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The Biological Role of Advanced Glycation End Products in the Development and Progression of Colorectal Cancer

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Abstract

"Colorectal cancer" (CRC) is one of the most prevalent cancers, posing a scientific challenge and serving as a model for investigating the molecular pathways underlying its development. "Advanced glycation end products" (AGEs) have drawn interest in this context. The buildup of these diverse, chemically complex groups, which are formed by a "non-enzymatic interaction" between reducing sugar and a range of macromolecules, significantly increases "inflammation and oxidative stress" in the body, which has long been associated to cancer formation. The traditional pathways that promote AGE formation, as well as the significance of AGEs' interaction with the receptor for "advanced glycation end products" (RAGE) and other means involved in CRC initiation and progression, are discussed in this review.

Introduction

Globally, cancer is one of the earnest well-being issues that threaten human life expectancy and quality [1], [2], [3]. According to the GLOBOCAN 2020 statistics (19.3 million), new cancer cases were identified in 2020, with almost 10 million deaths [4], "Colorectal cancer (CRC)" is considered one of the utmost frequent cancers, every year, about 1–2 million new cases are discovered; it represents the third most frequently interpreted cancer and the second driving reason of malignant tumor affined death [5]. However, CRC is more common and is on the rise in developed countries, as reported in Japan, Australia, Europe, and North America [6], [7].

CRC has a multifaceted and complicated etiology. Hereditary factors, inflammatory bowel diseases, modification of the bowel microbiota, and aging have been postulated as possible underlying contributors to the emergence of this cancer. Furthermore, numerous environmental factors have been strongly linked to CRC etiology, including sedentary lifestyle, Western diet style, central, and obesity. Hyperglycemia, hyperinsulinemia, oxidative stress, and inflammation are some of the significant metabolic repercussions of these exposures, all of which have been hypothesized as key triggering pathways for CRC onset and progression [6], [8], [9], [10], [11], [12].

Several studies have been conducted to improve our understanding of the underlying colorectal carcinogenesis, all of which offer opportunities to identify selective biomarkers for the early diagnosis, personalization of treatment approaches, and the provision of prognostic markers [13]. Interestingly, it has been discovered that the accumulation of "advanced glycation end products" (AGEs) can promote, exacerbate different cancers, or both [14], [15]. Exogenous AGEs originating from various environmental factors as well as endogenously formed AGEs have been reported to further subsidize the pathogenesis of CRC through the induction of different intracellular changes and mutations resulting in malignant cell transformation [16], [17], [18], [19].

AGEs

AGEs are a uniquely complex group of compounds produced using a variety of precursors, through different mechanisms, with the ability of their production exogenously or endogenously [20], [21]. They are irreversibly formed products from the

covalent modification of macromolecules, including proteins. These modifications are brought about by oxidative/non-oxidative reactions "(such as glycation or carbonylation)" that use reducing sugars (such as glucose, fructose, and pentose) or their breakdown products [22].

These glycotoxins are produced endogenously by the slow non-enzymatic Maillard reaction between reducing sugars and proteins. The non-enzymatic glycation and oxidation of nucleotides or lipids also play a significant role in their formation [17]. Louis-Camille Maillard first characterized the Maillard reaction in the early 20th century. A nucleophilic addition reaction can occur betwixt the protein's free amino groups and the reductive sugars' carbonyl groups. Within hours, this reaction produces a reversible Schiff base, which reverts to ketoamine or Amadori products within a few days. Within weeks to months, the Amadori products experience rearrangements and dehydration. The resulting dicarbonyl compounds then get involved by subsequent reactions to create irreversible AGEs. Pentosidine, glucosepane, and the *in vivo* "archetypal AGE N-carboxymethyl-lysine (CML)" are the most well-known AGEs generated from this glycoxidation pathway [23], [24].

Noteworthy, glycolysis and lipid peroxidation are significantly faster endogenous mechanisms that can contribute to the generation of AGEs. Intracellular glycolysis, resulting in the conversion of glucose to reactive carbonyl compounds, the most well-known of which is methylglyoxal (MG), which consecutively can result in AGEs. Lipid peroxidation handles formation of reactive carbonyl species from lipid biomolecules serving as a marker for oxidative stress profile. AGEs, or in this context also known as advanced lipid end products (ALEs), such as malondialdehyde, are formed as a result of this formation [22], [25].

Oxidative stress and hyperglycemia, for example, can enhance the formation of these deleterious compounds. High levels of AGEs in the plasma have been linked to aging, diabetes, and different immunological diseases, including "systemic lupus erythematosus, rheumatoid arthritis, and psoriasis" [26], [27].

In addition to the endogenous formation, exogenous AGE absorption, such as through cigarette smoke inhalation or the consumption of high AGE food products, considerably contributes to the AGE pool inside the body. Approximately 10–30% of the dietary AGEs (dAGEs) are absorbed into the bloodstream through the gastrointestinal system [28], [29].

According to several studies, the highest amount of dAGEs was found in foods of the Western style, which are high in protein and fat, while the lowest amount of dAGEs was found in cereals. However, this could vary depending on the processing. The rate at which dAGEs form can be influenced by many factors, for instance, their formation is enhanced by "alkaline pH" and cooking at a "high temperature" for long periods. Low pH and meals prepared with water, on the other hand, hinder the development of dAGEs. Fried, roasted, or grilled food thus contain more dAGEs than those that are boiled or steamed [29], [30], [31].

Kidney's clearance and the liver's metabolism both can affect the accumulation of these heterogeneous molecules. Patients with renal or hepatic failure have elevated AGE levels. In the perspective of improved kidney and liver function, the accumulation of AGEs in the blood is potentially reversible [22], [32], [33], [34].

Endogenous AGEs and dAGEs synergistically can boost the systematic load of AGEs. At the very least, AGEs could affect the health by two means: Accumulation in tissues, resulting in the disruption of proteins structure (crosslinking intra- and extra-cellular matrix proteins) and thus modifying their functions, and interaction with the AGE receptor (RAGE), ensuing in the enhancement of inflammatory and oxidant status [35], [36].

The Biological Role of AGEs in CRC

CRCs are a diverse group of illnesses caused by a variety of mutagens and mutations. A worthier understanding of the pathogenesis and pattern of this cancer, including its molecular evolution, progression, genetic, and environmental risk factors, will potentially contribute to preventing and curing this lethal neoplasm [11].

AGEs have been linked to the development of many chronic ailments, including different cancers. By triggering numerous signal transduction pathways, AGEs and their receptors have been demonstrated to play critical roles in "cell invasion, proliferation, and epithelial-mesenchymal transition." [23], [37], [38], [39], [40].

RAGE is a "transmembrane receptor" that belongs to the multiligand "immunoglobulin superfamily." Except for the lung, where expression is often high, these cell surface protein receptors are expressed at low levels in other tissue types. RAGE overactivity and expression have been seen in numerous malignancies, including the prostate, breast, colon, brain, and ovaries. When AGEs bind to their receptors, an array of signaling cascades is triggered. An intracellular inflammatory condition will result starting with the "activation of NF-κB (nuclear factor-kappa B)," a transcription factor that promotes the release of growth factors, adhesive molecules, and pro-inflammatory cytokines. In addition, AGEs binding to RAGE will result in increased "generation of reactive oxygen and nitrogen species" by NADPH oxidase activation, which also can boost NF-κB stimulation [41], [42], [43], [44], [45], [46], [47].

Since it has been found that inflammation is associated with about a quarter of all cancers, chronic inflammation stimulates oncogenes activation and tumorigenic signaling pathways. In addition, the reactive species can break down proteins, lipids, nucleic acids, and altering their biological characteristics, thus initiating the tumor growth process [38], [48]. Therefore, it is not surprising that sustained AGE-mediated RAGE activation is involved in the pathogenesis of different cancers, including colorectal carcinoma [38].

Several studies have addressed RAGE as one of the key factors in CRC's progression and metastasis. According to Sasahira *et al*., RAGE expression can be substantially linked to atypia and the size of colorectal adenomas. Furthermore, high RAGE positivity was found in adenomas with severe atypia and large-sized adenomas. In other words, RAGE expression is strongly connected to the malignant potential of colorectal adenomas [49]. Bedoui *et al*. conducted case–control research in Tunisians to look at unique RAGE gene (AGE) variants and associated link with CRC. The presence of CRC has been linked to the RAGE rs77170610 and rs2853807 variants, implying that these RAGE polymorphisms interpose to the systemic pro-inflammatory state associated with CRC and other malignancies [50].

Sakellariou *et al*. studied the clinical importance of the AGE-RAGE axis in CRC by comparing the expression levels of the mentioned molecules in CRC to surrounding normal tissues. They found that CRC tissue had greater levels of AGE and RAGE expression than the surrounding normal tissue. In addition, this investigation highlighted the overexpression of GLO-I in the investigated tumoral tissue. In short, the endogenous glyoxalase scavenging system can reduce the cytotoxicity of AGEs. Glyoxalase (GLO)-I is a ubiquitously expressed system enzyme that protects "proteins, nucleotides, and phospholipids" against advanced glycation processes by lowering AGEs precursors' levels. This glyoxalase detoxifying system is especially beneficial to tumor cells with a high glycolytic rate, such as colon cancer cells [51].

These findings are similar to those of Kuniyasu *et al*. who examined the diversities in activity between amphoterin and AGE as RAGE ligands in four different CRC cell lines. Both amphoterin and AGE have been shown to activate ERK1/2, p38, and JNK. However, their ERK1/2 activation ability is inconsistent. While AGE was found to have a superior impact on amphoterin in terms of increasing the production of inducible nitric oxide synthase and nuclear factor-Bp65, amphoterin had a higher effect on ERK1/2 phosphorylation, Rac1, and AKT, as well as the MMP9 generation. These two compounds were found to promote cancer, and their distinct activities were considered to be caused by intracellular signaling pathway selectivity [52].

A study was carried out to investigate the method by which advanced AGEs stimulate "proliferation, invasion, and epithelial-mesenchymal transition (EMT)" of SW480 "human colon cancer cells" to improve current understanding of the concepts allegedly involved by AGEs in their intervention in the pathogenesis of CRC. AGEs elevated PI3K and AKT expression, which ensued in enhanced levels of "proliferation, invasion, and EMT," thus indicating the link betwixt AGEs and colon cancer [53]. In another study, five CRC cell lines and 45 cases of CRC tissue specimens were tested for RAGE mRNA and protein. In addition to the overexpressed, it has been found that RAGE was linked to a higher microvessel density in CRC tissue. RAGE knockdown reduced the invasion ability of SW480 cells but had no significant effect on cell viability. Furthermore, these receptors knockdown decreased specificity protein 1 (Sp1) and VEGF production in CRC cells. Collectively, these findings imply that inhibiting CRC angiogenesis *in vitro* and *in vivo* can be accomplished by silencing RAGE expression [54].

AGE accumulation is enhanced in hyperglycemic circumstances, such as diabetes. According to intensive investigations, diabetic patients have a significantly higher risk of CRC [55], [56]. In 2017, Deng *et al*. discovered that glucose-derived AGEs, a key subtype of AGEs, triggered metastasis and invasion in CRC patients. This study revealed that patients with CRC had a higher concentration of glucose-derived AGEs in both serum and tumor tissue. RAGE, matrixmetallopeptidase2 (MMP2), and Sp1 expression were significantly higher in malignant tissues compared to non-tumor tissue in examined individuals with CRC. In addition, RAGE expression was strongly related to lymph node metastases and the TNM stage, according to a clinical data analysis. The AGE administration elevated RAGE, Sp1, and MMP2 expression dose dependently. Likewise, the AGE-persuaded influences were demoted using a RAGE blocking antibody and Sp1-specific siRNA. Moreover, the AGEs treatment enhanced ERK phosphorylation, whereas the MEK1/2 inhibitor reduced ERK phosphorylation, resulting in lower Sp1 expression [57].

Another study found that AGEs increased the expression and activation of the carbohydrate responsive element-binding protein (ChREBP), a vital transcription factor that has been linked to increased glycolytic and anabolic activity as well as the proliferation of "colorectal and liver cancer cells." AGE-induced ChREBP expression and cell proliferation in cancer cells were suppressed using siRNAs or an antagonistic antibody for the RAGEs. AGE-induced cancer cell growth was severely hampered when ChREBP expression was suppressed. Overall, these findings show that AGE-RAGE signaling promotes cancer cell proliferation, with AGE-mediated ChREBP activation playing a crucial role [36].

On a genetic level, AGEs-RAGE signaling can induce the "nucleus translocation of transcription factor Kruppel-like factor 5 (KLF5)," which was able to join

to the regulatory series of the oncogene MDM2 and promote its expression in the human colon cancer cell line. Through this pathway, overexpressed MDM2 joins and encourages immediately the degradation of cancer suppressors Rb and p53. These findings were verified in a diabetic mouse model, which showed high blood AGEs concentration, and both KLF5 and MDM2 protein levels were enhanced [58].

Aside from the basic mechanism of AGEs having caused biological function through binding to RAGE, AGEs are formed when nucleotides in DNA are directly glycated. The nucleotide AGEs include imidazopyrazinone derivatives "dG-G (3-(2-deoxyribosyl)-6,7-dihydro-6,7-dihydroxyimidazo[2,3-b]purin-9(8) one," "gdC (5-glycolyldeoxycytidine), and CMdG (N2-carboxymethyldeoxyguanosine)" produced from glyoxal, while "dG-MG (6,7-d CEdG [N2-(1-carboxyethyl) deoxyguanosine]" is a derivative of MG, whereas "dG-3DG [N2-(1-oxo-2,4,5,6-tetrahydroxyhexyl)deoxyguanosine]" derived from 3-deoxyglucosone and other compounds. Glyoxal and MG can cause DNA unwinding, multibase deletions, DNA strand breakage, and base-pair substitutions, with transversions occurring more commonly at G: C sites. As a result, glycation-induced mutations in DNA may play a role in the development of colon cancer and also other malignancies including ovarian and breast cancers [59], [60], [61], [62].

Czech *et al*. inspected the genotoxic activities of new chemicals spawned in non-aqueous conditions known as MAGEs. Human melanoma as well as all other investigated cells, such as "colorectal cancer cells," "lung cancer cells," and bronchial epithelial cells, are found to be susceptible to the genotoxic effects of high-molecular-weight MAGEs. However, in this study, CRC cells revealed the most intensive genotoxic effect [63].

Redox imbalance and increased "oxidative damage" to "proteins, lipids, and DNA" are conjoined to CRC [64], [65]. The combination of AGEs and RAGE creates oxidative stress in the cell, which causes DNA damage on the one hand and activates signal molecules like NF-B on the other. In addition to its effect on the inflammatory state, "activation of NF-κB results" in its translocation to the nucleus activates several genes, including Ang II, the gene for angiotensinogen. Ang II's precursor, is one of these genes. NADPH oxidase is activated when Ang II is produced from the cell and interacts with its receptor AT1. NADPH oxidase then paves the way for the generation of reactive oxygen species, which enhance DNA damage even more [66]. The study of oxidative stress-induced DNA damage in Type 2 diabetic individuals was conducted in this context. The effectiveness of DNA repair plus the level of "DNA damage" induced by oxidative stress, mainly by H_2O_2, have been assessed. Although oxidative DNA damage materialized to be related to an increased risk of cancer in type 2 diabetes, poor DNA repair appears to play a crucial role in carcinogenesis [67]. These findings collectively could explain why diabetic patients have a higher risk of CRC development and poor prognosis.

It is noteworthy that because tumors have high levels of glucose metabolic rates, some molecules are formed as a byproduct of glycolysis, such as MG, a highly reactive carbonyl species involved in AGE production [68]. The buildup of MG adducts is a common characteristic of high-stage CRC tumors. MG production and detoxifying levels are a pivotal biochemical link between increased glycolytic activity and the advancement of CRC [69]. The various pathways by which AGEs can cause CRC development, progression or both, as explored in this article, are summarized in Figure 1.

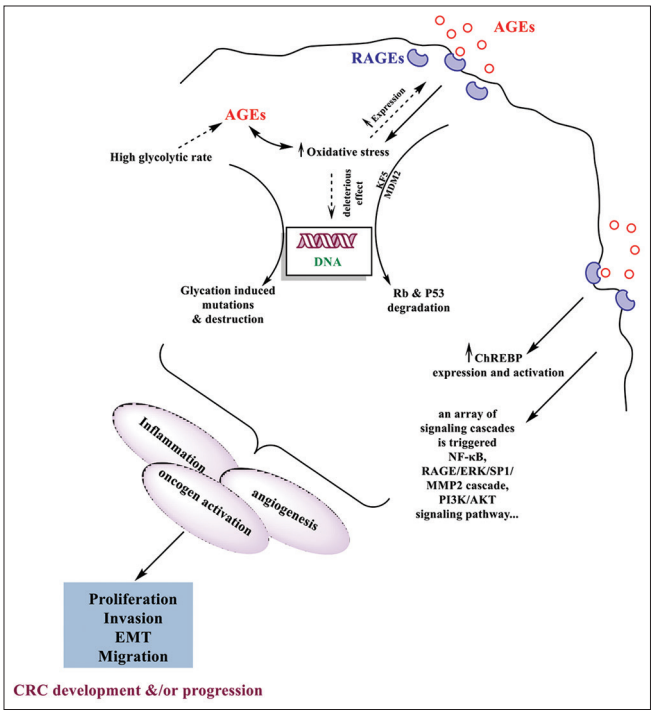

Figure 1: Illustration of the different pathways involves by advanced glycation end products in the colorectal cancer progression, induction, or both

Exogenous MG generated low-grade carbonyl stress can possess inflammatory and oxidant potential in the circulation and colon, all of which can worsen chemically produced colonic pre-neoplastic lesions. Carbonyl stress generated by MG can also stimulate tumor growth and increase the aggressiveness of tumor cells. Finally, carbonyl stress caused by MG generated either endogenously or from food may hasten the progression of colon cancer [70]. Contrarily, in a cohort study conducted by Aglago *et al*., an inverse association between dAGEs and CRC risk has been found. Using a European Prospective Investigation into Cancer and Nutrition cohort study, they explored the risk of CRC connected with dAGE intake. In 450,111 people, dietary intakes of three main dAGEs were estimated: "N-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MG-H1)," N"-carboxymethyllysine (CEL), and N"-carboxymethyllysine (CML), suggesting that more studies are needed to confirm these findings and

better distinguish the involvement of dAGEs in CRC development from that of endogenously generated AGEs and their precursors [71]. The interesting results of all of these studies prompted many researchers to consider this new vista and explore the main pillars of this pathway as prospective targets for various treatment strategies to prevent CRC formation and progression [72], [73]. Curiously, endogenous glycation can be avoided by keeping a healthy blood glucose level. As a result, it can be halted either by the natural defense system, which acts through enzymatic activities. "a-ketogluteraldehyde dehydrogenase, glyoxalase, and aldose reductase," for example, block glycation and AGE buildup, as do the natural inhibitors or the synthetically generated ones. Furthermore, it was shown that RAGE secreted isoforms called soluble RAGE (sRAGE) are released from cells and are capable of binding RAGE ligands and lowering the detrimental effects of RAGE signaling. AGE generation, on the other hand, is complicated and can occur through several steps and a variety of processes. Thus, it's challenging to be managed [14], [15], [74], [75].

Shortly, AGE inhibitors are medications that are either designed to prevent RAGE signaling or have the ability to intervene in the Maillard reaction and can exert their action at various stages of AGE generation or AGE-mediated injury. Natural compounds are more likely to be used as potent AGE inhibitors due to the adverse effects of synthetic ones which have been observed in clinical trials [23], [72], [73], [76].

This knowledge can be applied clinically by paying closer attention to blood glucose levels within normal ranges, especially in diabetic patients, to keep endogenous AGE formation to a minimum, as well as avoiding dietary sources of AGEs, which can play a role in the development and worsening of CRC, especially in high-risk individuals [15], [71]. On the other hand, ongoing attempts to employ AGES and sRAGE as promising biomarkers for the individual's risk of developing cancer linked with early recognition, assessment of the severity of illnesses, and the response to therapeutic intervention have the potential to be clinically beneficial [29], [14], [77]. In this regard, Zińczuk *et al*. conducted an AGE assessment in CRC patients' plasma. As a result, they found a statistically significant increase in AGE fluorescence in CRC patients' plasma compared to AGE fluorescence in the control group. This study emphasized the potential of using these compounds as non-invasive biomarkers for CRC diagnosis and monitoring [78].

Conclusion

The findings of various experimental studies reviewed in this study suggest that AGEs play a crucial role in aging, cancer, and chronic disease morbidity. Endogenous AGEs appear to be connected with the development and progression of CRC through distinct pathways, according to several studies that have been covered, particularly those that focus on diabetic patients. dAGEs are also likely to play a role.

Even though several promising pharmacologic anti-AGE drugs have been developed, their efficacy and safety are still being studied. The field of AGE research is still in its early stages, and it may be some time before the FDA approves a drug that targets AGE development or modification. Commitment to exercise and reduce Western style meals that contain large amounts of proteins and fats, and thus a large proportion of Maillard products, demonstrated a decrease of circulating AGEs along with the lowering of oxidative stress and inflammatory indicators. More study is needed to back up these findings and to use them in the combat against CRC formation and progression.

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