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REVIEW

Molecular pathological epidemiology in diabetes mellitus and risk of hepatocellular carcinoma

Chun Gao

Chun Gao, Department of Gastroenterology, China-Japan Friendship Hospital, Ministry of Health, Beijing 100029, China

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Correspondence to: Chun Gao, MD, Department of Gastroenterology, China-Japan Friendship Hospital, Ministry of Health, No. 2 Yinghua East Road, Beijing 100029, China. gaochun@bjmu.edu.cn
Telephone: +86-10-84205313
Fax: +86-10-64481924

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Abstract

Molecular pathological epidemiology (MPE) is a multidisciplinary and transdisciplinary study field, which has emerged as an integrated approach of molecular pathology and epidemiology, and investigates the relationship between exogenous and endogenous exposure factors, tumor molecular signatures, and tumor initiation, progression, and response to treatment. Molecular epidemiology broadly encompasses MPE and conventional-type molecular epidemiology. Hepatocellular carcinoma (HCC) is the third most common cause of cancer-associated death worldwide and remains as a major public health challenge. Over the past few decades, a number of epidemiological studies have demonstrated that diabetes mellitus (DM) is an established independent risk factor for HCC. However, how DM affects the occurrence and development of HCC remains as yet unclearly understood. MPE may be a promising approach to investigate the molecular mechanisms of carcinogenesis of DM in HCC, and provide some useful insights for this pathological process, although a few challenges must be overcome. This review highlights the recent advances in this field, including: (1) introduction of MPE; (2) HCC, risk factors, and DM as an established independent risk factor for HCC; (3) molecular pathology, molecular epidemiology, and MPE in DM and HCC; and (4) MPE studies in DM and risk of HCC. More MPE studies are expected to be performed in future and I believe that this field can provide some very important insights on the molecular mechanisms, diagnosis, personalized prevention and treatment for DM and risk of HCC.

Key words: Diabetes mellitus; Molecular pathological epidemiology; Hepatocellular carcinoma; Risk factor; Molecular mechanism

Core tip: Diabetes mellitus (DM) is an established independent risk factor for hepatocellular carcinoma (HCC); however, how DM affects the occurrence and development of HCC remains as yet unclearly understood. Molecular pathological epidemiology (MPE) may be a promising approach to investigate the molecular mechanisms of carcinogenesis of DM in HCC, and provide some

useful insights for this pathological process. This review highlights the recent advances in this field and more MPE studies are expected to be performed for this question in future.

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INTRODUCTION

Molecular pathology examines the expression of molecular markers within bodily fluids, tissues or organs, and focuses on the diagnosis and studies of diseases, such as tumors[1,2]. Epidemiology is focused upon the studies of distributions and determinants of diseases and health conditions in specific populations[3,4]. Molecular pathological epidemiology (MPE) is a multidisciplinary and transdisciplinary study field, which has emerged as an integrated approach of molecular pathology and epidemiology, and investigates the relationship between tumour molecular markers, exposure of endogenous and exogenous factors, and development, progression and prognosis of tumors[5-8]. Molecular epidemiology broadly encompasses MPE and conventional-type molecular epidemiology.

In MPE, researchers investigate the relationships between: (1) changes of extracellular or cellular molecules (disease molecular signatures); (2) genetic, dietary, environmental and lifestyle factors; and (3) development and progression of diseases, such as tumors[6]. In 2010, Professor Shuji Ogino and Professor Meir Stampfer[5] were the first to introduce the concept of MPE. They consolidated this concept mainly based on the researches of colorectal cancer (CRC), particularly the prototypical study in the evolving field of MPE, which was conducted by Professor Peter T Campbell and others[9].

This case-control study of Campbell *et al*[9] was conducted to determine the relationships between CRC microsatellite instability (MSI) status, risk of CRC, and human body mass index (BMI). The results showed that an increased CRC risk was found in those patients with a high BMI; however, this risk of CRC was associated with the MSI status. For patients with MS-stable, the adjusted odds ratio (OR) was 1.38 and 95%CI was 1.24-1.54, for an increment of 5 kg/m^2 of BMI; for patients with MSI-low, the OR was 1.33 and 95%CI was 1.04-1.72; however, for patients with MSI-high tumours, the value of OR and 95%CI were 1.05 and 0.84-1.31, respectively[9]. The authors concluded that the relationship between the high BMI and increased CRC risk was related to the tumor MSI status[9]. According to the concept and principle of MPE, this prototypical study addressed the relationship between exposure factor (high BMI), molecular change (CRC MSI status) and tumor initiation (risk of CRC)[5,10].

MPE addresses two questions: (1) the association of particular exposure factors with specific molecular changes; and (2) the interaction of particular exposure factors with specific molecular changes to affect development, progression and prognosis of tumors. The typical research of cancer MPE is used to examine the relationship between exposure factors and risk of tumors according to the status of tumor signatures[9,10]. Cancer MPE techniques and studies can help us understand the carcinogenesis of certain exposure factors, through the examination of molecular pathological signatures associated with initiation and progression of tumors, and the exposures[5,6].

HEPATOCELLULAR CARCINOMA AND RISK FACTORS

Hepatocellular carcinoma (HCC) has been confirmed as the third leading cause globally, among all the cancer-related deaths[10-12]. For primary liver cancers, more than 80% are HCC and the incidence rate annually of HCC is 4.9 per 100000 persons. Although some advances have been gained in the diagnosis and treatment of HCC, the prognosis remains very poor. Similarly, the annual mortality rate remains very high and HCC has also been ranked as one of the most lethal cancers[13].

With the using and popularization of hepatitis B virus (HBV) vaccination, the improvement of people's living standard and life style, and advancement of early diagnosis and treatment of premalignant lesions, the incidence of HCC had been anticipated to be decreased. However, the incidence rate of HCC has already been found to be increased significantly in the past thirty years in some countries, including the United States, China and Japan[14,15]. For example, during the period of 1981-1983 in the United States, the age adjusted incidence rate was 1.3 per 100000; however, this rate increased to 3.0 per 100000 during the period of 1996-1998[14,15]. Although more than fifty percent of this increase has been attributed to hepatitis virus C (HCV), other hepatitis viruses and alcoholic liver disease[16], the reason remains as unclear.

The identified risk factors of HCC include liver cirrhosis, HBV, HCV, heavy alcoholic consumption, alfatoxin exposure, non-alcoholic steatohepatitis, positive family history, male sex, and increasing age[17-19]. Over the past few decades, a number of epidemiological studies have demonstrated that diabetes mellitus (DM) is an established independent risk factor for HCC[12,20-23].

DM AS AN ESTABLISHED INDEPENDENT RISK FACTOR FOR HCC

In the year of 1986, for the first time, Lawson *et al*[24] proposed accidentally the positive association of DM with HCC. The authors observed that, in Western Europe, the incidence rate of primary liver cancers was increased, and deduced that this increase might in part be associated

with the induction of hepatic microsomal enzyme caused by long-term usage of some drugs. On the basis of this assumption, the authors designed and performed an observational case-control study, which included 105 patients with HCC and long-term drug use, and 105 age and sex-matched patients with colorectal tumors and with fractures of femur[24]. Surprisingly, the results demonstrated that compared to the control group, the HCC group patients had four-fold excess of diabetic cases, and this association was independent of those pre-existing diseases, for example viral hepatitis, alcoholic cirrhosis and haemochromatosis[24]. The relationship between DM and HCC was proposed clearly although some limitations could not be avoided.

Following the publication of this study, only a few researches attempted to elucidate the association of diabetes with HCC in the next more than ten years; however, over the past more than one decade, more and more researches have been designed and performed to address this relationship[21,25-27]. Earlier epidemiologic studies showed inconsistent findings relating to the association of DM with HCC[21,28-30] whereas more and more recent studies have identified DM as an established independent risk factor for HCC, especially two prospectively large-scale population-based cohort studies[31,32]. In 2008, a review published in the journal of LANCET ranked diabetes as the fourth risk factor for HCC, following cirrhosis, viral hepatitis B and C, and non-alcoholic steatohepatitis[17].

Of the two prospectively large-scale population-based cohort studies[31,32], one was performed in the Sweden, which used the Swedish In-patient Register and included 153852 patients diagnosed with diabetes during the period between 1965 and 1983[31]. The patients were followed up through December 31, 1989. The authors identified those incident cases of cancer using the database and excluded those patients who were diagnosed with liver cancers during the first year of follow-up. The results showed that an increased risk of developing primary liver cancers was found in the diabetic patients (standardized incidence ratio, SIR = 4.1; 95%CI: 3.8-4.5). After exclusion of those concomitant diseases which have been associated with HCC, for example hepatitis, cirrhosis, and alcoholism, the persistence of an approximately threefold excess risk was observed[31].

The conclusion from the Swedish study was supported by another followed cohort study conducted in the United States[32], which was performed by doctors in the Department of Veterans Affairs. In this study, the authors also used the computerized records to identify all the patients with a hospital discharge diagnosis of DM in the period from 1985 to 1990, and matched randomly three patients without DM for every diabetic patient. Follow-up of these patients was taken through December 31, 2000. The major strength of this study was the strict inclusion and exclusion criteria and they were pre-determined perfectly on the basis of our current knowledge. The authors decided and used three periods, including: (1) the period dating back to 1980; (2) the period of index hospitalization; and (3) the period of the first year of follow-up. During these three above-mentioned periods, those patients with all kinds of liver diseases, abnormal liver function tests, alcoholism, or other identified risk factors for HCC, such as HBV and HCV, had been excluded from the study population[32]. The authors concluded that among men with diabetes, the risk of HCC was increased, which was not associated with demographic features, viral hepatitis, cirrhosis, and alcoholic liver disease.

The recently published systematic review in this field was designed to evaluate the impact of DM on the risk of HCC among patients with HCV infection[33]. This research included seven articles and all of them were conducted in Asian cohorts, including three studies from Taiwan, China, and four from Japan[34-40]. Among these studies, six were observational cohorts and six studies were of good quality. The results showed that a significantly increased risk of HCC was associated with DM in five of these seven studies and the effect sizes ranged from HR = 1.73 (95%CI: 1.30-2.30) to RR = 3.52 (95%CI: 1.29-9.24)[33].

MOLECULAR PATHOLOGY, MOLECULAR EPIDEMIOLOGY AND MPE IN DIABETES

Molecular pathology in diabetes

Pathology is an important constituent part of diagnostics, modern medicine and causal studies of diseases, which focuses upon four research fields of diseases: Etiology (causes), pathogenesis (mechanisms of development and progression), morphologic alterations (structural changes of cells, tissues and organs), and clinical manifestations (consequences of alterations)[41,42]. Molecular pathology (MP), whose focus is the examination of molecular signatures, has some similar aspects of practice to other disciplines, such as anatomic pathology, genetics, biochemistry, proteomics, molecular biology, and clinical pathology. Application of modern MP often encompasses three components: (1) exploration and confirmation of predictive molecular biomarkers for development, progression and treatment of diseases; (2) development of genetic and molecular approaches for diagnosis and classification of human diseases; and (3) susceptibility of individuals of different genetic constitution to particular disorders.

Molecular pathological studies in diabetes provide better insight into the etiology. For example type 1 or insulin-dependent diabetes, at least 20 genes have been identified and the dominant susceptibility locus maps to the major histocompatibility complex[43,44]. Major areas of MP research include environmental trigger factors, modification of the beta cells, infiltration of the islets by immuno-inflammatory cells, and autoimmune-mediated destruction of the beta cells. For T2DM, since the early genome-wide association studies (GWAS) in 2007, hundreds of genetic loci have been identified. Elucidating the pathology of DM at the molecular level is very important for developing innovative, personalized, and evidence-based treatments[45,46].

From the viewpoint of MP of DM in cancers, disruption of homeostatic glucose metabolism has been significantly associated with the malignant cellular transformation and tumor progression. In addition, the pathophysiology of disrupted glucose-insulin axis pathways of DM has been understood deeply at the subcellular level, thanking for the recent advances in biochemical and molecular technology. They may be useful for better understanding of the malignant cellular transformation, such as HCC.

Molecular epidemiology in diabetes

In the late 20th century, with great advancement of biomedical sciences, a number of molecular signatures or biomarkers were identified as predictors of disease initiation, progression, and response to treatment, including diabetes and tumors. Since the identification of these molecular signatures, molecular epidemiology has evolved and been broadly named, which refers to the branch of epidemiology, where investigators examine these signatures in special study populations and its interaction with environmental, lifestyle or dietary factors, to perform the causal studies of diseases with aetiological factors[6,10]. Since the 2000s, GWAS has been commonly performed to identify genetic risk factors for diseases and health conditions[47,48].

Molecular epidemiology in diabetes is focused upon the contribution of possible environmental and genetic risk factors, to the distributions and determinants of DM within families and across populations, at the molecular level. For example, a number of molecular epidemiological studies demonstrate that some growth factors, including insulin, growth hormone, insulin-like growth factors and their binding proteins, may be important in the pathophysiological processes of T2DM[49]. In addition, many physiological changes have been associated with T2DM, including insulin resistance and hyperinsulinemia, increased estrogen levels, increased inflammatory cytokines such as tumor necrosis factor (TNF)-α, and interleukin (IL)-6, as well as altered levels of circulating adipokines[50]. It is well known that some of these molecular signatures and physiological changes may contribute to the development of cancers. Therefore, the relationship between DM and cancers, such as HCC, may be built *via* these molecular signatures or biomarkers.

MPE in diabetes

MPE emerges as an integrated approach of molecular pathology and epidemiology, and investigates the relationship between risk factors, molecular signatures, and development and progression of diseases[10]. According to the concept and principle of MPE, the MPE approaches can also be used in non-neoplastic diseases, such as DM[51]. Although great advancements have been made in molecular pathology and molecular epidemiology, and a lot of molecular signatures have been associated with DM, no MEP studies in DM have been performed and the reason may be deduced that no identified risk factors are found for DM, such as HBV or HCV for HCC.

However, a few MPE studies had been performed when DM was treated as the risk factor for other diseases, such as cancers and coronary artery lesions, before the proposal and/or use of the concept of MPE, and they were conducted usually under the umbrella of molecular epidemiology. For example, one MPE study was designed to determine the relationship between 8-oxoguanine glycosylase (hOGG1) Ser326Cys gene polymorphism and coronary artery lesions in patients with DM[52]. In this study, 323 diabetic patients were included and the results showed that hOGG1 Ser326Cys polymorphism was correlated with coronary artery lesions in patients with DM, and Cys/Cys genotype may be associated with the more severity of lesions[52].

MOLECULAR PATHOLOGY, MOLECULAR EPIDEMIOLOGY AND MPE IN HCC

Molecular pathology in HCC

For human cancers, including CRC and HCC[53-55], molecular pathology is commonly used in the diagnosis and classification. Traditional molecular pathology studies are focused upon the molecular characteristics in cancer cells to improve our understanding of tumor cell behavior and carcinogenic processes[1,6,10]. However, human cancers are complex multifactorial diseases. Recent studies suggest that cancers should be classified based on salient clinical and pathologic features as well as on molecular fingerprints, which has been named "molecular classification", because of the premise that tumors with similar characteristics share common pathogenic mechanisms and progression patterns, despite each tumor undergoing its own unique neoplastic transformation[5,6,56]. Molecular classification is helpful to better understand the pathogenesis of tumors, predict the development and progression of each tumor, and for personalized cancer medicine, optimize the preventive and treatment strategies[5,6,56]. For cancer molecular classification, informative biomarkers are needed to be identified to stratify tumors or patients[57-62].

Examples of well-established informative biomarkers include ESR1 (ER-α), PGR and ERBB2 (HER2) expression in breast cancer[63-65], EGFR mutations in lung cancer[66,67], MSI in colorectal cancer[68-70], TMPRSS2-ERG translocation in prostate cancer[71], and TP53, PIK3CA, BRAF and KRAS mutations, and CpG island methylation in multiple cancers[72-74]. Some molecular changes or biomarkers in HCC have also been previously identified. Ojanguren *et al*[75] showed that the positive expression of mutant p53 was related to alcohol abuse (42%) and HBV infection (21%). Park *et al*[76] found that TNF and IL-6 signaling was correlated with obesity-associated HCC development. In the obese patients, insulin and insulin-like growth factors, TNF-α, IL-1 and IL-6, leptin, adipokines, adiponectin, and plasminogen activator inhibitor-1 are significantly associated with the occurrence and development of some cancers, including HCC[77].

Molecular epidemiology in HCC

HCC is also very complex, for example it occurs in about

1%-7% of cirrhotic patients annually, whereas most of the cirrhotic patients do not progress to HCC during their lifetimes[78]. Molecular biomarkers are expected to satisfy this need and resolve the question at the molecular level. To date, molecular epidemiology studies show that a number of molecular risk factors of HCC have been identified, such as numerous genetic polymorphisms reported as host genetic factors[79]. Most of HCC-associated single-nucleotide polymorphisms are identified in genes involved in biological pathways, including oxidative stress (GSTT1, GSTM1), cell cycle (MDM2), immune response (IL10, TNF), DNA damage repair (XPC), growth signaling (EGF), and iron metabolism (HFE) in viral hepatitis- or alcohol-related HCC[80-84]. Recent GWAS identifies the DEPDC5 locus as the risk loci in viral hepatitis-related HCC[85].

Molecular factors associated with etiological agents, for example HBV and HCV could also influence the risk of HCC. It is well known that a high level of serum HBV DNA is indicative of increased risk of HCC. Some studies have demonstrated that HBV genotype is related to the HCC risk[86]. Genomics technology has revealed that HCC should be regarded as a heterogenous group of diseases, not one single disease entity, because each sub-group HCC has different sets of epigenetic and genetic alterations[87]. The heterogeneous molecular features of HCC tumors are associated with the biological behavior, clinical outcome and prognosis[87-91]. Molecular classification is recommended to HCC, and previous studies have identified subsets of HCC tumors characterized by TP53 and CTNNB1 activation mutations, progenitor cell–like features, Met activation, Myc activation, and transforming growth factor-β activation[92-94]. These molecular risk factors of HCC would play important roles in the design and implementation of MPE studies.

MPE in HCC

Epidemiological studies have showed that DM is an established independent risk factor for HCC[12,20-23]; however, how DM affects the development and progression of HCC has not been explained clearly. MPE approaches and studies may be helpful to improve our understanding of the molecular mechanisms of carcinogenesis of HCC. MPE can be used to investigate the relationship between DM and risk of HCC by molecular subtypes. A few MPE studies have been performed for this question, although they were usually under the umbrella of molecular epidemiology. They would be described in the next section in detail. MPE can provide some useful insights for the pathological processes of DM in HCC, although a few challenges must be overcome.

MPE IN DM AND RISK OF HCC

Currently, based on our knowledge, very few MPE researches are available for DM and risk of HCC[95-97]. For these studies, the original design are not for MPE, and the term of "molecular pathological epidemiology" have not appeared in their articles, but they can be treated as MPE researches, according to the objectives and methods.

One MPE research which was performed in the Japan was designed to determine the relationship between PNPLA3 and JAZF1, and risk of HCC, in patients with non-viral hepatitis and type 2 DM[95]. The objective of this research was to identify genetic determinants associated with T2DM patients who have a high risk of developing HCC by genotyping T2DM susceptibility loci and PNPLA3. This study included 389 T2DM patients, including 59 patients with HCC (DM-HCC) and 330 patients without HCC (DM-non-HCC). Those patients who followed these criteria were included: (1) history of T2DM > 10 years; (2) alcohol intake < 60 g/d; and (3) negative for anti-HCV Ab and HBs-Ag. The authors found that the SNP rs738409 located in PNPLA3 was the greatest risk factor associated with HCC in these diabetic patients. Compared to DM-non-HCC patients, DM-HCC patients had the significantly higher frequency of the PNPLA3 G allele (OR = 2.53, $P = 1.05 \times 10^{-5}$). Moreover, among the 115 DM patients homozygous for the PNPLA3 G allele, HCC patients had the significantly higher frequency of the JAZF1 rs864745 G allele (OR = 3.44, $P = 0.0002$)[95]. They concluded that PNPLA3 and JAZF1 were associated with an increased risk of developing HCC among T2DM patients without viral hepatitis[95].

Another study was designed to evaluate the cytokinome profile, including the serum levels of growth factors, chemokines, cytokines, as well as of other diabetes and cancer biomarkers, in a cohort of patients, including 17 patients with T2DM, 20 patients with chronic hepatitis C infection, 34 patients with HCC, 10 patients with T2DM-HCC, and 20 healthy controls[96]. The results demonstrated that: (1) T2DM-HCC patients had the higher levels of IL-2R, sIL-6Ra, IL-16, IL-18, HGF, β-NGF, CXCL1, CXCL12, ADIPOQ, and IFN-α than those with T2DM or HCC; (2) T2DM-HCC patients had the lower level of LEP than those with T2DM or HCC; (3) T2DM-HCC and only HCC patients had the similar levels of CXCL9, PECAM-1, Prolactin, glucagon, sVEGFR-1 and sVEGFR-2; (4) T2DM-HCC patients had the higher levels of CXCL9, PECAM-1, Prolactin, and glucagon than those with only T2DM; and (5) T2DM-HCC patients had the lower levels of sVEGFR-1 and sVEGFR-2 than those with only T2DM[96]. The major limitation of this study was the very limited number of included patients; however, these molecular changes could be used to design and perform the MPE researches in DM and risk of HCC in future.

Some molecular pathology researches can also be regarded as MPE studies, for example one study which was conducted in the Second Military Medical University, Shanghai, China[97]. The objectives of this study were to determine the effect of p-Ser9-GSK-3β (glycogen synthase kinase-3β) on the prognosis in HCC patients and to explore the interaction between GSK-3β, T2DM and prognosis of HCC. This research included 178 HCC patients after curative partial hepatectomy and showed that expression of P-Ser9-GSK-3β was significantly

higher in tumor tissues than that in their normal counterparts[97]. Moreover, the authors also found that: (1) over-expression of p-Ser9-GSK-3β was associated with T2DM; (2) T2DM and over-expression of p-Ser9-GSK-3β were closely related with each other; and (3) these two variables were independently associated with poor prognosis of HCC[97]. Therefore, p-Ser9-GSK-3β may be regarded as the mediator between T2DM and HCC.

One case report which was published in 2015 was also considered to be related to this field[98]. This report describes a 23-year-old woman with HCC and type 2 DM; and results of histological and immunohistochemical examination showed that this HCC arose in the background of hepatocyte nuclear factor-1α mutated hepatocellular adenomas (H-HCA). However, traditionally, we consider that H-HCA have no minimal malignant potential. For the molecular changes and tumor biomarkers of HCC, the authors found that by immunohistochemical tests, CD34 expression in sinusoidal endothelial cells and expression of glutamine synthetase in tumor cells were increased, whereas exon 3 of CTNNB1 and TERT promoter mutations, and nuclear expression of β-catenin were absent in this patients with HCC and DM. Although such cases are rare, they reinforce the potential of H-HCA for HCC, which may be related to DM[98].

Considering that DM is an independent risk factor for HCC, some efforts have been focused on understanding of the molecular mechanisms of DM in the development and progression of HCC, which may be useful for the design and implementation of MPE studies. For example, one mini-review focused on the impact of TNF-α and IL-6 along with epigenetic regulations[99]. Two approaches are suggested as followed: (1) the first is about the role of TNF-α and IL-6 as inflammatory mediators, from the point of role of apoptosis and inflammation in HCC; and apoptotic regulators can be used for this purpose, such as Bax (bcl-2-like protein 4 encoded by the BAX gene) and Bcl-2 (B-cell lymphoma 2 protein encoded by *BCL2* gene); and (2) the second is about the possible epigenomic reprogramming, from the point of role of epigenetic modification of DNA in HCC. According to these two approaches, apoptotic and inflammatory markers (Bcl2 and Bax), and DNA methylation, hypomethylation or histone modifications can be used as the candidated molecular biomarkers for the understanding of role of DM in HCC[99].

Another review focused on the influence of insulin resistance and hyperinsulinemia of DM in the pathogenesis of hepatocarcinogenesis, and the author summarized that some molecular pathways were involved, for example phosphatase and tensin homolog/P13K/Akt and MAPK kinase[100]. It is well known that different anti-diabetic medications have different influences on the risk of HCC in diabetic patients[23,100]. Metformin has been associated with the decreased risk of HCC in patients diagnosed with DM[23]. The molecular mechanism is deduced that metformin can activate 5-adenosine monophosphate-activated protein kinase (AMPK) and decrease the expression of protein Livin[100]. AMPK can inhibit its downstream target mammalian target of rapamycin, and then inhibit the growth of human cancer cell lines. Livin has been involved in both cell proliferation and survival. Thiazolidinediones seem to inhibit peroxisome proliferator-activated receptor gamma-independent regulation of nucleophosmin and prevent tumor formation[100].

Although these studies are not enough for understanding of molecular mechanisms of DM in the increased risk of HCC, they and the involved molecular biomarkers can be very useful for future MPE researches. I hope that more and more MPE researches are performed exploring the molecular mechanisms as well as novel biomarkers.

CONCLUSION

DM is an established independent risk factor for HCC; however, how DM affects the occurrence and development of HCC remains as yet unclearly understood. "MPE" is the branch of epidemiology and pathology, and its basis is the molecular classification of tumors. MPE is a multidisciplinary, interdisciplinary and transdisciplinary study field, and molecular pathology plays a central role in this relatively new field. In MPE, investigators examine the relationship between tumor molecular signatures, endogenous and exogenous factors, and development, progression and prognosis of tumors. I believe that this research field can be very helpful to improve our understanding of the pathogenesis, molecular mechanisms, diagnosis, personalized prevention and treatment for DM and risk of HCC in future.

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