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Contents

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EDITORIAL

REVIEW

MINIREVIEWS

World Journal of Gastrointestinal Oncology

Monthly Volume 16 Number 6 June 15, 2024

Contents

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Contents

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Contents

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REVIEW

Early monitoring values of oncogenic signalling molecules for hepatocellular carcinoma

Min Yao, Rong-Fei Fang, Qun Xie, Min Xu, Wen-Li Sai, Deng-Fu Yao

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Abstract

The prevention and early diagnosis of liver cancer remains a global medical challenge. During the malignant transformation of hepatocytes, a variety of oncogenic cellular signalling molecules, such as novel high mobility group-Box 3, angiopoietin-2, Golgi protein 73, glypican-3, Wnt3a (a signalling molecule in the Wnt/β-catenin pathway), and secretory clusterin, can be expressed and secreted into the blood. These signalling molecules are derived from different signalling pathways and may not only participate in the malignant transformation of hepatocytes but also become early diagnostic indicators of hepatocarcinogenesis or specific targeted molecules for hepatocellular carcinoma therapy. This article reviews recent progress in the study of several signalling molecules as sensitive biomarkers for monitoring hepatocarcinogenesis.

Key Words: Hepatocarcinogenesis; Cell signals; Specific biomarkers; Early diagnosis

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Core Tip: The early monitoring or diagnosis of hepatocellular carcinoma (HCC) are still medical challenge, and identifying novel biomarkers with high sensitivity and specificity for HCC are urgently needed. Recent progress in several oncogenic cellular signalling molecules that derived from different signalling pathways were reviewed, such as novel high mobility group-Box 3, angiopoietin-2, Golgi protein 73, glypican-3, Wnt3a (a signalling molecule in the Wnt/β-catenin pathway), and secretory clusterin. They might not only participate in the malignant transformation of hepatocytes but also become early diagnostic indicators of hepatocarcinogenesis or specific targeted molecules for HCC therapy.

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INTRODUCTION

The prevention, early monitoring or diagnosis of hepatocellular carcinoma (HCC) are still urgent medical problems[1,2]. Hepatocarcinogenesis is mainly related to chronic persistent hepatitis virus infection [hepatitis B virus (HBV), hepatitis C virus (HCV) or hepatitis D virus][3,4], chemical carcinogen intake, and increased metabolic dysfunction-associated fatty liver disease (MAFLD)[5,6]. Recently, MAFLD has become one of the most chronic liver diseases and a possible etiological factor for liver cancer[7,8]. Abnormal cell signalling or genome instability in the setting of chronic hepatitis (CH) that promotes liver fibrosis and angiogenesis leads to tumorigenesis, which can be used to develop new monitoring methods or treatment methods[9,10]. The oncogene activation or some other genes during the embryonic period and the inactivation of anti-oncogenes can induce malignant transformation of hepatocytes[11]. Many kinds of specific signalling molecules in malignantly transformed hepatocytes can be expressed in liver tissues and secreted into the circulating blood during the occurrence, development and progression of hepatocarcinogenesis[12,13]. Upregulating signals at the early stage of HCC can not only elucidate the underlying mechanisms but also lay a foundation for early monitoring and future targeted therapy for HCC[14].

Liver cancer is still the sixth most common cancer in the world and the third leading cause of cancer death. HCC is the 6th most common cancer worldwide and is the 3rd leading cause of tumour death. HCC is the 3rd most common cause of cancer-related deaths worldwide[15]. Early diagnosis of HCC or monitoring of hepatocyte malignant transformation is of utmost importance[16]. To date, few markers have early monitoring or specific diagnostic value. It is therefore essential to reduce the incidence and impact of these diseases by understanding risk factors and prevention strategies at early stage [17]. Clinically, therapeutic options for advanced HCC at the time of diagnosis are limited; in many cases, these treatments are not effective and typically result in recurrence and poor prognosis. Many blood markers are now available for HCC screening, diagnosis and prognosis. Routine circulating alpha-fetoprotein (AFP) is a useful marker for high-risk populations of patients with HCC, with approximately 40% of patients having normal levels of AFP[18]. Despite concerted efforts in both basic and clinical medicine, less than 5% of patients with liver cancer now five-year survival rate because of some factors such as delayed clinical diagnosis or late visits.

Although routine AFP detection is combined with other clinical parameters, the combined detection of multiple markers is often more sensitive or specific than the use of a single marker. A new GALAD score (sex, age, AFP, AFP-L3 and des-γ-carboxy prothrombin) has been developed[19,20] and used to detect early HCC in a population at high risk of HCC or in a cohort of patients with nonalcoholic steatohepatitis, multicentre derivation, validation and comparison[20,21]. However, identifying potential molecular mechanisms or monitoring markers with high sensitivity and specificity or identifying new therapeutic targets for HCC are urgently needed[22,23]. Recently, several specific signalling molecules related to hepatocyte malignant transformation have been reported in HCC tissues and blood, such as circulating high mobility group-Box 3 (HMGB3), Wnt3a from the Wnt/β-catenin pathway, secretory clusterin (sCLU), angiopoietin-2 (Ang-2), Golgi protein-73 (GP73), and glypican-3 (GPC3) (Figure 1). This review presents new advances in identifying promising signalling molecules for monitoring hepatocarcinogenesis in high-risk populations.

HMGB-3 SIGNALLING

The high mobility group (HMG) protein superfamily[24] includes the HMGA[25], HMGB[26] and HMGN[27] families, which have different biological functions. The HMGB family consists of HMGB1, HMGB2, HMGB3 (Figure 2) and HMGB4 and encodes proteins that contain one or more DNA-binding motifs; these proteins are involved in multiple cellular processes, including HBV infection, cell differentiation, migration, and inflammation-related activities[28-30]. HMGB3 expression has been investigated in the cancerous tissues of patients with HCC and in the sera of patients with HBV-related chronic liver diseases[31]. HMGB3 expression in HCC samples was marked greater than that in noncancerous ones and was related to with tumour size, tumor node metastasis (TNM) stage, high recurrence rates, and there was no significant difference in patient age, sex, AFP, HBV infection or liver cirrhosis (LC). HMGB3 levels in sera of patients were analyzed in a cohort of cases with chronic liver disease, with progressive increases from benign liver disease to HCC progression. The sensitivity was 75.6 for HMGB3, 56.7 for AFP, and up to 89.0% for both combinations for

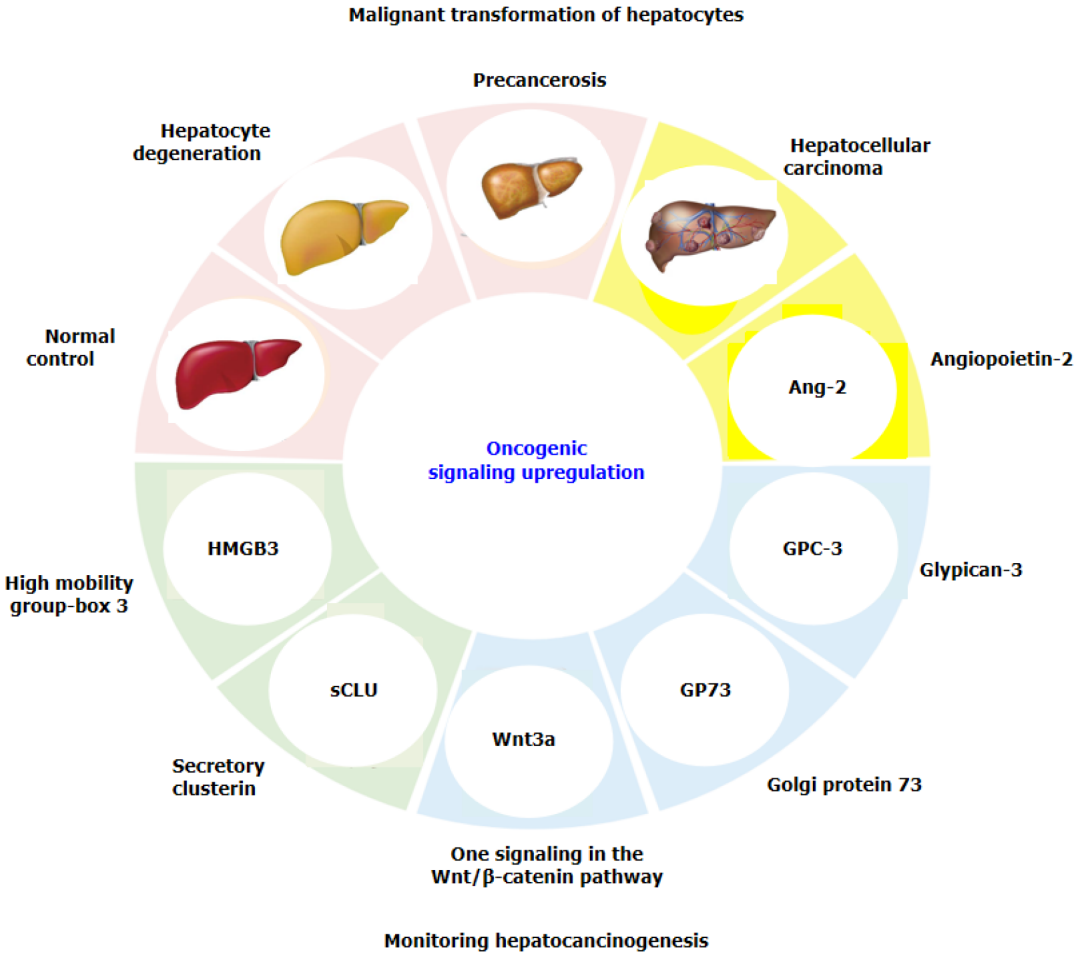

Figure 1 Novel signalling molecules involved in hepatocarcinogenesis[7,9,11,14]. Based on the data from animal models, the progressive alterations revealed by liver pathological examination ranged from normal liver to hepatocyte degeneration to precancerosis to hepatocellular carcinoma. Ang-2: Angiopoietin-2; GP73: Golgi protein 73; GPC-3: Glypican-3; HMGB3: High mobility group-Box 3; Sclu: Secretory clusterin; Wnt3a: A signalling molecule from the Wnt/β-catenin pathway.

HCC diagnosis. Interestingly, the percentage of HMGB3-positive patients was 55.3%, the percentage of AFP-positive patients was 39.5%, and the percentage of small-size HCC patients was 71.1%[32]. These findings indicate that HMGB3 detection is helpful for the diagnosis and differential diagnosis of benign and malignant liver diseases and might play an important role in HCC progression.

The common etiological causes of liver cancer progression are persistent CH and LC. It has been suggested that precancerous lesions of the liver include all stages of the disease, from dysplastic lesions and dysplastic nodules to early liver cancer[33,34]. A dynamic model of hepatocyte malignant transformation was developed in male SD rats according to the China National Invention Patent (ZL201810077848.2) by using 2-fluorenylacetamide (2-FAA) as a carcinogen. Dynamic changes in liver HMGB3 at the protein or mRNA level were analysed by immunohistochemistry (IHC) or reverse transcription-quantitative polymerase chain reaction. Pathology revealed that haematoxylin and eosin (H. After staining, the livers were divided into the hepatocyte degeneration (HD), precancerosis (PC), HCC and normal control (NC) groups. HMGB3 expression at the protein or mRNA level was not detected in the NC group, 50% in the HD group at the early stage, 100% in the PC group at the middle stage or 100% in the HCC group at the last stage, suggesting that HMGB3 expression is associated with malignant transformation of hepatocytes and could be a promising monitoring signal for hepatocarcinogenesis[35].

ANG-2 SIGNALLING

Ang-2, Ang-1, Tie2 Ligand-receptor, and vascular endothelial growth factor pathways are critical for regulating vascular maturation or stability and are associated with physiological angiogenesis or control of liver cancer[36]. Ang-2 is a key driver of HCC angiogenesis[37]. Neovascularization of HCC is a fundamental process that involves a lot of pathological processes and maintains HCC progression. The establishment of new angiogenesis depends on the complex processes of endothelial cell proliferation and organization. In addition, it may enhance the proliferation of HCC cells and the resistance to apoptosis, and promote HCC metastasis[38]. Comparative analysis revealed that the serum Ang-2 levels in the HCC, CH and LC groups were more higher ($P < 0.001$) than those in the NC group. The percentage of cells that were

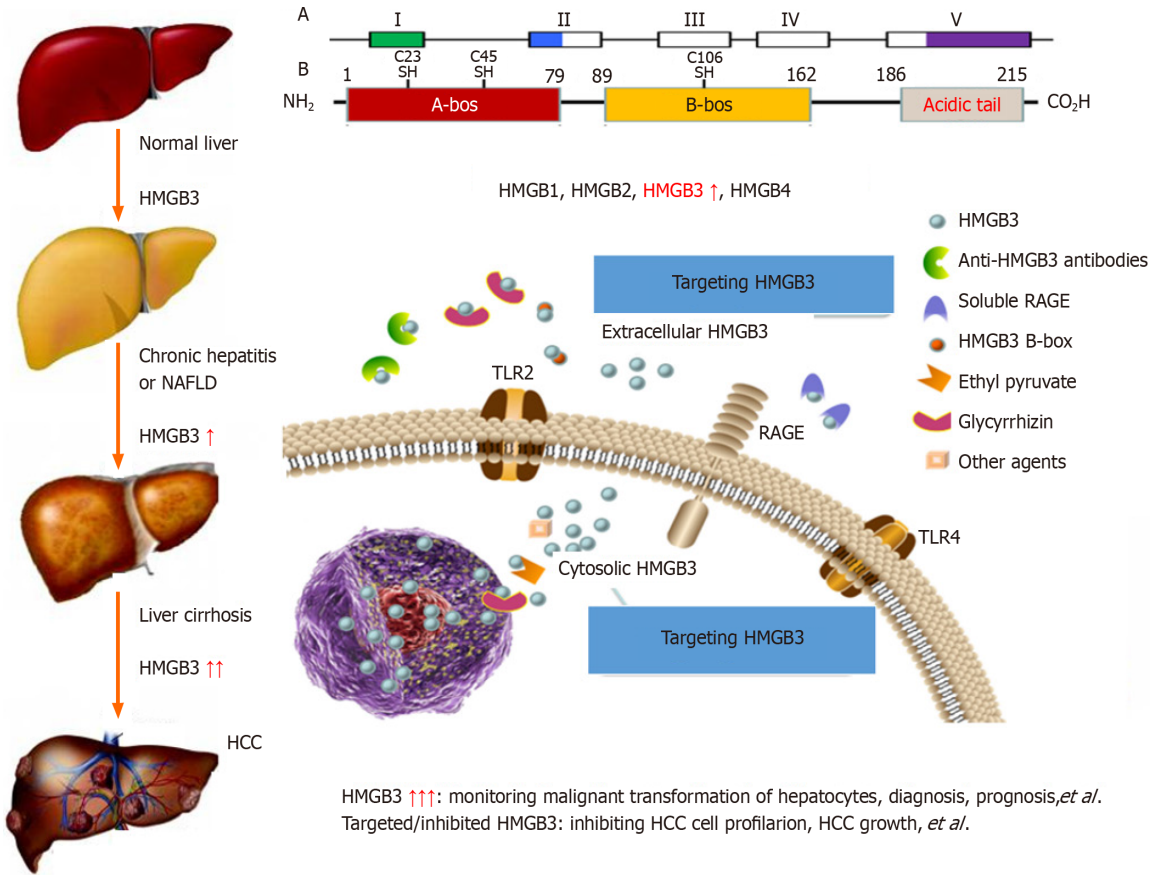

Figure 2 High mobility group-Box 3 during hepatocellular carcinoma progression[21,31-33,35]. Based on the data of basic or clinical studies, the progressive upregulation of high mobility group-Box 3 (HMGB3) at the mRNA or protein level occurred from the normal liver to chronic hepatitis to liver cirrhosis to hepatocellular carcinoma (HCC). An abnormal level of HMGB3 is helpful for monitoring hepatocyte malignant transformation and diagnosing or determining the prognosis of patients with HCC. In addition, interfering with HMGB3 transcription inhibited HCC cell proliferation *in vitro* or HCC xenograft growth *in vivo*. RAGE: Receptor for advanced glycation end products; TLR: Toll-like receptor; HCC: Hepatocellular carcinoma; HMGB3: High mobility group-Box 3.

positive for Ang-2 (more than 35 μg/L) was 90.0% in HCC, 6.0% in LC, 4.0% in CH cases, and 0.0% in NC. Clinicopathological characteristics of Ang-2 in HCC patients were strongly associated ($P < 0.001$) with tumour size (≥ 5 cm), differentiation degree (well/moderate *vs* poor), gross classification (unifocal *vs* multifocal), AFP (≥ 50 μg/L), LC, HBV infection, portal vein invasion or lymph node metastasis and TNM stage (I-II *vs* III-IV). Ang-2 was positively related to vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α ($P < 0.001$, Figure 3), suggesting that Ang-2 is upregulated during the progression of HCC[3,39-41].

It has been reported that ectopic expression of Ang-2 can promote the rapid development of human liver cancer and produces hemorrhage in nude mice tumor[42]. Recently, abnormal upregulation of Ang-2 was detected in a model of normal hepatocyte malignant transformation to HCC. Compared with those in the NC group, there were 70 or 93 up- or down-regulated differentially expressed genes (DEGs) at the HD stage, with Ang-2, oxidoreductase, acid mercaptoenzyme activities, peptide antigens, cofactor binding, endoplasmic reticulum and endoplasmic reticulum membrane; 1015 or 437 DEGs at the PC stage, with Ang-2, growth factors, calcium-dependent phospho-lipids, alloproteins, VEGF, insulin-like growth factor binding, oxidoreductase, acid-mercaptoenzyme, microtubule cytoskeleton in centromeric region, plasma membrane, extracellular and spindle as the main components; and 1234 or 504 DEGs at the HCC stage, with Ang-2, organic sodium transporter, microtubule movement, protein dimerization activity, alloprotein, calcium ion and cytoskeleton protein binding in the extracellular fraction, microtubule cytoskeleton, VEGF, plasma membrane and cellular components. The specific concentration (in ng/mg of liver tissue) or serum concentration (in μg/L) of Ang-2 was quantitatively investigated from the NC group to the HD group at the early stage, the PC group at the middle stage, and the HCC group at the later stage[43]. In both the liver and blood, Ang-2 levels are dynamically up-regulated in early HCC to accelerate neovascularization to meet the need for oxygen, suggesting that Ang-2 signalling is a useful biomarker for monitoring the malignant progression of chronic liver diseases or molecular targeted therapy[39,44,45].

WNT3A SIGNALLING

The over-expression of some members in the Wingless (Wnt)/β-catenin pathway is related to HCC occurrence or progression[46,47]. Cancer-associated Wnt molecules regulate a variety of cellular events, such as cell proliferation, apoptosis, differentiation and HCC growth, *via* β-catenin-dependent classical or non-classical pathways[48,49]. Wnt3a (a

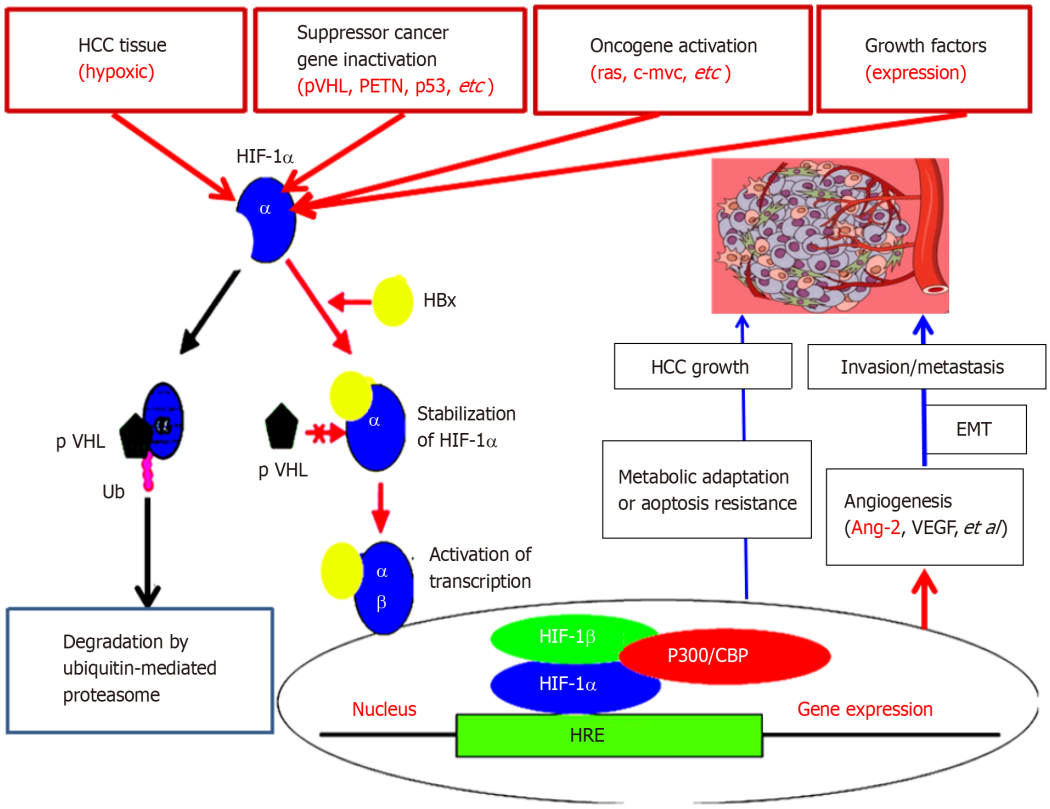

Figure 3 Abnormal angiopoietin-2 expression during hepatocarcinogenesis[37-39,43]. Neovascularization is a fundamental process involved in a variety of pathological processes that sustain the progression of hepatocellular carcinoma. angiopoietin-2 (Ang-2) is a key driver of tumour angiogenesis, and abnormal Ang-2 during hepatocarcinogenesis in rats is closely related to hepatic hypoxia. Ang-2 could be used as an early index to monitor the malignant transformation of hepatocytes. EMT: Epithelial-mesenchymal transition; HRE: Hypoxia-responsive element; VEGF: Vascular endothelial growth factor; HCC: Hepatocellular carcinoma.

member of the Wnt-type MMTV integration site family) is a critical signalling molecule among 19 mammalian Wnt proteins. Located on chromosome 17 (17q21) *Wnt3a* is regarded as a canonical Wnt pathway an activator (Figure 4), which induces β-catenin accumulation[50,51]. HBx in HBV-related HCC can inhibit GSK-3β activity *via* activating Src kinase, induce the accumulation of intracellular β-catenin and activating DNA methyltransferase I. Wnt3a can bind or silence secreted frizzled-related proteins (SFP) 1 or SFP5. In HBV-related HCC, HBx can promote HCC formation by activating the Wnt pathway and reduce the inhibiting role of deacetylase 1 on β-catenin[4,52,53]. Additionally, HCV core protein during HCC progression can induce Wnt3a expression and TCF-dependent transcription, with inhibiting GSK-3β production, increasing intracellular β-catenin to nuclear transport by upregulating c-myc, WISP2, cyclin Dl, Wnt1, Wnt3a and cTGF levels for HCC growth or DNA synthesis[54,55]. These studies indicated that Wnt3a has a key role in HCC with high expression.

High Wnt3a levels in the sera or tissues of HCC patients were reported for the first time in a cohort of cases with HBV-related chronic liver diseases. The incidence of oncogenic Wnt3a expression in the cancerous group reached 96.3%, which was significantly higher ($P < 0.001$) than that in the surrounding group[56]. Hepatic Wnt3a in liver tissues was brown staining with gradually up-regulated expression with clinical stage, especially in advanced HCC. Clinicopathological characteristics of liver Wnt3a up-regulation in HCC were associated with differentiation degree ($P < 0.001$), LC ($P < 0.004$), HBV infection ($P < 0.001$), high TNM stage ($P < 0.001$), and poor survival rate ($P < 0.001$). The levels of Wnt3a were investigated in the sera of 186 patients with chronic liver disease. The incidence of circulating Wnt3a levels more than > 800 ng/L was 92.5% in patients with HCC. It was significantly associated with AFP, LC, HBV, differentiation grade, TNM, and distal metastasis. Serum Wnt3a level was obviously higher ($P < 0.001$) in HCC cases than that in CH, LC or NC group[57,58]. Comparative analysis between serum Wnt3 and AFP, the diagnostic specificity was 94.34% *vs* 69.81%, and area under the receiver operating characteristic curve was 0.994 *vs* 0.710 for HCC, respectively. These data indicated that up-regulated Wnt3a expression be associated with HCC progression and higher Wnt3a be a new sensitive molecular marker for HCC diagnosis or differential diagnosis[59,60].

A dynamic model of rat hepatocarcinogenesis was successfully established to investigate the alteration of Wnt3a and its monitoring value in early HCC[61]. Based on liver pathological examination with HE staining, the rats were divided into the NC, HD, PC and HCC groups. The total number of DEGs that were up- or downregulated in the liver transcriptome with a signal log ratio more than 8. There were 55 or 48 genes in HD rats, 268 or 57 genes in PC rate, and 312 or 201 genes in HCC rats, respectively. Significantly up- or down-regulated DEGs from dynamic model rats were involved in liver cell proliferation, molecular signal transduction, cancer cell metastasis, and cell apoptosis. Also, the up-regulating expression of Wnt3a mRNA was 4.6-fold, 7.4-fold, and 10.4-fold higher ($P < 0.001$) in HD, PC and HCC rats than that in

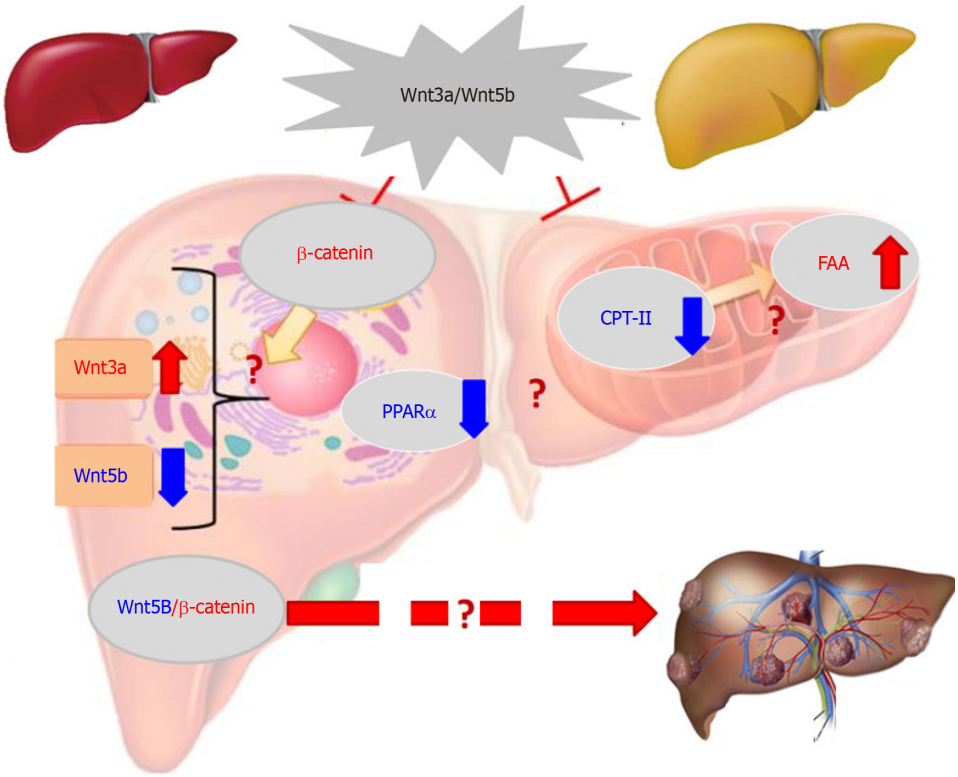

Figure 4 Abnormal activation of Wnt3a in hepatocarcinogenesis[49,53,56,57,61]. The Wnt/β-catenin signalling pathway contains 19 mammalian Wnt proteins. Wnt3a gene located on chromosome 17q21 is regarded as an activator of the canonical Wnt pathway, which induces β-catenin accumulation. An increase in Wnt3a is closely related to hepatocyte malignant transformation and could be a marker for monitoring hepatocarcinogenesis. FA: Fatty acid; PPARα: Peroxisome proliferation activated receptor α.

NC group. The percentages of positive Wnt3a were 66.7%, 100% and 100% from HD, PC and HCC rats, with significantly higher ($P < 0.001$) than that in NC rats. The serum Wnt3a levels (ng/mL) were 1.19 ± 0.22 in the NC group, 5.91 ± 2.28 in the HD group, 8.63 ± 2.76 in the PC group, and 9.60 ± 6.91 in the HCC group. These data indicate that elevated Wnt3a at the mRNA or protein level might be a useful marker for monitoring hepatocarcinogenesis[62,63].

HEPATIC GPC3 SIGNALLING

Carcinoembryonic GPC3 is a heparan sulfate proteoglycan that binds to cell membranes through glycosylphosphatidylinositol[64]. GPC3 is widely expressed in human embryos tissues, can't been detected in livers of healthy adult persons, but GPC3 is over-expressed in hepatocarcinogenesis[65]. However, because of the deficiency of the clinical analysis method of GPC3, it is very important to detect GPC3 accurately and sensitively for the diagnosis of liver cancer. Recently, new high-sensitivity GPC3 detection technologies based on a variety of optical sensors or electro-chemical technologies have been developed, providing new perspectives for the challenges and future development of the field and also contributing to the early detection of liver cancer[16,66,67]. For HCC, the discovery of GPC3 as a promising tumor-associated antigen because GPC3 is over-expressed in cancerous tissues and is significantly associated with poor prognostic disease-free survival and overall survival[67,68]. Indeed, clinical and basic studies have demonstrated that GPC3 is a carcinoembryonic proteoglycan anchored to the membrane of HCC cells and is involved in promoting HCC growth and invasion through a variety of signaling cascades; including the Wnt pathway, which plays a well-known role in embryogenesis[69,70]. It was found that the up-regulated expression of GPC3mRNA, gene or protein in the tissues or serum of patients with liver cancer could not only specifically diagnose liver cancer, but also had a bad prognosis with the patients with liver cancer[71].

Studies of the mechanisms by which GPC3 promotes HCC progression have shown that GPC3 functions by binding to molecules such as the Wnt/β-catenin signaling or growth factors in hepatocarcinogenesis[14,72]. In addition, because of the specificity of GPC3 for HCC, serum GPC3 detection has been used in the diagnosis, prognosis and molecular targeted therapy of liver cancer[73,74]. An HCC model in SD male rats induced with 0.05% 2-FAA was confirmed by HE staining. Hepatic GPC3mRNA was analyzed by quantitatively PCR or DNA sequencing. GPC3 up-regulation has been confirmed by animal model, with brown granule-like GPC3 positive expression localized in cytoplasm by IHC, and the pathological alterations of rat hepatocytes divided into HD, PC and HCC morphological stages, with a progressive increase in total RNAs or gamma-glutamyl transferase levels in livers. The positive rates of liver GPC3mRNA, liver GPC3 and serum GPC3 expression were 83.3% or 83.3% and 38.9% in the HD group, 100% or 100% and 66.7% in the PC group, 100% or 100% and 77.8% in the rat HCC group, respectively. None in livers or blood was founded in the NC group. Significantly

positive correlation was founded between hepatic liver GPC3 mRNA and total RNAs (r = 0.475), hepatic GPC3 (r = 1.0) or circulating GPC3 (r = 0.994), indicating that GPC3 is a useful marker for monitoring hepatocarcinogenesis[75].

GP73 SIGNALLING

Liver Golgi apparatus specific membrane GP73 (GOLPH2) is commonly found in epithelial cells containing GP73 mRNA transcripts (approximately 3.0 KB), the membrane consists of a short N-terminal cytoplasmic domain, a transmembrane domain and a larger C-terminal domain located on the surface of the lumen of the Golgi apparatus[76]. The bile duct epithelial cells expressed GP73 in normal liver. The overexpression of GP73 in liver has been proved to be closely related to the progression and poor prognosis of HCC[77]. Recent studies have shown that GP73 immunologically mediates chronic liver disease by enhancing sterol regulatory element binding protein (SREBP)-cleavage activating protein interactions to regulate steatosis; epithelial-mesenchymal transition and invasion are promoted through TGFβ1/ SMAD2 signaling activation and cause chemotherapy resistance in HCC. Increasing data suggest that GP73 is over-expressed in HCC tissues and subsequently secreted into the blood[77]. The levels of GP73 expression in HCC and their surrounding tissues were examined by IHC technology, and the survival time of HCC cases was analyzed by the univariate/ multivariate analysis. The GP73 expression in HCC tissues was significantly higher than that in non-HCC tissues, with a shorter survival rate, and the percentage of GP73 in HCC tissues was 53.3%, 84.0%, 84.6% and 60.0% from stage I to IV. Serum GP73 levels are significantly higher in HCC cases than those in cases with LC or CH, indicated that up-regulated GP73 might be a novel useful marker for HCC diagnosis or prognosis[78,79].

The GP73 expression in cancerous tissue is heterogeneous and inconsistent, especially for early stage HCC[80]. Dynamic models of hepatocarcinogenesis in SD rats were generated with a diet containing 2-FAA, and the rats were divided into the NC, HD, PC and HCC groups to observe alterations in GP73 at the protein or mRNA level during the malignant transformation of rat hepatocytes. There were no increases in hepatic GP73 expression at the protein or mRNA level in NC, 66.7% or 44.4% in HD, 88.9% or 77.8% in PC, and both 100% in HCC rats. There was a positive correlation (r = 0.91, P < 0.01) between liver GP73 and serum GP73 in rat hepatocarcinogenesis, indicating that abnormal GP73 levels are a sensitive and valuable biomarker in hepatocarcinogenesis[81,82].

LIVER SCLU SIGNALLING

Liver sCLU, located on chromosome 8q21-q12, is a heterodimeric sulfated glycoprotein that has cytoprotective roles and highly conserved among species[83]. The biological function of sCLU as a small-molecule chaperone is similar to that of heat shock protein[84]. Lots of basic medicine and clinical cases studies have confirmed that liver sCLU is low expression in normal liver tissues and gradually over-expressed during the malignant transformation of hepatocytes, which is closely associated with HCC progression by contributing to angiogenesis[85,86], chemoresistance[87-89], survival and distal metastasis[90,91]. The incidence of liver sCLU expression was up to 73.3% at stage I according to IHC results[92]. The sCLU expression at mRNA or protein level increases with HCC staging, indicating that sCLU abnormality could be a useful marker to differentiate benign or malignant liver diseases[93,94].

The up-regulating expression of sCLU at early stage is considered to promote HCC progression or exacerbate patient survival, which may be related to AKT/GSK-3β phosphorylation[95]. Up to now, increasing reports have confirmed that higher sCLU expression could be a novel diagnostic or prognostic marker for HCC, and this finding should be more important role in the individualized therapy for HCC[96,97]. Regulating signal pathways by sCLU could be critical for revealing MDR in HCC. Therefore, silencing sCLU or inhibiting sCLU expression by specific inhibitors have provided new mechanistic insight into HCC targeted-therapy in injected or orthotopic models[98], indicating that sCLU could be an early monitoring biomarker or potential molecular target for HCC therapy[99,100].

CONCLUSION

In conclusion, hepatocarcinogenesis is characterized by abnormalities in key signalling pathways activated by related pathways, accompanied by complex mechanisms such as DNA methylation or the regulation of noncoding RNAs[101,102]. Monitoring abnormal signalling during hepatocarcinogenesis in high-risk populations is helpful for the early detection or diagnosis of HCC (Table 1) and can be used for timely treatment of HCC patients. On the other hand, immunotherapy targeting specific signalling pathways can be combined with other effective ways to improve or prolong survival. Despite the multiomics rapid development, advances in gene silencing, genetic engineering, molecular pharmacology or pathology, DNA splicing, transcription interference and monoclonal antibodies are expected to increase specificity and decrease side effects of immunotherapy. This technology can directly block signal molecules involved in HCC growth or molecular targets, such as radionuclides, drug carriers and immunotherapies, and might play a unique role in increasing effect of HCC treatment.

Table 1 Summary of univariate and multivariable analysis of overall survival for hepatocellular carcinoma

Variables	Univariate analysis		Multivariable analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
HMGB3[32]				
Tumor diameter: ≤ 5 *vs* > 5 cm	1.863 (1.300-2.671)	< 0.001	1.400 (0.964-2.034)	0.077
TNM stage: I/II *vs* III/IV	3.870 (2.373-6.309)	< 0.001	2.471 (1.350-4.525)	0.003
HMGB3 expression: High *vs* low	3.658 (2.208-6.061)	< 0.001	3.042 (1.809-5.115)	< 0.001
Ang-2[39]				
Tumor diameter: ≤ 2 *vs* > 2 cm	1.704 (0.994-2.921)	0.052	1.120 (0.622-2.015)	0.706
TNM stage: I/II *vs* III/IV	1.690 (1.283-2.228)	< 0.001	1.531 (1.041-2.252)	0.030
Ang-2 expression: High *vs* low	3.080 (1.742-5.466)	< 0.001	3.144 (1.738-5.689)	< 0.001
Wnt3a[56,57]				
Tumor diameter: ≤ 2 *vs* > 2 cm	2.056 (1.056-4.089)	0.030	2.018 (1.058-3.912)	0.031
TNM stage: I/II *vs* III/IV	0.686 (0.328-1.436)	0.318	NA	NA
Wnt3a expression: High *vs* low	5.656 (2.682-11.926)	< 0.001	3.651 (1.973-6.757)	< 0.001
GPC-3[73]				
Tumor diameter: ≤ 3 *vs* > 3 cm	2.011 (1.498-3.869)	0.034	NA	NA
TNM stage: I/II *vs* III/IV	1.961 (1.443-2.486)	< 0.001	NA	NA
GPC-3 expression: High vs low	12.697 (3.097-52.050)	< 0.0001	4.259 (2.030-8.934)	< 0.001
GP73[78,79]				
Tumor diameter: ≤ 2 *vs* > 2 cm	0.990 (0.506-1.938)	0.978	NA	NA
TNM stage: I/II *vs* III/IV	0.231 (0.121-0.440)	< 0.001	0.221 (0.114-0.426)	< 0.001
GP73 expression: High *vs* low	1.008 (1.002-1.014)	0.005	0.477 (0.272-0.837)	0.010
sCLU[92,95]				
Tumor diameter: ≤ 5 *vs* > 5 cm	1.758 (0.987-2.968)	0.036	NA	NA
TNM stage: I/II *vs* III/IV	3.056 (1.756-5.321)	< 0.001	1.474 (0.589-3.690)	0.407
sCLU expression: High *vs* low	2.030 (0.987-4.175)	0.004	NA	NA

Ang-2: Angiopoietin-2; CI: Confidence interval; GP73: Golgi protein 73; GPC-3: Glypican-3; HMGB3: High mobility group-box 3; HR: Hazard ratio; NA: Not available; Sclu: Secretory clusterin; TNM: Tumor node metastasis; Wnt3a: One of the signaling molecules in the Wnt/β-catenin pathway.

FOOTNOTES

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