

Review Article

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

Wanming Zheng¹, Minghua Deng², Jianping Gong^{3*}

¹Department of General Surgery, Chongqing Traditional Chinese Medicine Hospital of Yubei District, Chongqing, China

²Department of Hepatobiliary Surgery, Yubei District People's Hospital of Chongqing, Chongqing, China

³Department of Hepatobiliary Surgery, Second affiliated Hospital of Chongqing Medical University, Chongqing, China

Received: 12 October 2020

Accepted: 19 November 2020

*Correspondence:

Dr. Jianping Gong,

E-mail: gongjianping11@126.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

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 NF- κ B 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.¹¹ 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.¹² The activated IGF-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.¹³ 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.¹⁴ 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 decreased 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.¹⁵

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.¹⁶ 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.¹⁷ Multiple studies have found that the mutual of β -catenin or the activation of β -catenin could contribute to HCC.^{18,19} 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.²⁰

GSK-3 β , 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.²¹ In physiological conditions, GSK-3 β could mediate the ubiquitination and degradation of β -catenin by phosphorylation.²² However, the Phosphorylation of N-terminal domain serine residue (p-Ser9-GSK-3 β) can lead to the stabilization of β -catenin.²³ Qiao et al found that p-Ser9-GSK-3 β was significantly upregulated in HCC patients. They also found that the expression level of p-Ser9-GSK-3 β was significantly related with T2DM, which indicate GSK-3 β might play a significant role in mediating the impact of T2DM on HCC prognosis.²⁴ 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.²⁵ 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.²⁶ 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.²⁷ The occurrence in NASH patients with diabetes mellitus was significantly increased.²⁵ Inflammatory cytokines and activated immune cells, such as IL-6, TNF- α , Kupffer cells and hepatic stellate cells were involved this progress.²⁸ 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.²⁹ 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- κ B pathway to release inflammatory cytokine, such as IL-1, IL-6 and TNF- α .³⁰ 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- κ B, which could be abolished by pharmaceutical inhibition of TLR4. This study showed that TLR4 is key molecule for palmitic to cause inflammation.³¹

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.³²

THE EFFECT OF ESTROGEN METABOLISM-RELATED GENES ON DIABETES AND LIVER CANCER

Estrogen and estrogen receptor α (ER α) had been shown to be 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.³³

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 ER α -mediated transcription. When under the stimulation of estrogen, NCOA5 and ER α were upregulated and recruited to the IL-6 promoter and further suppressed the expression of IL-6.³⁴ IL-6 is widely reported to be 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 $^{+/-}$ male mice resulted in hepatic inflammation and steatosis, and dysplasia, as well as 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 confirmed that the morbidity of HCC and DM is closely related. Many evidences which were focused on the cell metabolism indicate that the two diseases 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 be 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.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2019;394(10204):1145-58.
2. Rendell M, Akturk HK, Tella SH. Glargine safety, diabetes and cancer. *Expert Opin Drug Saf*. 2013;12(2):247-63.
3. Umetsu S, Mizukami H, Saito T, Uchida C, Igawa A, et al. Diabetes, an independent poor prognostic factor of non-B non-C hepatocellular carcinoma, correlates with dihydropyrimidinase-like 3 promoter methylation. *Scientific Rep*. 2020;10(1):1156.
4. Mori M, Saitoh S, Takagi S. A Review of Cohort Studies on the Association Between History of Diabetes Mellitus and Occurrence of Cancer. *Asian Pac J Cancer Prev*. 2000;1(4):269-76.
5. Wang C, Wang X, Gong G. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Int J Cancer*. 2012;130(7):1639-48.
6. Niwa Y, Ishikawa K, Ishigami M. Effect of hyperglycemia on hepatocellular carcinoma development in diabetes. *Biochem Biophys Res Commun*. 2015;463(3):344-50.
7. He G, Yu GY, Temkin V. Hepatocyte IKK β /NF- κ B inhibits tumor promotion and progression by preventing oxidative stress-driven STAT3 activation. *Cancer Cell*. 2010;17(3):286-97.
8. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nature Rev Immunol*. 2011;11(2):98-107.
9. Mendonca FM, de Sousa FR, Barbosa AL. Metabolic syndrome and risk of cancer: which link? *Metabolism*. 2015;64(2):182-9.
10. Bell DS, Allbright E. The multifaceted associations of hepatobiliary disease and diabetes. *Endocr Pract*. 2007;13(3):300-12.
11. Lombay B, Szilagy R, Szalay F. Type 2 diabetes mellitus, insulin resistance and hepatocellular carcinoma in chronic hepatitis C patients. Data from Northeastern Hungary. *Orv Hetil*. 2019;160(40):1591-602.
12. Denduluri SK, Idowu O, Wang Z. Insulin-like growth factor (IGF) signaling in tumorigenesis and the development of cancer drug resistance. *Genes Dis*. 2015;2(1):13-25.
13. Singh MK, Das BK, Choudhary S. Diabetes and hepatocellular carcinoma: A pathophysiological link and pharmacological management. *Biomed Pharmacother*. 2018;106:991-1002.
14. Martinez-Quetglas I, Pinyol R, Dauch D. IGF2 Is Up-regulated by Epigenetic Mechanisms in Hepatocellular Carcinomas and Is an Actionable Oncogene Product in Experimental Models. *Gastroenterology*. 2016;151(6):1192-205.
15. Ampuero J, Romero-Gomez M. Prevention of hepatocellular carcinoma by correction of metabolic

- abnormalities: Role of statins and metformin. *World J Hepatol.* 2015;7(8):1105-11.
16. Elghazi L, Gould AP, Weiss AJ. Importance of beta-Catenin in glucose and energy homeostasis. *Scientific Rep.* 2012;2:693.
 17. Ferrarini A, Di Poto C, He S. Metabolomic Analysis of Liver Tissues for Characterization of Hepatocellular Carcinoma. *J Proteome Res.* 2019;18(8):3067-76.
 18. Liu P, Chen B, Gu Y. PNMA1, regulated by miR-33a-5p, promotes proliferation and EMT in hepatocellular carcinoma by activating the Wnt/beta-catenin pathway. *Biomed Pharmacother.* 2018;108:492-9.
 19. Senni N, Savall M, Cabrerizo Granados D. Beta-catenin-activated hepatocellular carcinomas are addicted to fatty acids. *Gut.* 2019;68(2):322-34.
 20. Hung MH, Chen YL, Chen LJ. Canagliflozin inhibits growth of hepatocellular carcinoma via blocking glucose-influx-induced beta-catenin activation. *Cell Death Dis.* 2019;10(6):420.
 21. Cervello M, Augello G, Cusimano A. Pivotal roles of glycogen synthase-3 in hepatocellular carcinoma. *Adv Biol Regul.* 2017;65:59-76.
 22. Gattinoni L, Ji Y, Restifo NP. Wnt/beta-catenin signaling in T-cell immunity and cancer immunotherapy. *Clin Cancer Res.* 2010;16(19):4695-701.
 23. Jin H, Yang X, Zhao K. Glycogen synthase kinase-3 beta inhibitors protect against the acute lung injuries resulting from acute necrotizing pancreatitis. *Acta Cir Bras.* 2019;34(6):201900609.
 24. Qiao G, Le Y, Li J. Glycogen synthase kinase-3beta is associated with the prognosis of hepatocellular carcinoma and may mediate the influence of type 2 diabetes mellitus on hepatocellular carcinoma. *PloS one.* 2014;9(8):105624.
 25. Yang JD, Ahmed F, Mara KC, Addissie BD, Allen AM, Gores GJ, et al. Diabetes Is Associated With Increased Risk of Hepatocellular Carcinoma in Patients With Cirrhosis From Nonalcoholic Fatty Liver Disease. *Hepatology.* 2019.
 26. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA.* 2015;313(22):2263-73.
 27. White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clin Gastroenterol Hepatol.* 2012;10(12):1342-59.
 28. Hu M, Phan F, Bourron O. Steatosis and NASH in type 2 diabetes. *Biochimie.* 2017;143:37-41.
 29. Takeda Y, Fujita Y, Bessho R. Increment of plasma glucose by exogenous glucagon is associated with present and future renal function in type 2 diabetes: a retrospective study from glucagon stimulation test. *BMC Endocr Disord.* 2019;19(1):99.
 30. Lee JY, Sohn KH, Rhee SH. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. *J Biol Chem.* 2001;276(20):16683-9.
 31. Shen C, Ma W, Ding L. The TLR4-IRE1alpha pathway activation contributes to palmitate-elicited lipotoxicity in hepatocyte. *J Cell Mol Med.* 2018;22(7):3572-81.
 32. Kanda T, Goto T, Hirotsu Y. Molecular Mechanisms: Connections between Nonalcoholic Fatty Liver Disease, Steatohepatitis and Hepatocellular Carcinoma. *Int J Mol Sci.* 2020;21(4).
 33. Nadal A, Alonso-Magdalena P, Soriano S. The role of oestrogens in the adaptation of islets to insulin resistance. *J Physiol.* 2009;587(21):5031-7.
 34. Dhar D, Seki E, Karin M. NCOA5, IL-6, type 2 diabetes, and HCC: The deadly quartet. *Cell Metab.* 2014;19(1):6-7.
 35. Chan LC, Li CW, Xia W. IL-6/JAK1 pathway drives PD-L1 Y112 phosphorylation to promote cancer immune evasion. *J Clin Investig.* 2019;129(8):3324-38.
 36. Gao S, Li A, Liu F. NCOA5 haploinsufficiency results in glucose intolerance and subsequent hepatocellular carcinoma. *Cancer Cell.* 2013;24(6):725-37.
 37. Liu X, Liu F, Gao S. A single non-synonymous NCOA5 variation in type 2 diabetic patients with hepatocellular carcinoma impairs the function of NCOA5 in cell cycle regulation. *Cancer letters.* 2017;391:152-61.

Cite this article as: Zheng W, Deng M, Gong J. The molecular mechanism on the association of diabetes mellitus with hepatocellular carcinoma. *Int Surg J* 2021;8:436-9.