Mini-Review

Glycation: a new hope in targeting hepatocellular carcinoma?

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Abstract: Hepatocellular carcinoma (HCC) is the second most common cause of cancer mortality worldwide and is the most rapidly growing indication for liver transplantation globally. There is, therefore, an urgent need to explore novel areas which may be contributing to pathogenesis such as advanced glycation pathways, to better understand HCC progression. Advanced glycation end-products (AGEs) are a group of biologically active compounds that are formed when sugar moieties react non-enzymatically with amino groups. They are abundant in Western diets and found endogenously at an increased rate in diabetes. This article will summarise the association between AGEs in liver disease and HCC progression. In elucidating mechanisms in HCC pathogenesis, the underlying aetiologies are important with viral hepatitis, alcoholic and non-alcoholic liver disease being the most common causes. Future directions lie in elucidating mechanism with disease specific *in vivo* animal models and complementary *in vitro* studies. A consideration of multiple AGE receptors as well as AGE effects on gut microbiota inflammatory pathways is also important. Ultimately, translational research in glycation pathways involved in HCC may offer novel biomarkers to detect early HCC or monitor disease progression. It may also provide important dietary insights into prevention and generate targets for novel pharmacotherapy.

Keywords: Hepatocellular carcinoma (HCC); advanced glycation end-products (AGEs); receptor for AGEs (RAGE); non-alcoholic fatty liver disease (NAFLD); metabolic syndrome

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The increasing impact of hepatocellular carcinoma (HCC)

A review published by Jabir (1) *et al.* in *Seminars in Cancer Biology* highlights the need to explore novel areas, in particular glycation pathways, to combat the burgeoning problem of HCC (2) This need is urgent, since HCC is the most rapidly growing indication for liver transplantation not only within the United States (3) but also globally (4). Indeed, liver cancer is the second most common cause of cancer mortality worldwide and HCC accounts for around 90% of liver cancer cases (5). Current management evolves around surgery, percutaneous local therapies and liver transplantation. Molecular therapy includes anti-angiogenic drugs such as bevacizumab [anti-vascular endothelial growth factor (anti-VEGF) antibody] and sorafenib (which blocks VEGF tyrosine kinase receptor). Erlotinib is another molecular therapy targeting epidermal growth factor receptor (EGFR) tyrosine kinase to control angiogenesis. Local regional therapies in current use include radiofrequency ablation (RFA), percutaneous ethanol ablation (PEI), transarterial chemoembolization (TACE) and radioembolization (2). These therapies improve short-term survival of HCC but recurrent disease remains a

fundamental problem (2).

Advanced glycation end-products (AGEs)

AGEs are a complex and diverse group of biologically active compounds that are formed via a process known as the Maillard reaction in which reducing sugar moieties, such as glucose, react non-enzymatically with amino groups in proteins, and nucleic acids (6). Although AGEs are a heterogeneous group of compounds, they have a common structure which can be identified immunologically. The predominant AGE detectable *in vivo* is Nε-carboxy(methyl) lysine (CML) (7).

The endogenous production of AGEs is a normal phenomenon in aging (8) and occurs at an increased rate in diabetes (9). The rate is also influenced by the concentration of reducing sugars in serum, the turnover of the proteins and the extent of the oxidative stress in the environment (9). Exogenous sources of AGEs are abundant in Western diets, especially foods containing meat and animal products, and their intake is correlated with tissue levels of AGEs (10). Tobacco is also a major environmental source of AGEs (11).

Advanced glycation and disease

There is now very strong evidence that accumulation of AGEs results in changes in extracellular matrix structure and function and there are numerous studies to implicate these compounds in the pathogenesis of diabetic renal, neurological, retinal and vascular complications (12). In fact, AGE levels may be a better predictor for the development of diabetic complications than HbA1c concentrations (13). In support of the primary pathogenic role of AGEs, in nondiabetic rats exogenously administered AGEs have been shown to induce glomerular sclerosis and albuminuria (14) and treatment of diabetic rats with aminoguanidine (an inhibitor of AGE formation) prevents the development of nephropathy (15). These effects are not confined to endogenously produced AGEs, since animal studies have shown that a high-AGE diet is associated with the development of chronic tissue damage, including nephropathy and atherosclerosis (16).

Although most research in AGEs has focused on their role in diabetes complications, accumulation of AGEs has also been implicated in the pathogenesis of a number of other conditions, including atherosclerosis, Alzheimer's disease, arthritis, and amyloidosis (17). Specifically, advanced glycation has been implicated in cardiovascular stiffness, impaired endothelial cell repair, endothelial dysfunction, glomerular hyperfiltration and sclerosis, tubulointerstitial injury, insulin resistance and obesity (10).

Advanced glycation and liver disease

A number of studies have shown that the receptor for AGEs (RAGE) plays a role in acute liver injury and that blockade of RAGE can ameliorate toxic, ischaemic and cholestatic liver damage (18-20). In chronic liver injury, hepatic expression of RAGE is significantly increased (21) and in non-alcoholic fatty liver disease (NAFLD), AGE levels correlate with the severity of fibrosis, leading to speculation that they play a primary role in disease pathogenesis (22). Furthermore, diabetes, which increases AGE formation and RAGE expression, worsens the progression of fibrosis in a number of human liver diseases, including NAFLD and hepatitis C (23).

Independent of cirrhosis, type 2 diabetes has also been shown to be an independent risk factor for HCC (24). Recent studies have shown that serums levels of AGEs are elevated in patient with HCC not due to hepatitis B or C (25). In NAFLD specifically, insulin resistance likely plays a role in disease progression (26) and our group has found that a diet low in AGEs increased insulin sensitivity in just 2 weeks in a double-blind, randomised, crossover trial (27).

The underlying aetiology of liver disease is important when elucidating mechanisms in HCC pathogenesis

There can be major differences in the mechanisms driving HCC development and progression in different diseases. Jabir *et al.* (1) rightly point out that different aetiologies underlying HCC will affect the degree to which glycation may affect pathogenesis. Similarly, as discussed below, the activation of specific arms of glycation chemistry and subsequent receptor interactions for each liver disease is likely to be variable (28). The leading indications for adult liver transplantation and causes of HCC in Australia and New Zealand are viral hepatitis, alcoholic liver disease and NAFLD, and much of this disease is preventable (29).

Hepatitis B

Of the viral causes, hepatitis B, a small enveloped DNA virus that causes chronic hepatitis in 350 million people

worldwide, is felt to be one of the most oncogenic viruses driving HCC morbidity and mortality through direct and indirect mechanisms (30). HBV DNA integration into the host genome induces both genomic instability and direct insertional mutagenesis of diverse cancer-related genes, especially gene S and X (30,31). Given the availability of highly efficacious and well-tolerated oral treatments for hepatitis B, a major component of managing the problem of HCC in hepatitis B is via increased awareness through programs like the Jade Ribbon Campaign and improving access to early screening and management (32).

Hepatitis C

Hepatitis C, a RNA virus, is also a major driver of HCC progression via progression to cirrhosis. Directly, the core protein of hepatitis C induces overproduction of oxidative stress by impairing the mitochondrial electron transfer system, through modulating the function of the molecular chaperon, prohibitin (33). Indirectly, it also disrupts DNA damage-induced p53 responses by activating protein kinase R (34). Interestingly, especially in genotype 3 hepatitis C patients, the core protein of hepatitis C interacts with cellular proteins to change lipid synthesis, proliferation and apoptosis (35). With the remarkable advent of highly effective, curative, direct-acting antivirals, there is a real hope that hepatitis C can be eliminated by 2030 if there is a co-ordinated community approach to screening and accessing hepatitis C treatment worldwide (36).

Alcoholic liver disease

Excess alcohol consumption is a primary cause of liver-related mortality and HCC in many countries (37). Important public health and cultural measures are required to manage this increasing problem as recovery is highly dependent on remaining abstinent (37). For those already with the disease and who continue to drink alcohol, targeted therapies are being explored in animal models. However, current therapies are of limited efficacy. Hence, prevention and abstinence remain the most important components of management (37).

NAFLD

Currently and into the foreseeable future, an increasingly important driver of HCC carcinogenesis is NAFLD. NAFLD is the most common liver disease in the world, largely due to rapidly rising rates of diabetes and obesity. Although most patients with NAFLD are asymptomatic and do not develop significant liver injury, a significant proportion progress to non-alcoholic steatohepatitis (NASH), cirrhosis and liver cancer (38). The prevalence of fatty liver and NASH has increased to 46% and 12% respectively in some studies (38) and amongst diabetics, biopsy proven NAFLD occurs in 74% and NASH in 22% (38). The main risk factors for developing NAFLD are central obesity, type 2 diabetes, dyslipidaemia and insulin resistance (39).

NAFLD is associated with an increased annual incidence of HCC of 76-201 per 100,000 (40) compared to a background incidence of sporadic HCC of 4.9-16 per 100,000 (41). Indeed, our group and others have found that that HCC can develop in NAFLD without cirrhosis. At diagnosis, such tumours were larger than those in cirrhotics, conferring a poorer prognosis (42).

Glycation should be explored as a driver of HCC development in particular in this population. Indeed, NAFLD is often thought of as the hepatic manifestation of the metabolic syndrome (43). However, this association is so strong that NAFLD can be regarded as a pathogenic component of this syndrome with the relationship between the two complex and bidirectional (43). The liver is the site of synthesis of glucose and triglycerides, two key components of the metabolic/insulin resistance syndrome (44). It appears that amelioration of insulin resistance is not necessary for the treatment of NASH, but is important for the prevention of cardiovascular disease and type 2 diabetes (44).

There has been considerable interest in factors which act as a "second hit" driving progression from simple steatosis to NASH and progressive liver fibrosis (45). Our group and others have discovered that the AGE-RAGE axis is implicated in NAFLD progression in murine models of NAFLD (46-48). Others have found a similar role in NAFLD related HCC (49).

The importance of appropriate animal models to study glycation effects on HCC progression

The importance of studying glycation and its effects on HCC progression is highlighted by the strong clinical associations between diabetes and impaired glycaemic control with HCC, as well as increasing

associations found with AGEs, oxidative stress, RAGE and HCC.

Crucial to the success of this initiative is the need to utilise appropriate models of HCC that ideally reflect the physiological disease course in humans (50). Given the underlying aetiology is important in HCC progression, the appropriate use of spontaneous, xenograft and syngeneic models needs to be considered (50). As there is likely to be a central role of glycation in the metabolic syndrome, it will be important to include work which includes dietary models of obesity and insulin resistance (51).

Considering cellular aspects and mechanism

Jabir *et al.* (1) conclude that to establish a direct linkage between glycation and HCC, there needs to be further exploration of inflammatory signalling cascades, such as mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation. We would also argue that one should look at the various AGE receptors as potential novel targets. There are multiple AGE receptors, including macrophage scavenger receptor type I and II, oligosaccharyl transferase-48 (AGE-R1), 80k-H phosphoprotein (AGE-R2), galectin-3 (AGE-R3) and the RAGE (52). Indeed, AGE-R3 expression has been associated with a poor prognosis in HCC (53). Of the receptors, RAGE is best characterized (54). It is expressed in a number of cell types, including endothelial cells, vascular smooth muscle cells, peripheral blood mononuclear cells, macrophages (including Kupffer cells), and hepatic stellate cells (55). Hence *in vitro* study in these cell types with a view to elucidating mechanism will be important (56).

Not forgetting the microbiota

A rapidly emerging field of pathogenesis that should not be ignored when elucidating the effects of glycation pathways in the progression of HCC is the role of gut microbiota (57,58). There has been considerable interest in this for multiple aetiologies of HCC (57,59,60). Studying this component is important but logistically complex and difficult (57,61). A number of studies have looked at practical implications such as improving intestinal barrier function and decreasing bacterial translocation as adjunctive therapy in HCC (62). The potential importance of AGEs in this area is that they can induce changes in the gut microbiota that may drive liver inflammation (63).

Conclusions

There is an urgent need to stem the burgeoning rise of HCC. Reducing the burden of disease due to viral hepatitis requires increased awareness, screening and management with highly effective therapies. Alcoholic liver disease also requires innovative social strategies. Perhaps NAFLD is the area where novel therapies targeting glycation are likely to have the greatest impact (64). Consideration of glycation pathways may help in a number of ways. They may offer novel biomarkers to detect disease progression and/or early HCC, allowing more curative options to be implemented (65). In particular, studies looking at plasma levels of soluble RAGE and *RAGE* gene polymorphisms may be promising in this regard (66). By studying mechanisms, such as the AGE-RAGE axis, novel targets can be considered for effective pharmacotherapy. Already, treatments targeting the AGE-RAGE axis, including cross-link breakers, direct RAGE inhibitors and dicarbonyl compound scavengers (e.g., aminoguanidine) are in clinical trials for other indications (67). Teasing out what will likely be complex mechanisms by which glycation pathways contribute to HCC progression may therefore have considerable translational impact for these and other novel therapies

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Footnote

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