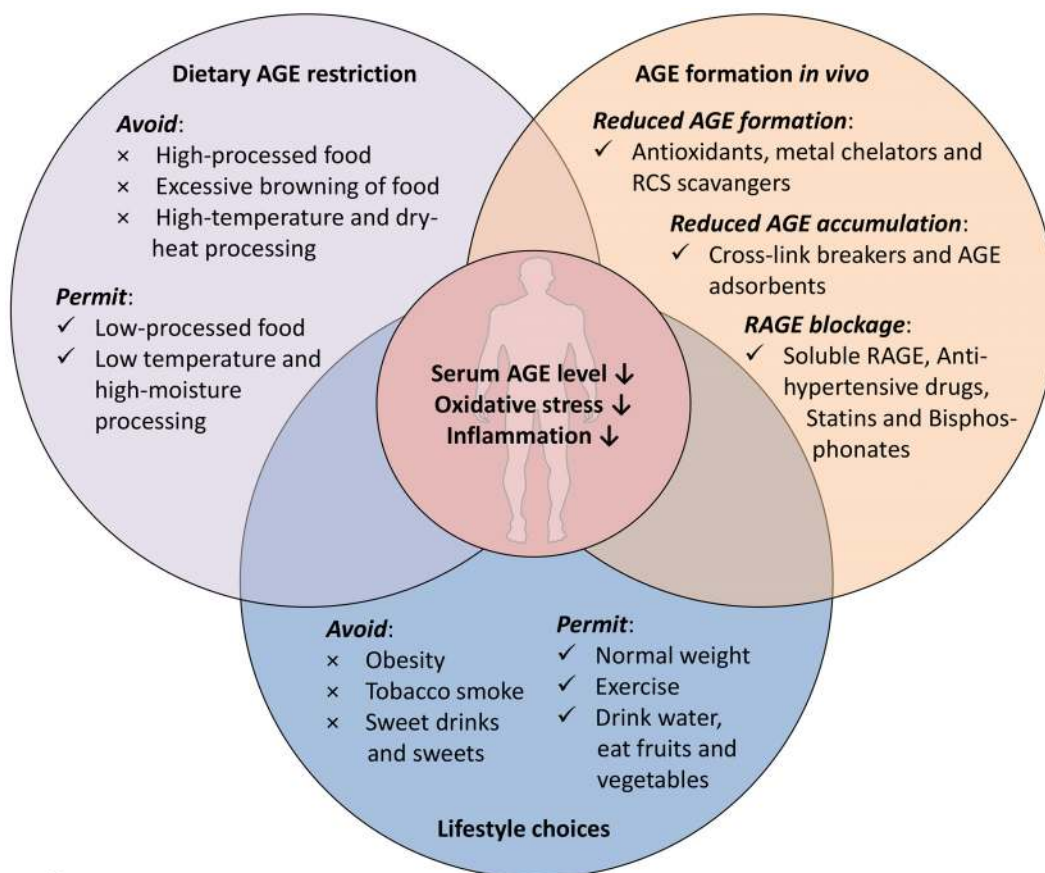


Fig. (2). The paradigm of AGE restriction, inhibition of AGE formation and accumulation.

diet) was shown to positively impact on oxidative stress and inflammatory diseases by decreasing AGE formation in food and *in vivo* [87, 88]. The connection between the consumption of polyphenol-rich diets and protection against cancer as well as other chronic diseases was profoundly reviewed by Vauzour *et al.* [89].

In addition, several metal-chelators such as diethylenetriaminepentaacetic acid (DETAPAC), desferrioxamine (DFO) and triethylenetetraamine (TETA) might inhibit the formation of AGES *in vitro* and *in vivo* as conclusively reviewed by Aldini *et al.* [90]. Furthermore, RCS quenching compounds reduce AGE/ALEs formation and accumulation by scavenging the RCS before they react with proteins. Compounds that were shown to possess RCS scavenging activity include thiol-containing compounds (such as glutathione, N-acetylcysteine and cysteamine *etc.*), guanidine/hydrazine derivatives (such as aminoguanidine, β -resorcyldiene aminoguanidine and ALT-946 (N-(2-acetamidoethyl)-hydrazine-carboximidamide hydrochloride)) and heterocycle-based compounds (such as pyridoxamine, carnosine and polyphenols (*e.g.* theaflavin and genistein)) as already reviewed in detail [89-91]. Other strategies to reduce AGE accumulation and RAGE activation *in vivo* comprise cross-link breakers (*e.g.* Alagebrium (ALT-711)[92]), AGE adsorbents (AST-120 (Kremezin) and galectin-3) [93, 94], anti-hypertensive drugs, statins and bisphosphonates [95], respectively. All of the mentioned pharmaceuticals, however, may have individual drawbacks in humans and are not yet established for clinical applications.

The most common way to reduce AGE accumulation is the dietary restriction of AGE consumption [34, 37, 51]. Generally, food preparation and processing determines the rate of dietary AGE formation. Therefore, lower temperature, shorter cooking times and lowering the pH lead to a decreased AGE formation rate in food. In

addition, the water content is important for AGE formation; therefore, changing the cooking style from frying or grilling to boiling or steam-blanching will significantly reduce the AGE contents of food. Finally, avoiding obesity (by exercise) and tobacco smoke might serve as treatments to lower AGE accumulation in the human body.

5. AGES AS CANCER BIOMARKERS

The connection between elevated AGE accumulation *in vivo* and development and disparity of cancer is highlighted by numerous recent studies and reviews all emphasizing the elevated susceptibility to cancer initiation and progression by an increase in AGE-RAGE-dependent stress response, resulting in increased oxidative stress and chronic inflammation. While, indeed, cancer patients show overall increased AGE levels in their plasma as well as in tumor tissue [96-99], using specific AGE levels of tissues as biomarkers for the development of specific cancers is questionable. This is due to the systemic impact of AGE accumulation on several other metabolic disorders and chronic diseases such as type-II diabetes. Increased AGE levels are, therefore, intrinsically connected to the lifestyle of an individual, and can be considered as an individual's oxidative status and risk for the development of metabolic disorders. The glycoxidation of specific defense and DNA-repair enzymes might lead to an elevated risk of cancer initiation and progression, but also contributes to diabetic complications [100]. Overall, the development of metabolic disorders is facilitated by increased AGE levels *in vivo* and clearly highlights the interconnection among these diseases in the human body. Thus, restriction of AGE intake and accumulation might serve as a tool to counteract the progression and severity of cancer as well as several diseases connected to Western-style diets and lifestyle.

Also, it has to be mentioned that there are limitations regarding the routine assessment of specific AGEs. Accessibility to blood/plasma for repeated measurements of AGEs is much easier than tissue-requiring biopsies, but so far plasma AGE assays have not been shown to be directly related to tissue AGE content.

On the other hand, and as described above, RAGE is overexpressed in multiple cancers. In addition, the secreted isoform of RAGE, termed soluble RAGE (sRAGE) was found to be released from cells to bind the ligands of RAGE, and to be capable of preventing the adverse effects of RAGE-signaling, therefore representing a naturally occurring competitive inhibitor of RAGE-mediated events. Treatment with exogenous sRAGE might be able to block deleterious effects caused by RAGE ligands. Furthermore, sRAGE levels may provide a novel biomarker for tracking inflammatory diseases including cancer, potentially helping to assess the severity of diseases, but also the response to therapeutic intervention [101].

In summary, AGE/sRAGE levels might serve as a factor to assess the individual's risk to develop cancer associated with early recognition. But currently, there is no evidence that measurement of both AGEs and sRAGE will become accepted and applicable for clinical use.

CONCLUSION AND PERSPECTIVES

There is ample evidence that AGEs play an important role in cancer development and progression. Many studies proposed that the cancer-promoting effect of AGEs is predominantly mediated by AGE-RAGE interaction leading to increased ROS formation and inflammatory processes. Therapeutic inhibition of AGEs, such as cross-link breakage, has yet to yield clinically viable and applicable therapeutics. The development of reliable analytical methods to detect plasma and tissue AGE levels would facilitate the applicability of novel medications. Currently, the simple application of dietary restriction and raising dietary awareness (*e.g.* polyphenol-rich, low processed food) may be useful in restricting AGEs and might have a potential for both cancer prevention and therapy. Education on the consequences of lifestyle choices, *e.g.* smoking or exercise, and home cooking behavior represents affordable prevention of AGE formation and accumulation, both for the individual and from a societal perspective. Following the paradigm of AGE restriction might not only be useful for cancer prevention but to counteract the development of a multitude of diseases connected to western lifestyle and aging.

LIST OF ABBREVIATIONS

AGEs	=	Advanced glycation end products
ALEs	=	Advanced lipidoxidation end products
CML	=	N ^ε -(carboxylmethyl)-L-lysine
DETAPAC	=	Diethylenetriaminepentaacidic acid
DFO	=	Desferrioxamine
3-DG	=	3-Deoxyglucosone
GO	=	Glyoxal
GOLD	=	Glyoxal-lysine dimer
HMGB1	=	High-mobility group box 1
MG-H1	=	N ^ε -(5-hydroxy-5-methyl-4-imidazolone-2-yl)-L-ornithine
MGO	=	Methylglyoxal
MOLD	=	Methylglyoxal-lysine dimer
RAGE	=	Receptor for advanced glycation end products
RCS	=	Reactive carbonyl species
TETA	=	Triethylenetetraamine

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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