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Review

An insight on the association of glycation with hepatocellular carcinoma

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ABSTRACT

Hepato-cellular carcinoma (HCC) is one of the frequent cause of cancer-related death worldwide and dominant form of primary liver cancer. However, the reason behind a steady increase in the incidence of this form of cancer remains elusive. Glycation has been reported to play a significant role in the induction of several chronic diseases including cancer. Several risk factors that could induce HCC have been reported in the literature. Deciphering the complex patho-physiology associated with HCC is expected to provide new targets for the early detection, prevention, progression and recurrence. Even-though, some of the causative aspects of HCC is known, the advanced glycation end products (AGEs) related mechanism still needs further research. In the current manuscript, we have tried to uncover the possible role of glycation in the induction of HCC. In the light of the available scientific literature, we advocate in-depth comprehensive studies which will shed light towards mechanistic association of glycation with HCC.

1. Introduction

Hepato-cellular carcinoma (HCC) is one of the frequent cause of cancer-related death worldwide and dominant form of primary liver cancer [1]. It accounts sixth most common cancer type in men worldwide, with 1.2 million reported incident annually [2]. However, the reason behind a steady increase in the incidence of this form of cancer remains elusive. The occurrence of HCC in men has been noted twice compared with women [3].

HCC is an implacable malignancy and the existence of tumor is often detected at late stages [4]. It is a belligerent malignancy with a poor diagnosis and < 5% survival rates after 5-year [5]. In this form of cancer, the participation of hepatic parenchymal cells took place which impairs endogenous repair and degradation systems and ultimately results an alteration in different molecular pathways [6,7]. They represent clinically heterogeneous vascular tumors with different architectural patterns and cytological variants which is necessary during the tumorigenic process [5]. A combination of direct and indirect oncogenic effects such as chronic inflammation, oxidative liver damage, tumor microenvironment, cirrhosis, gut microbiota and exposure to dietary hepato-carcinogens are often spotted with this form of cancer [8,9].

Several mechanisms related with HCC patho-physiology have been proposed that involves dysregulated telomere function, damaged DNA checkpoints and the induction of inflammatory and oxidative stress pathways [10]. Additionally, growth factor signaling pathways of cell differentiation and angiogenesis along with some major signaling mediators, downstream of tyrosine kinase receptors (Ras/Raf/MEK/ERK and P13K/AKT/mTOR cascades) are also involved in the initiation and progression of HCC [11]. Among the possible causatives of HCC, hyperglycemia and associated disorders gained increased attention lately because of their involvement in liver function. Moreover, the glycemic imbalance has also been suggested as an independent risk factor for HCC [12].

Persistent hyperglycemic events lead to glycation reaction that involves non-enzymatic bonding of sugar molecules to different complex bio-molecules such as proteins, lipids and DNA [13–15]. Eventually, it leads to the generation of an irreversible glycation end product which causes cellular anomalies and results into more lethal clinical consequences. The glycation reaction could also activate several cellular signals through different receptors and their toxic by-products accelerate the pathogenesis of cancer, tumor proliferation and survival [16].

Deciphering the complex patho-physiology associated with HCC is expected to provide new targets for the early detection, prevention,

Abbreviations: AGEs, advanced glycation end products; CEL, Nε-(carboxyethyl) lysine; CMA, Nω-(carboxymethyl) arginine; CML, Nε-(carboxymethyl) lysine; H2O2, hydrogen peroxide; HCC, hepato-cellular carcinoma-; HMGB1, high mobility group box-1; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PTPs, protein tyrosine phosphatases; RAGE, receptor for advanced glycation endproducts; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; sRAGE, soluble RAGE; STAT3, signal transducer and activator of transcription 3; T1DM, type 1 diabetes mellitus; TAGE, toxic AGEs; TGF-β1, transforming growth factor β1; TKs, tyrosine kinases; VEGF, vascular endothelial growth factor

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progression and recurrence of this form of cancer. Even-though, several causative aspects of HCC is known, the AGE related mechanism is yet to be much explored. In the current manuscript, we have tried to uncover the possible association of glycation in the induction of HCC. For the easy understanding of this article, we have also introduced various indirect/direct factors that could lead to HCC.

2. Association of diabetes and glycemic imbalance with HCC

Diabetes and glucose metabolism share a common molecular constituents that could lead to the pathogenesis of HCC [17]. Scientific evidence suggests, diabetes as an independent risk factor of HCC with the approx 2–4-fold rise [18,19]. In addition, diabetes has also been noted to show the synergistic effect on most of the HCC contributors such as fatty liver, liver failure and cirrhosis [17]. More than 60% of diabetic or obese individuals (> 50 years of age) are believed to have HCC risk factors including nonalcoholic steatohepatitis (NASH) with advanced fibrosis [20]. Insulin also has pleiotropic effects on cellular proliferation and could lead to carcinogenesis [21]. Moreover, hyperinsulinemia has been noted to be associated with a 3-fold rise in HCC risk [17]. Obesity has also been suggested to increase the risk of HCC by 1.5–4-fold. It has also been independently associated with several HCC risk factors such as nonalcoholic fatty liver disease (NAFLD), steatosis of liver and cryptogenic cirrhosis [22,23].

It is well known that the cancerous cells undergo metabolic adaptations as per their pathological status. Glucose has been considered as the potential fuel that accelerate carcinogenic process in various types of cancer [24–26]. The glycemic status of the cancer cells could also influence intracellular oncogenic signalings such as the generation of reactive oxygen species (ROS), protein tyrosine phosphatases (PTPs) and tyrosine kinases (TKs) signaling viz. Erk, Jnk, and Lyn [27,28]. In the following sections, we have highlighted the possible role of glycation specifically advanced glycation end products (AGEs) in the induction of HCC through different mechanism.

3. Glycation overview

Prolonged hyperglycemia has been considered as the major culprit behind the pathophysiology of glycation dependent events [24,29]. Non-enzymatic glycosylation or glycation or Maillard reaction is the patho-physiological consequences of hyperglycemia and connecting link between the micro and macro vascular complications [14,30,31]. The spontaneous and naturally occurring glycation initiates with the covalent linkage of the carbonyl group of reducing sugar (glucose, galactose, fructose, mannose or ribose) to lysine residues of various biomolecules such as proteins, lipids and DNA to produce a Schiff-base intermediate [32–34]. This Schiff bases rearrange over a period of days to create a more stable ketoamine or Amadori products which further rearranges itself into a hemiketal structure [34–36]. These Amadori products undergo dehydration and further rearrangements, resulting into a variety of more stable diverse compounds known as AGEs [37,38]. The glycation reaction leads to the production of various highly active intermediate molecules viz. glyoxal, methylglyoxal and 3-deoxyglucosone that has also been considered as important contributors of HCC related pathology [39–41].

The formation of AGE took place under normal physiological conditions but the rate of production is accelerated in the case of hyperglycemic individuals [42]. Moreover, the production of AGEs from non-glucose sources have also been reported in the literature [42].

4. Association of AGEs with HCC

Advanced glycation end-products are a complex heterogeneous group of compounds and have been embroiled in several diseases related complications [14,43]. The presence of AGEs has been reported in a variety of cellular and tissue types viz. heart, lung and liver [44]. AGEs could lead to the modification of cellular function, inhibit protein degradation and result into formation of intracellular and extracellular cross-linked products [45]. The AGEs could also causes blockage of a proteasomal core and leads to an increase in oxidized and damaged proteins, which can promote further protein modification [16,46]. Together with the alterations of extracellular proteins, AGEs could also affect various intracellular signaling pathways involved in numerous cellular functions which ultimately lead to patho-physiological effects. The binding of AGEs with receptor for advanced glycation endproducts (RAGE) causes different signaling events such as activation of protein kinase C, accumulation and activation of NF-κB, generation of ROS and activation of inflammatory signaling cascades such as MAPK pathway, IL-6, TNF-α, expression of ICAM-1 and VCM-2 which together causes the pathogenesis of several diseases [47]. The interaction of AGEs with their specific RAGE has been suggested to plays a critical role in several chronic diseases. Tumor-promoting functions of the AGE-RAGE axis *in-vitro* or *in-vivo* has also been suggested in the scientific literature [48–50].

Over the past few years, the role of AGEs in tumor initiation and progression has been given a great deal of attention. Some studies also revealed the possible role of AGEs in cancer proliferation, migration, invasion, and survival in breast, prostate and lung cancer cell lines [51–53]. Although very little data is available related with human studies, the higher rate of AGEs accumulation has been reported in malignant tissues compared with benign ones [54]. Some epidemiologic studies also suggested an inverse relation of soluble RAGEs and the risk of pancreatic and colorectal cancer [55,56].

The high demand of energy utilization in tumors points its association towards glucose metabolism and liver function. The increase in the aerobic glycolysis leads to the accumulation of AGEs and its derivatives that evoke tumor-promoting inflammation which includes proliferation, invasion, metastasis, angiogenesis and apoptosis evasion [57]. This glycative stress could also contribute to the genomic instability and collagen cross-linking that could play an important role in cancer progression [58]. On the other hand, the intermediates of AGE metabolism could also accelerate the carbonylation of DNA and cause chemically induced gastric carcinoma [57].

Different types of AGEs such as fluorescent, cross-linking AGEs and nonfluorescent, noncrosslinking AGEs have been reported in the literature [59]. Glyoxal and/or methylglyoxal-lysine dimer and pentosidine are considered as fluorescent, cross-linking AGE. Moreover, Nε-(carboxymethyl) lysine (CML), Nε-(carboxyethyl) lysine (CEL), Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl) ornithine, Nω-(carboxymethyl) arginine (CMA), S-carboxymethyl cysteine argpyrimidine and pyrraline have been included in non-fluorescent, non cross-linking AGE category [43]. The role of different types of AGEs in the pathogenetic complications of HCC are summarized in Table 1.

Carboxymethyl-lysine (CML) is one of the most abundant AGEs in tissue proteins and can induce various vascular and inflammatory complications [60]. It is formed by the oxidative breakdown of Amadori products and during metal-catalyzed oxidation of polyunsaturated fatty acids. Several studies suggested the presence of CML in different human tumors of various origins [57,61]. Scientific studies also suggested their ability to bind with RAGE and macrophage scavenger receptor [62,63]. CML-modified proteins and their binding to corresponding receptors have been suggested to be involved in various tumor promoting mechanisms [60,64].

Accumulation of CML has been reported in various HCC risk factors such as diabetes, obesity, fatty acids, steatosis and steatohepatitis [65–67]. In diabetic individuals, the formation of AGE is accelerated due to the rise in the level of circulating glucose, AGE precursors and oxidative stress [65]. In serum and tissues of type 1 diabetes mellitus (T1DM) and T2DM patients, increased levels of AGEs viz. CML methylglyoxal-derived hydroimidazolone, pentosidine or glucosepane have been reported [65,68,69]. Gaen et al. [66] reported the accumulation of CML in the liver of obese individuals and suggested its