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The receptor of advanced glycation end-products axis and gallbladder cancer: A forgotten connection that we should reconsider

Rojas A *et al.* RAGE axis and gallbladder cancer

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Abstract

Compelling pieces of evidence derived from both clinical and experimental research have demonstrated the crucial contribution of chronic inflammation in the development of neoplasms, including gallbladder cancer. In this regard, data derived from both clinical and experimental studies have demonstrated that the receptor of advanced glycation end-products (RAGE)/AGEs axis plays an important role in the onset of a crucial and long-lasting inflammatory milieu, thus supporting tumor growth and development. AGEs are formed either in biological systems or in foods, and food-derived AGEs, also known as dietary AGEs are known to contribute to the systemic pool of AGEs. Once they bind to RAGE, the activation of multiple and crucial signaling pathways are triggered, thus favoring the secretion of several pro-inflammatory cytokines also involved in the promotion of gallbladder cancer invasion and migration. In the present review, we aimed to highlight the relevance of the association between high dietary AGEs intakes and high risk for gallbladder cancer, and emerging data supporting that dietary intervention to reduce gallbladder cancer risk is a very attractive approach that deserves much more research efforts.

Key Words: Gallbladder cancer; Advanced glycation end-products; Receptor of advanced glycation end-products; Chronic inflammation; Nutrition

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Core Tip: A growing body of data has demonstrated a positive association between the risk of gallbladder cancer and high dietary intake of advanced glycation end-products (AGEs). These noxious compounds are important contributors to the onset of a chronic inflammatory response, through the activation of the receptor of advanced glycation end-products (RAGE). We herein discuss how RAGE activation is crucial in the development of gallbladder cancer and the relevance of new incoming data supporting the role of dietary interventions to reduce the risk of gallbladder cancer.

INTRODUCTION

Gallbladder cancer development is linked to both genetic and environmental factors, and where the onset of chronic inflammation is a crucial contributor to gallbladder carcinogenesis. This chronic inflammatory condition can be triggered by several factors including not only chronic infection by *Salmonella sp.*, or *H. pylori*^[1-4] but also some dietary habits or metabolic conditions^[5-9], which are associated with an overactivation of the receptor of advanced glycation end-products (RAGE).

At present, the onset of many of both age- and diet-related non-communicable diseases, including different cancer types, is widely associated with the chronicity of low-grade inflammation^[10,11]. At this point, the diet is widely recognized as an important modulator of this of chronic and systemic inflammation^[12,13], particularly the Western-type dietary patterns^[14].

One common and important element in this unhealthy diet is the advanced glycation end-products (AGEs), which are a large and heterogeneous group of compounds that

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were initially recognized in the “Maillard reaction”, but they can also form by other reactions, including the oxidation of sugars, lipids, and amino acids^[15,16].

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Food-derived AGEs, also known as dietary AGEs (dAGEs), substantially contribute to the systemic pool of AGEs. Their intake has been linked in both humans and mice to an increased level of oxidative stress and inflammation, thus playing an important role in the onset and development of several health disorders^[17,18].

The pathogenic mechanisms of dietary AGEs are the same as those endogenously produced, either by activation of the RAGE or by covalent crosslinking of proteins, thus altering protein structure and function. The receptor-dependent and receptor-independent mechanisms are recognized as important contributors to tumor growth and development^[19,20].

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In the present review, we aim to highlight the burden of RAGE axis activation on gallbladder cancer, its therapeutic potential, as well as the significance of lowering dietary consumption of AGEs in subjects at risk.

THE RAGE/AGES AXIS AND GALLBLADDER CANCER. NEW INCOMING PIECES OF EVIDENCE

Over the last years, there has been growing evidence supporting the key role of diet-derived AGEs as major contributors to the systemic pool of AGEs^[21], which notably increase oxidative stress and chronic/acute inflammation, contributing to the pathophysiology of many human inflammatory and malignant diseases^[18,22,23].

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Since the multi-center prospective European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, which has investigated the relationship of dietary and environmental factors with the incidence of cancer and other chronic diseases^[24-27], a growing body of evidence has revealed strong findings to support that a pro-inflammatory diet with high levels of dietary AGEs intake increases the risk of several types of cancer^[28], such as breast, skin and those originated from the digestive tract^[29-31]. Recently, Mayén *et al*^[32] conducted a multinational cohort study using the EPIC database to characterize the daily dietary intake (mg/d) of three AGEs including Nε-

[carboxymethyl] lysine (CML), Nε-[1-carboxyethyl] lysine (CEL), and Nδ-[5-hydro-5-methyl-4-imidazol-2-yl]-ornithine (MG-H1) for each study participant, to assess the AGEs consumption with the hepatobiliary cancer risk. Noteworthy, in this study, the authors found a positive association between the risk of gallbladder cancer and high dietary intake of CML HR = 1.30 (95% CI, 1.07-1.57) and MG-H1 HR = 1.26 (95% CI, 1.06-1.50), and thus suggesting that higher intakes of dietary AGEs may increase the risk of gallbladder cancer.

Although the study of Mayen *et al*^[32] has some limitations, particularly in estimating dietary AGEs exposure, other epidemiological studies have revealed an increased tumor progression and mortality of gallbladder cancer patients, with inflammatory comorbidities related to overactivation of the RAGE axis, such as high-fat diet consumption^[33], metabolic syndrome^[34], and diabetes mellitus (DM)^[35-38], due to the increased endogenous formation of AGEs reported in these entities.

Some studies have shown increased expression of RAGE in gallbladder cancer cells, which were directly in concordance with the invasion ability of the neoplastic cell lines^[39]. Additionally, compelling evidence has been reported of a strong increase in AGEs formation under hyperglycemic conditions^[40,41]. Noteworthy, the gallbladder accumulation of AGEs is significantly higher in the gallbladder of diabetic mice when compared to control animals. These findings support the role of the RAGE/AGEs axis activation in gallbladder carcinogenesis^[42].

Furthermore, other *in vivo* analyses of adenocarcinoma cells treated under a hyperglycemic milieu, a condition favoring the increased accumulation of AGEs, have revealed to promote tumor cell proliferation and migration^[43].

Emerging *in vitro* and *in vivo* analyses have revealed overexpression of several RAGE ligands such as HMGB1 and members of the S100P protein family in malignant gallbladder epithelial cells compared to benign tissue^[44,45].

This increased expression of those RAGE ligands in gallbladder cancer cells has been closely correlated with malignant progression and therefore may then be considered an independent risk factor for poor prognosis and proliferation in gallbladder cancer^[45-47].

A key consequence of RAGE binding with its ligands is the activation of multiple and crucial signaling pathways^[48], that are involved in gallbladder carcinogenesis, such as reactive oxygen species (ROS)^[49], Erk1/2 (p44/42) MAP kinases^[50], JNK and p38 MAP kinases^[51], and PI3K pathways^[52].

These signals trigger important downstream inflammatory and pro-carcinogenic consequences such as activation of STAT-3^[53,54], AP-1^[55], and Nf-κB pathways^[49,54,56-58], favoring the secretion of several pro-inflammatory cytokines also involved in the promotion of gallbladder cancer invasion and migration such as TNF-α^[59,60]. Hence, this pro-inflammatory milieu continuously fuels chronic inflammation in gallbladder carcinogenesis in a RAGE-dependent manner^[19,61].

THE THERAPEUTIC POTENTIAL OF THE RAGE/AGES AXIS IN TUMOR BIOLOGY

RAGE is recognized as a pattern recognition receptor, and its activation plays a pivotal role in the propagation of immune responses and inflammatory reactions^[62].

It is expressed at low levels in most differentiated adult cells in a regulated manner. However, the up-regulation of RAGE expression has been associated with many inflammation-related pathological entities, including cancer^[63].

Noteworthy, RAGE engagement subsequently converts transient cellular stimulation into a sustained cellular dysfunctional state driven by long-term activation of the nuclear factor-kappaB^[64]. Compelling pieces of evidence support that RAGE activation promotes many crucial steps during tumorigenesis, from DNA damage and genetic instability to supporting many phenotypic changes in tumor cells favoring their growth and dissemination^[65].

Since the work conducted by Taguchi *et al*^[66], which experimentally reported that the *in vivo* blockade of the RAGE-amphoterin axis suppresses tumor growth and dissemination, intense research efforts have been raised towards the development of new therapeutic approaches to modulate both deleterious pro-inflammatory and pro-carcinogenesis effects of RAGE axis activation^[67,68].

The use of novel RAGE-targeting antibodies and blocking peptides derived from RAGE ligands such as S100P and HMGB1 has demonstrated to block the ability of ligands to stimulate RAGE activation in cancer cells both *in vitro* and *in vivo* models, thus inhibiting tumor growth, metastasis, and inflammation^[69], as well as significant reductions in tumor growth with acceptable toxicity levels in several *in vivo* mouse adenocarcinoma models^[70,71].

Furthermore, the treatment of cancer cell lines with anti-RAGE antibodies demonstrates that RAGE blocking may even enhance the chemotherapeutic effects of antineoplastic drugs^[72,73].

Recent evidence has also revealed that the antibody targeting of RAGE ligands such as HMGB1 and AGEs may effectively decrease tumor progression in solid malignancies^[74]. Furthermore, this approach can even enhance the anti-tumoral response of cancer immunotherapies by remobilizing the antitumor immune response^[75].

Another emerging therapeutic approach is based on the high binding affinity to RAGE of some members of the family of glycosaminoglycans such as chondroitin sulfate, heparan sulfate (HS), and low molecular weight and semisynthetic glycosaminoglycan^[76]. These molecules have been reported to be involved in effectively inhibiting RAGE signaling pathways in both *in vitro* and *in vivo* models^[71,77].

Strikingly, new shreds of evidence have revealed that HS acts as a crucial element for RAGE signaling, leading to the formation of stable RAGE-HS complexes, which drive the RAGE oligomerization and subsequent downstream functional signaling^[78,79].

These interesting observations have revealed a new strategy for treating RAGE-associated diseases by hindering RAGE oligomerization.

The use of synthetic compounds with both anti-carcinogenic and anti-inflammatory activities based on their capacities to interfere with the HMGB1-RAGE axis seems to be a promising strategy for several cancer types, including gallbladder cancer^[80,81].

A novel molecule, recently discovered by Tanuma *et al*^[82], the 7-methoxy-3-hydroxy-styrylchromone (c6), is not only an effective suppressor of cell cycle/proliferation but

also an initiator of apoptosis in cancer cells, and a promising potentiator of the anti-cancer effects of DNA-damaging antineoplastic agents.

Moreover, the *RAGE* gene silencing has been demonstrated to significantly downregulate the AGEs-induced inflammation and RAGE-dependent release of pro-inflammatory cytokines in normal human cells^[83], while in malignant cells, *RAGE* gene silencing can decrease the colony-forming ability, proliferation, migration, and the invasive potential of cancer cells, throughout inhibiting RAGE-dependent mechanisms which sustain the cancer cell progression and invasion^[84].

The requirement of the cytoplasmic tail of RAGE to interact with its molecular effector DIAPH1 to mediate downstream signal transduction has been highlighted as a promising approach to inhibit RAGE signaling^[85-87].

This novel screening strategy of searching for molecules able to block protein-protein interactions has been demonstrated to be successful to inhibit the RAGE-mediated expression of inflammatory genes in diabetes complications^[88,89] and atherosclerosis^[90].

A growing body of experimental data using the DNA-aptamer technology against RAGE has demonstrated that this novel approach can inhibit the inflammatory reactions triggered by the activation of the RAGE axis in different *in vivo* models^[91-93].

Furthermore, experimental research has reported interesting results in different cancer types, as revealed in tumor-bearing mice treated with RAGE-aptamers, where marked inhibition of tumor growth was achieved^[94]. The use of this technology on tumor-bearing mice is also able to inhibit macrophage infiltration and neoangiogenesis through the inhibition of RAGE/NFκB/VEGF-A-dependent signaling pathways^[94-96] (See Figure 1).

In many clinical entities where the activation of the RAGE/ AGEs axis is crucial in the underlying pathogenic mechanisms, restriction of dietary AGEs has been extensively studied in clinical trials^[97-101] (See Table 1).

Recently and under the same rationale, and based on the active role of RAGE-mediated mechanisms on tumor biology, new interventional clinical trials on cancer patients are now in course, as documented on the website ClinicalTrials.gov

(ClinicalTrials.gov identifier: NCT03712371, NCT04716764, NCT02946996, NCT03092635, NCT01820299, NCT01363141, NCT03147339).

However, it must be emphasized that therapeutic interventions, including dietary interventional actions on the RAGE axis, have been focused on getting clinical improvements of disease course, including dietary interventional actions, and therefore the potential of modulating RAGE activation in terms of cancer prevention is still controversial.

REDUCING THE DIETARY AGES INTAKE IN SUBJECTS AT RISK OF GALLBLADDER CANCER. A HOPEFUL APPROACH?

International consensus estimates that almost 40% of cancer cases are preventable through a healthy lifestyle^[108]. Compelling pieces of evidence derived from epidemiological studies of different cancer types suggest that lifestyle changes, including dietary habits, may play a crucial role in determining the risk of various cancers^[109-113]

Currently, ²the Western diet (WD) is considered a major driver of chronic, low-grade, metabolic inflammation, which is a crosswise element in the pathogenesis of many human diseases, including cancers^[114]. Noteworthy, ²data derived from preclinical investigations, and observational and interventional studies, has conclusively provided evidence that the WD is associated with an increased incidence of many malignancies, such as colorectal, pancreatic, prostate, and breast cancers^[115-118].

In modern society, dAGE consumption – as a component of modern Westernized diets – is markedly increased. Therefore, dAGE restriction is now recognized as a useful intervention, as demonstrated in several pathologies^[119-123].

WD generally contains large amounts of fructose, thus promoting AGE formation^[124]. Furthermore, this diet is also an important source of AGE precursors, such as methylglyoxal, and glyoxal^[125].

In light of these findings, dAGEs have gained particular importance due to their capacity to support the onset of many human diseases, including cancer, mainly due to their pro-inflammatory and pro-oxidant properties^[17,18].

Furthermore, the role of the RAGE/AGEs axis activation has emerged as a crucial element in the tumor microenvironment to promote cancer cell migration, invasion, survival, and even resistance to chemotherapy^[19].

Additionally, the accumulation of AGEs in tissues can promote not only protein structural damage but also the modification of the mechanical and physiological functions of the extracellular matrix, thus contributing to carcinogenesis and inflammation^[20].

Therefore, the report recently published by Mayén *et al*^[32], showed a positive association between dietary AGEs and the risk of gallbladder cancer in the EPIC cohort, which deserves special attention. We believe that actions such as dietary recommendations for the reduction of dietary AGEs intake to individuals at risk of gallbladder cancer will be highly beneficial.

In this regard, it is important to highlight that some pre-existing clinical conditions such as Diabetes mellitus and metabolic syndrome are risk factors for the development of gallbladder cancer^[34,35-38]. Additionally, the demonstrated links between genetic ancestry and gallbladder cancer development may represent another risk factor for some populations^[126,127].

In addition, other recommendations focused on reducing the RAGE/AGEs axis activation are attractive, particularly the consumption of polyphenol-rich foods due to the inhibitory activities of polyphenols on the RAGE/AGEs axis at different levels, such as by ⁸inhibition of ROS formation during glycation reactions, chelation of transition metal ions, trapping dicarbonyls, and activation of AGEs detoxification pathways^[128].

CONCLUSION

Gallbladder cancer is an aggressive and rare neoplasm with an unusual geographic distribution. Most patients are diagnosed in the advanced stages of the disease, and

therefore the life expectancy is very low. Compelling evidence supports the role of several risk factors, which are linked to the onset, and chronicity of an inflammatory reaction. The report of Taguchi *et al*^[66], represented a critical point in understanding the role of the RAGE axis in tumor biology, and highlighting the potential of therapeutic interventions on a hyperactive cellular signaling pathway that causes disease, as the RAGE axis is^[129].

The role of RAGE axis activation in gallbladder cancer is supported by its active contribution to the pathogenic framework of the main risk factors associated with this neoplasm, such as infectious agents^[130,131], some metabolic conditions^[132,133], and dietary habits^[32].

Although much research is needed, lowering dietary AGEs intake as well as increasing the consumption of foods rich in polyphenols in subjects at risk of gallbladder cancer, either by preexisting metabolic conditions or genetic ancestry, seems to be a plausible recommendation, to avoid the hyperactivation of the RAGE/AGEs axis.

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