Review Article

The molecular mechanism on the association of diabetes mellitus with hepatocellular carcinoma

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ABSTRACT

Many studies have shown a complex link between diabetes mellitus and hepatocellular carcinoma. Diabetes mellitus is an independent risk factor for the development of hepatocellular carcinoma (HCC), and increase both the morbidity and mortality of HCC in many ways, including insulin resistance, hyperglycemia, hyperinsulinemia, inflammation and metabolic dysfunction. Insulin-like growth factor (IGF) axis, WNT/β-catenin pathway and glycogen synthase kinase 3 (GSK3) were dysregulated in liver metabolism of diabetics and cause damage to hepatocytes, which would increase risk for HCC. The toll-like receptor 4 (TLR4) could affect the two diseases through the NFκB pathway, when the liver is under metabolic dysfunction. Moreover, single nucleotide variation (SNV) (T445A) in NCOA5 is a confirmed pathogenic in these HCC patients with diabetes mellitus.

Keywords: Diabetes mellitus, Hepatocellular carcinoma, Insulin-like growth factor, Toll-like receptor 4, NCOA5

INTRODUCTION

Primary liver cancer is the fourth most common cancer as well as the second leading cause of cancer-related death in China, which is a serious problem to the people’s health. Hepatocellular carcinoma (HCC) accounts for the 85-90% of the primary liver cancers, and the morbidity of HCC was 35/100,000 in China, higher than the world average level.¹,²

Hepatitis due to the hepatitis B virus, hepatitis C virus infection is still the main cause of HCC. However, the patients of HCC without the two viral hepatitis increased rapidly.³ Diabetes mellitus (DM) is positively allied with risk of numerous common human malignancies.⁴ Studies have found DM is associated with 2-3 fold increased risk of HCC.⁵ On the other hand, diabetics with dietary diabetes could not only be good to DM, but also decrease the risk of HCC. Nevertheless, the exact pathophysiological mechanisms of this significant association are still unclear.

According to the mainstream views, possible intermediary mechanisms are insulin resistant, glycometabolism and lipometabolism disorder (including excess reactive oxygen species and advanced glycosylation end production), aberrant expression of inflammatory mediator (including interleukin-6 i.e. IL-6 and tumour necrosis factor-α i.e. TNF-α).⁶,⁷ Inflammation molecule and estrogen was the common pathogenic factor of DM and HCC.⁸-¹⁰

In this review, we attempt to elucidate the effect of diabetes on HCC at the molecular level by summarizing recent reports on diabetes and HCC.
EFFECTS OF GLYCOLIPID METABOLISM-RELATED MOLECULES ON THE ASSOCIATION OF DIABETES MELLITUS AND HEPATOCELLULAR CARCINOMA

Type 2 diabetes mellitus (T2DM), characterized by insulin resistance and hyperinsulinemia, is the most common forms of diabetes. Hyperinsulinemia plays a key role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD), which is significantly associated with HCC. Hyperinsulinemia can upregulate some proteins related to the insulin-like growth factor (IGF) axis, including IGF-I, IGF-II and their receptors. IGF-I and IGF-II both can directly bond to and activate IGF-I receptor (IGF-IR), and then activate P13-AKT and MAPK pathway, which can lead to the improvement of cell proliferation and anti-apoptosis. The activated ICF-IR also indirectly cause the phosphorylation of the insulin receptor substrates such as insulin receptor substrate IRS1 and IRS2, the key molecular for insulin signaling and associated with the tumor size. IGF-II was found overexpression by 20-fold in some HCC tissues compared with non-tumor tissues and increased tumor cell aggressive and promote formation of liver tumor in mice experiment model. So, the IGF axis may deregulate in diabetes mellitus and contributed to the development of HCC, but there is need more studies to investigate whether inhibiting this axis in patients of diabetes mellitus could deceased the risk for HCC.

The WNT signaling is another pathway that participates in both diabetes and HCC. Studies have found that WNT can regulate metabolic homeostasis and the dysfunction of WNT related molecular, such as β-catenin, glycogen synthase kinase 3 (GSK3) can influence both diabetes and HCC.

In canonical WNT pathway, β-catenin is a core protein which was originally identified as a kind of adhesion protein binding to the cytoplasmic domain of E-cadherin and a-catenin to maintain cell connection. β-catenin also was a multifunctional protein and had important influence to normal physiological function. Moreover, β-catenin was involved in the regulation of the proliferation of β cells and metabolism and energy homeostasis, and deregulation of WNT/β-catenin was associated with DM. Different from normal tissue cells, large amount of glucose entered the glycolytic pathway in tumor tissue cells even in sufficient oxygen microenvironment, in order to support sufficient energy and substrate material for the rapid proliferation of tumor cells. Multiple studies have found that the mutual of β-catenin or the activation of β-catenin could contribute to HCC. Hung et al found that high-glucose-containing culture medium significantly enhanced the expression of β-catenin which could further increase the glucose influx in HCC cells and promote aerobic glycolysis in those cells. They also found canagliflozin, sodium/glucose cotransporter 2 (SGLT2), downregulate β-catenin and may provide new strategies on treating HCC patient with concurrent diabetes.

GSK-3β, an isoform of GSK-3, is an important mediator in insulin-dependent glycogen metabolism, and also found to be involved in cell differentiation, proliferation and survival in several cancers. In physiological conditions, GSK-3β could mediate the ubiquitination and degradation of β-catenin by phosphorylation. However, the Phosphorylation of N-terminal domain serine residue (p-Ser9-GSK-3β) can lead to the stabilization of β-catenin. Qiao et al found that p-Ser9-GSK-3β was significantly upregulated in HCC patients. They also found that the expression level of p-Ser9-GSK-3β was significantly related with T2DM, which indicate GSK-3β might play a significant role in mediating the impact of T2DM on HCC prognosis. Taking together, the IGF axis and WNT pathway maybe the key point to the association of the two increased prevalence diseases.

INFLAMMATION IN THE ASSOCIATION OF DM AND HEPATOCELLULAR CARCINOMA

Inflammation may an overlapping mechanism for HCC and DM. DM promotes hepatocarcinogenesis through activation of inflammatory cascades with production of proinflammatory cytokines and reactive oxygen species, which cause genomic instability, promote cellular proliferation, and inhibit apoptosis of hepatocytes. The non-alcoholic steatohepatitis (NASH) is pivotal to link diabetes with HCC. 10% to 20% of NASH patients would develop into end-stage liver disease within 5-10 years. Once NASH progresses to cirrhosis, the probability of HCC occurring within 5 years is 11.3% in Japan and 12.8 in the United States. The occurrence in NASH patients with diabetes mellitus was significantly increased. Inflammatory cytokines and activated immune cells, such as IL-6, TNF-α, Kupffer cells and hepatic stellate cells were involved this progress. Therefore, the study of inflammatory mechanism may help clarify the interaction between the two diseases. Recently, some studies have found toll-like receptor 4 (TLR4) have influence simultaneously on HCC and diabetes mellitus.

Insulin resistance in liver can leads to gluconeogenesis and the release of fatty acids. Many kinds of fatty acids can activate chronic inflammatory via the TLR4 pathway, such as lauric, palmitic, and stearic acids, and lauric acid have the greatest activation capacity through TLR4, which then activate the NF-kB pathway to release inflammatory cytokine, such as IL-1,IL-6 and TNF-α. Moreover, palmitic, a kind of saturated fatty acids, could upregulate TLR-4 at both mRNA and protein level in hepatocytes and contribute to inflammatory response and cell death by activating NF-kB, which could be abolished by pharmaceutical inhibition of TLR4. This study showed that TLR4 is key molecule for palmitic to cause inflammation.

It is well known that chronic inflammation, caused by metabolic syndrome such as obesity, diabetes mellitus and NASH, was association with the initiation of HCC.
THE EFFECT OF ESTROGEN METABOLISM-RELATED GENES ON DIABETES AND LIVER CANCER

Estrogen and estrogen receptor α (ERα) had been shown to involved in regulating the expression of inflammatory cytokine expression, glucose and lipid homeostasis and pancreatic β cell, which was another molecule mechanism to regulate both HCC and diabetes.31

The nuclear receptor coactivator 5 (NCOA5), also called coactivator independent of AF2 (CIA), is a unique coactivator that contains both coactivator and corepressor domains and is known to modulate ERα-mediated transcription. When under the stimulation of estrogen, NCOA5 and ERα were upregulated and recruited to the IL-6 promoter and further suppressed the expression of IL-6.34 IL-6 is wildly reported to associated with the development of HCC.35 Thus, NCOA5 could be a protective role for human body. What’s more, Gao et al. found that NCOA5 haploinsufficiency in NCOA5+/- mice resulted in hepatic inflammation and steatosis, and dysplasia, as well elevated level of IL-6, insulin intolerance and HCC, which indicated that NCOA5 would be a susceptibility gene for HCC and diabetes mellitus.36 Their latest studies also found that a single nucleotide variation (SNV) (T445A) in NCOA5, causing an amino acid threonine to alanine substitution, was only found in the HCC and/or DM patient. This SNV can impair the function of NCOA5 in cell cycle and regulation in vitro and the effect of NCOA5 on suppression of HCC tumor growth in vivo.37 Those studies indicate a good explanation for NCOA5 in the association of HCC and DM in molecular level. But not all the HCC patients and DM patients have this SNV, some other mechanisms need to be found to make this pathological process more clear.

CONCLUSION

It’s firmed that the morbidity of HCC and DM is closely related. Many evidences which were focused on the cell metabolism indicate that the two disease can be caused by certain specific susceptibility genes. The pathologic changes in diabetics, including hyperglycemia and insulin resistance, can influence metabolism, heredity, immunity of hepatocyte, which increase the risk of HCC. The interaction between the two diseases is complex and long-lasting. The complex pathogenesis suggests that there are still many molecule mechanisms and genes that are need to explored, which, in turn, will provide new methods and ideas for preventing and curing these two diseases. Although it is difficult to completely clarify the relationship between these two diseases, there is no doubt that diabetes is an independent risk factor for liver cancer. Whether new-onset diabetes can be used as an early warning of primary liver cancer needs further research.

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