Editorial

Glycation and hepatocellular carcinoma: where we stand

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Hepatocellular carcinoma (HCC) is currently the most common liver cancer and the third cause of cancer-related mortality worldwide, thus becoming a serious public health concern of international interest (1). HCC, such as other type of cancers, is a heterogeneous disease that results by a combination of several risk factors and co-factors including genetic, environmental and lifestyle factors.

In addition to the well-known impact of hepatitis B virus and hepatitis C virus infections and persistent alcohol consumption, over the past years clinical evidences have demonstrated that also metabolic syndrome-related disorders have been emerged as significant etiological factors predisposing to the development of cirrhosis and primary liver cancer (2).

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), in fact, have been identified as an additional cause of cirrhotic and non-cirrhotic HCC (3). Moreover, several lines of evidence have highlighted the role of diabetes mellitus in increasing the risk of developing HCC in HCV-infected patients (4).

Interestingly, the high fasting glucose levels, a clinical complication that mainly characterizes diabetes mellitus, as well as obesity and other metabolic disorders has been recently suggested to have a possible causative role in the pathophysiology of HCC development. Several direct or indirect pro-oncogenic effects of high level of glucose have been described in different type of liver cancer cells (5,6). These studies, in particular, have demonstrated that high glucose may control signalling pathways involved in cell proliferation, apoptosis and invasion. The potential role of intermediate metabolites, resulting from altered metabolism of sugars, lipid or protein, in cancer cell homeostasis is not surprising considering the new concept of oncometabolism that defines all active products and enzymes that are able to sustain the high proliferation rate of tumour cells (7).

A recent publication by Jabir and colleagues presents an interesting review concerning the role of glycation reaction occurring during the persistent hyperglycaemia condition in HCC development (8). Glycation is a non-enzymatic process (non-enzymatic glycosylation) in which free amino groups of proteins promptly react with the free carbonyl groups of reducing sugar or with the reactive carbonyl species and results in the formation of Schiff's base producing advanced glycation end-products (AGEs) (9). Jabir *et al.* (8) provide an overview of some evidence about the role of AGE accumulation as a potential molecular mechanism linking persistent hyperglycaemia with induction of HCC. AGEs may have a different origin. They are a class of heterogeneous endogenous compounds generated during prolonged hyperglycaemia state by the non-enzymatic glycosylation process or they may be a sort of glycotoxins of exogenous origin, mainly produced in food during heating (10).

Consequently, special attention must be paid to exogenous AGEs and their cross-talk with the gut microbiota composition. It is estimated that approximately 10–30% of these dietary AGEs are absorbed in the small intestine, while the most part of these glycotoxins may be used as a substrate for encouraging the preferential growth of detrimental colonic bacteria leading to dysbiosis (11,12). Indeed, therapeutic manipulation of the gut microbiota and restoration of eubiosis might contribute to reduce the levels of circulating AGEs improving the metabolic health status of individuals.

It is known that AGEs may exert their harmful effects through two main mechanisms: direct cross-link with proteins causing changing in their structure and function,

and alteration of intracellular signalling by a receptor- and non-receptor-mediated mechanisms, leading to regulation of gene expression and the release of reactive oxygen species (ROS) and pro-inflammatory molecules (13). Therefore, these multiple actions of AGEs at the cellular level might explain their pathogenetic role in diabetes-related complications and several chronic diseases (14).

Endogenous and food-derived AGEs exert their damaging and pro-inflammatory effects mainly by the binding to the 'Receptors of AGE' (RAGE). RAGEs belong to an immunoglobulin superfamily of cell-surface molecules. These are pattern recognition receptors which preferentially interact with different type of ligands such as AGEs, pro-inflammatory S100/calgranulin family members, and high motility group box 1 protein (HMGB1), amyloid-β protein and phosphatidylserine. RAGEs are expressed by a variety of cell types, including endothelial cells, neurons, smooth muscle cells, lymphocytes, dendritic cells, and macrophages (15).

The main effect of RAGE-AGE is the increase of oxidative stress generation and activation of several signalling pathways including nuclear factor (NF)-κB, mitogen-activated protein kinase (MAPK), Janus kinase-signal transducers and activators of transcription (JAK-STAT), thus evoking in a context of tissue damage and inflammatory, proliferative and angiogenic processes in numerous cell types. Moreover, some evidences suggest that RAGE expression is upregulated in cells and tissue affected by chronic disease (16). For that reason, the inhibition of RAGEs is regarded as a therapeutic option to prevent diabetes complications (17).

Interestingly, Jabir *et al.* (8) provided a detailed description of mechanisms by which each different type of AGEs may contribute to modification of cellular homeostasis promoting a pro-oncogenic phenotype in liver cells. Of note, carboxymethyl-lysine, one of the best-characterized AGE, accumulated in the serum and in tissue of patients affected by different metabolic disorders, such as diabetes mellitus, NAFLD and NASH, which predispose to HCC development by a pro-inflammatory role. Additional non cross-linking AGEs, including nω-(carboxymethyl) arginine, argpyrimidine and hydroimidazolone MG-H1, and some others AGE-intermediates may play multiple roles in HCC induction by altering the function of proteins involved in the control of oxidative stress and DNA-damage response, cell migration and invasion, angiogenesis and fibrosis.

The authors also focused on the pathophysiological production/accumulation of glycer-AGEs a class of glyceraldehyde-derived AGEs, also called toxic AGEs, which are implicated in enhancing diabetes mellitus complications and liver malignant phenotype in cancer liver cells, including tumor cell migration and invasiveness, by increasing the intracellular expression of cyclooxygenase-2 protein and vascular endothelial growth factor.

Finally, the review analyzes the active involvement of AGE-RAGE axis and the association of the RAGEs expression in HCC. According to the literature, RAGEs are expressed in human HCC cell lines, and it has also been shown that RAGEs exert a detrimental effect on insulin signaling in these type of cells. Otherwise in hepatic stellate cells they promote the expression of several pro-fibrogenic mediators such as transforming growth factor β1 (TGFβ1), collagen type I alpha-2 and α-smooth muscle actin, then sustaining the development of various hepatic disorders, which in turn may precede the onset and progression of HCC. Accordingly, the expression of RAGEs was found upregulated in poorly differentiated HCC (8,18). Interestingly, the final consideration of the authors emphasizes the detrimental role of AGE-RAGE-induced ROS and reactive nitrogen species overproduction as key event underlining the implication of oxidative stress as critical mediator of AGE-RAGE/HCC axis.

In summary the review by Jabir *et al.* (8) highlight that the glycation reaction and their products, mainly AGEs, may play a crucial role in HCC pathogenesis. The production of most of the glycation intermediates, in fact, could be enhanced during the setting of hyperglycemic phenotype. It is reasonable that in a context of HCC cell proliferation an increase of the aerobic glycolysis may lead to AGEs/RAGEs axis activation promoting other oncogenic properties including invasion, metastasis, angiogenesis and apoptosis evasion. However, as suggested by Jabir *et al.* (8), the molecular networks that link glycation to HCC pathogenesis has not been reported or found to date. Experimental *in vitro* and *in vivo* studies by using intervention strategies to reduce AGE formation and AGE signalling at various levels, accompanied by a comprehensive characterization of glycated proteome (19) could be extremely important to identify targets of glycation leading to the discovery of novel intervention strategies against HCC.

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