

## Encouraging specific biomarkers-based therapeutic strategies for hepatocellular carcinoma

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### Abstract

The prevention, early discovery and effective treatment of patients with hepatocellular carcinoma (HCC) remain a global medical challenge. At present, HCC is still mainly treated by surgery, supplemented by vascular embolization, radio frequency, radiotherapy, chemotherapy and biotherapy. The application of multikinase inhibitor sorafenib, chimeric antigen receptor T cells, or PD-1/PD-L1 inhibitors can prolong the median survival of HCC patients. However, the treatment efficacy is still unsatisfactory due to HCC metastasis and postoperative recurrence. During the process of hepatocyte malignant transformation, HCC tissues can express and secrete many types of specific biomarkers, or oncogenic antigen molecules into blood, for example, alpha-fetoprotein, glypican-3, Wnt3a (one of the key signaling molecules in the Wnt/ $\beta$ -catenin pathway), insulin-like growth factor (IGF)-II or IGF-I receptor, vascular endothelial growth factor, secretory clusterin and so on. In addition, combining immunotherapy with non-coding RNAs might improve anti-cancer efficacy. These biomarkers not only contribute to HCC diagnosis or prognosis, but may also become molecular targets for HCC therapy under developing or clinical trials. This article reviews the progress in emerging biomarkers in basic research or clinical trials for HCC immunotherapy.

**Key Words:** Hepatocellular carcinoma; Immunotherapy; Carcinoembryonic proteins; Specific biomarkers; Wnt/ $\beta$ -catenin pathway; Signal molecules

**Core Tip:** Tissues in hepatocellular carcinoma (HCC) or hepatocyte malignant transformation can express and secrete a variety of molecules such as specific biomarkers or oncogenic antigens into blood. These biomarkers not only contribute to the diagnosis or prognosis of HCC, but may also become molecular targets for HCC therapy under developing or clinical trials. This article reviews the recent novel progress of some emerging biomarkers in basic studies or clinical trials for HCC immunotherapy.

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## INTRODUCTION

The prevention, early monitoring or diagnosis and accurate or effective treatment of hepatocellular carcinoma (HCC) are still urgent medical problems[1,2]. The occurrence of HCC is mainly associated with chronic persistent infection of hepatitis B virus (HBV) or hepatitis C virus (HCV), intake of chemical carcinogens, and nonalcoholic fatty liver disease (NAFLD)[3]. In the past decade, NAFLD has become a leading cause of chronic hepatitis and liver cirrhosis, as well as an important risk factor for HCC[4]. Innate and adaptive immunity play a pivotal role in determining tumor control *vs* progression. Genomic instability and abnormal signaling in the setting of chronic liver inflammation that promotes fibrogenesis and angiogenesis lead to tumorigenesis, and it is necessary to determine how they may be exploited in the development of novel therapeutics[5]. The activation of oncogenes or HCC-related genes, inactivation of anti-oncogenes or activation of some oncogenes during the embryonic period can induce malignant transformation of hepatocytes[5], many types of specific markers can be expressed, and then secreted into blood during the process of initiation, promotion and evolution[1]. Notably, HCC oncoimmunology depends on diverse genetic and environmental factors that together shape cancer-promoting inflammation and immune dysfunction-critical processes that control HCC malignant progression and response to therapy[6,7].

Currently, HCC is still treated mainly by surgery, with auxiliary vascular embolization, radio frequency, radiotherapy, chemotherapy, and biological therapy[8,9]. Application of the multikinase inhibitor sorafenib can prolong the median survival of HCC patients. However, its efficacy in HCC treatment remains unsatisfactory due to tumor metastasis or postoperative occurrence[10,11]. Undoubtedly, the integration of data obtained from both preclinical models and human studies can help to accelerate the identification of robust predictive biomarkers of response to targeted or immunotherapy[12,13]. HCC tissues express specific antigens such as the key molecules of HCC-related signal pathways, growth factors and receptors, vascular endothelial growth factor (VEGF), and the products of oncogenes that mediated tumor progression and could be potential molecular targets for anti-cancer therapy with high specificity and application prospects[14,15]. This review presents new advances in a few promising carcinoembryonic biomarkers for HCC immunotherapy from basic studies or clinical trials.

## ALPHA-FETOPROTEIN

A glycoprotein of alpha-fetoprotein (AFP) synthesized from fetal liver or HCC tissues[16], consisting of 609 single-chain amino acid polypeptides and containing 24 leading signal points (9 ~ 10 amino acid) residues located in three N-terminal domains, the major histocompatibility complex (MHC) class I or II molecules recognize these precursor signals and present them to CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells, and the activated T cells recognize the body's immunodominant or sub-immunodominant epitopes[17]. Amino acid peptide sequences and immunogenicity of human AFP epitopes are shown in Table 1. These immunogenic or sub-immunogenic AFP peptide chains could play an immunomodulatory role in humans, as they have the function and ability of a polypeptide vaccine, and could induce or stimulate anti-AFP specific immune responses.

AFP peptide chains have several fragments showing immunodominant or sub-immunodominant epitopes, which can be recognized by the MHC-I molecules, and specifically induce T cells to activate or recognize AFP antigen. AFP positive peripheral blood mononuclear cells (PBMC) containing five human leukocyte antigen (HLA)-A\*24:02 restricted T cell epitopes, AFP-derived peptide induces cytotoxic T lymphocytes (CTL) to produce interferon- $\gamma$  (INF- $\gamma$ ), which can kill AFP-positive cancer cells.

Table 1 Amino acid peptide sequences and immunogenicity of alpha-fetoprotein epitopes

No.	Starting	Numbers	Fragment	Immunogenicity
1	7	9	IFLIFLLNF	Sub-immunodominant Ag
2	137	9	PLFQVPEPV	Immunodominant Ag
3	150	9	AYEEDRETF	Sub-immunodominant Ag
4	158	9	FMNKFIYEI	Immunodominant Ag
5	218	9	LLNQHACAV	Sub-immunodominant Ag
6	235	9	FQAITVTKL	Sub-immunodominant Ag
7	249	10	KVNFTEIQKL	Immunodominant Ag
8	307	9	TTLERGQCII	Sub-immunodominant Ag
9	321	9	KPEGLSPNL	Immunodominant Ag
10	325	10	GLSPNLNRFL	Immunodominant Ag
11	357	9	EYSRRHPQL	Immunodominant Ag
12	364	10	QLAVSVILRV	Immunodominant Ag
13	403	9	KYIQESQAL	Immunodominant Ag
14	414	9	RSCGLFQKL	Immunodominant Ag
15	424	9	EYYLQNAFL	Immunodominant Ag
16	434	9	AYTKKAPQL	Immunodominant Ag
17	485	10	CIRHEMTPV	Sub-immunodominant Ag
18	492	9	PVNPGVGQC	Sub-immunodominant Ag
19	503	9	SYANRRPCF	Sub-immunodominant Ag
20	507	10	NRRPCFSSLV	Sub-immunodominant Ag
21	542	9	GVALQTMKQ	Immunodominant Ag
22	547	10	TMKQEFLINL	Sub-immunodominant Ag
23	555	9	NLVKQKPQI	Sub-immunodominant Ag
24	591	9	CFAEEGQKL	Sub-immunodominant Ag

Ag: Antigen; Fragment: Fragment of alpha-fetoprotein (AFP) peptide chain; Numbers: Amino acid numbers of AFP peptide chain; Starting: Starting point of AFP peptide chain.

Although it has been shown in clinical trials, the function of dendritic cells (DC), specific CTL, and CD8<sup>+</sup> T cell response, targeting therapy for AFP positive cancer cells remains to be studied. The T cell receptor (TCR) has been prepared by induction and screening *in vitro*, which can specifically recognize and bind AFP/HLA-A\*02 antigen that is restricted to AFP158-166 peptide (FMNKFIYEI) to lay the foundation for HCC immuno-therapy[18]. A novel HLA-A\*24:02 antigen was found to be more common than the HLA-A\*02:01 among Asian HCC patients. Its restrictive peptide (KWVESIFLIF, AFP2-11 signal) was found to be soluble in healthy human monocyte AFP 2-11-HLA-A\*24:02-specific TCR (KWV3.1). T cells could be activated specifically and kill AFP-positive T2-A24 HCC cells that contained AFP 2-11 and HLA-A\*24:02<sup>+</sup> antigen, indicating that AFP+HLA-A\*24:02<sup>+</sup> antigen might be a new immunotherapeutic target for HCC[19].

The combination of anti-CTL-A-4 therapy (tremelimumab) together with ablation in advanced HCC cases has shown that killing tumors by direct methods can result in the immune system being activated or switched on. There are new drugs available known as immune checkpoint inhibitors (ICIs) which can enhance the anti-HCC effect. In patients treated with tremelimumab, blood CD4<sup>+</sup>-HLA-DR<sup>+</sup>, CD4<sup>+</sup>PD-1<sup>+</sup>, CD8<sup>+</sup>HLA-DR<sup>+</sup>, CD8<sup>+</sup>PD-1<sup>+</sup>, CD4<sup>+</sup>ICOS<sup>+</sup>, and CD8<sup>+</sup>ICOS<sup>+</sup> T cells increased, the patients with higher CD<sup>+</sup>PD-1<sup>+</sup> cells responded well to treatment, with increasing specific CD8<sup>+</sup>PD-1 T cells for AFP and survivin, and higher CD3<sup>+</sup>T cells for tumor infiltration, suggesting that tremelimumab with ablation is a novel potential method for increasing CD8<sup>+</sup> T cells and decreasing circulating HCV, and an effective therapy for advanced HCC patients[20].

## ANGIOGENIC FACTORS

Most patients with HCC are diagnosed at an advanced stage of disease. Until recently, systemic treatment options that showed survival benefits in HCC have been limited to tyrosine kinase inhibitors, antibodies targeting oncogenic signaling pathways or VEGF receptors[21]. Angiogenesis plays an important role in HCC progression, and VEGF and angiopoietin (Ang) are key drivers of tumor angiogenesis. A better understanding of the relation between VEGF and angiogenesis or progression may reveal their potential as biomarkers for liver cancer diagnosis and therapy. VEGF-targeting strategies already represent an important component of today's systemic treatment for HCC, whereas targeting the Ang/Tie2 signaling pathway may harbor future potential in this context due to reported beneficial anticancer effects when targeting this pathway[22,23]. Following a decade of negative Phase III trials since the approval of sorafenib, more recently several drugs have proven efficacy both in first line *vs* sorafenib (lenvatinib) or in second line *vs* placebo (regorafenib, cabozantinib, ramucirumab/Cyramza®). A fully human anti-VEGFR-2 recombinant IgG1 monoclonal antibody (ramucirumab) has been approved as monotherapy for HCC patients with AFP levels over 400 ng/mL who have been treated with sorafenib, with significantly prolonged overall survival (OS) and progression-free survival. Its safety profile was consistent with that expected for agents targeting the VEGF/VEGFR axis. The potential clinical development of systemic treatments for HCC, focuses on combination therapies with immunotherapy and treatment sequences as a way to maximize survival benefit[24,25].

The HCC microenvironment is characterized by dysfunction of the immune system through multiple mechanisms, including accumulation of various immunosuppressive factors, recruitment of regulatory T cells and myeloid-derived suppressor cells, and induction of T cell exhaustion accompanied by the interaction between immune checkpoint ligands and receptors. ICIs interfere in this interaction and have altered the therapeutic landscape of multiple cancer types including HCC. HCC patients with different levels of liver function, tumor size, and number of lesions may all have intermediate-stage disease according to the BCLC staging system. Their treatment includes conventional or drug-eluting bead transarterial chemoembolization, yttrium-90 radioembolization, thermal ablation, bland embolization, and combination therapy with VEGF inhibitors or ICIs. Clinical evidence supports the available locoregional treatment options for intermediate-stage HCC[26]. Although optimal sequencing is an area of ongoing investigation, multiple targeted therapies have improved OS in intermediate or advanced HCC[27]. Several targeted agents including multi-tyrosine kinase inhibitors and immunotherapy agents have been approved for use beyond the frontline setting in advanced HCC patients, and combining therapeutic strategies is an evolving approach showing early promise[23,28]. The success of PD-1 monotherapy, combining regimens with PD-1/PD-L1 inhibitors plus VEGF targeted agents has shown positive results in various malignancies including HCC. These innovative approaches enhance the intensity of cancer-directed immune responses and will potentially impact the outcome of this aggressive disease[29].

## GLYPICAN-3

With regard to HCC, a promising antigen appears to be glypican-3 (GPC3) which is over-expressed in HCC tissues and has been associated with worse disease-free survival and OS. GPC3 is involved in many signaling cascades that promote cell growth and invasion, including the Wnt pathway that is well-known for its role in embryogenesis. GPC3 as an oncofetal proteoglycan anchored to the cell membrane of HCC, and is normally detected in the fetal liver but not in the healthy adult liver[30,31]. However, abnormal GPC3 in tissues or sera of HCC patients is expressed as GPC3 mRNA gene transcription or protein levels, and predicts a poor prognosis of HCC. Mechanistic studies have revealed that GPC3 functions by binding to molecules such as the Wnt/ $\beta$ -catenin signaling or growth factors during HCC formation and progression. Moreover, specific serum GPC3 has been used as a diagnostic or prognostic serological marker, and a molecular target for molecular imaging or therapeutic intervention in HCC[32-34]. GPC3 as a molecular target for HCC immunotherapy is shown in Table 2. To date, GPC3-targeted magnetic resonance imaging, positron emission tomography, and near-infrared imaging have investigated the early stage of HCC, and immunotherapeutic protocols targeting GPC3 have been developed, including the use of humanized anti-GPC3 cytotoxic antibodies, peptide/DNA vaccines, immuno-toxin therapies, and genetic therapies.

Different synergisms have been postulated based on the potential interplay between anti-angiogenic drugs and immunotherapy, with several clinical trials currently ongoing. As the most extensively tested combination regimens for advanced HCC comprise anti-PD-1/anti-PD-L1 agents plus anti-angiogenic agents, oncogenic GPC3 is an ideal promising candidate for HCC immunotherapy as it is highly expressed in cancerous tissues but limited in normal livers. Recently, the adoptive transfer of hGPC3-specific chimeric antigen receptor T (CAR-T) cells for HCC treatment has been conducted in clinical trials. Due to rigid construction, conventional CAR-T cells have some intrinsic limitations, such as uncontrollable overactivation and inducing severe cytokine release syndrome. By using co-culturing assays and a xenograft mouse model, the *in vitro* and *in vivo* cytotoxicity and cytokine release of the split

Table 2 Glypican-3 as molecule-target for hepatocellular carcinoma immunotherapy

Group	Name	Species	Epitopes	Verifying/applying
Antibody	M18D04/19B11	Mouse	N-terminal (aa: 25-358)	Basic studies
	A1836A	Mouse	N-terminal	Basic studies
	GPC3-C02	Mouse	C-terminal	Basic studies
	GC33	Mouse	C-terminal (aa: 524-563)	Preclinical trial studies
	hGC33	Human	C-terminal (aa: 524-563)	Clinical trial-II
	HS20	Human	Heparan sulfate chain	Preclinical trial
	sGPC3	Human	–	Preclinical trial
Vaccines	GPC3 <sub>298-306</sub>	Mouse	298-306 peptide	Clinical trial-II
	GPC3 <sub>144-152</sub>	Mouse	144-152 peptide	Clinical trial-II
miRNA	miR-219-5p	Human	–	<i>In vitro</i> or <i>in vivo</i> studies
	miR-520c-3p	Human	–	<i>In vitro</i> studies
	miR-1271	Human	–	<i>In vitro</i> studies
shRNA	GPC3 shRNA	Human	–	<i>In vitro</i> or <i>in vivo</i> studies
siRNA	GPC3 siRNA	Human	–	<i>In vitro</i> or <i>in vivo</i> studies

GPC-3: Glypican-3; aa: Amino acid; miR: MicroRNA; shRNA: Small hairpin RNA; siRNA: Small interfering RNA.

anti-hGPC3 CAR-T cells were evaluated against various HCC cell lines and compared with conventional CAR-T cells. *In vitro* data demonstrated that split anti-hGPC3 CAR-T cells could recognize and lyse hGPC3-positive HepG2 or Huh7 cells in a dose-dependent manner. Impressively, the split anti-hGPC3 CAR-T cells produced and released a significantly lower amount of pro-inflammatory cytokines, including IFN- $\gamma$ , TNF- $\alpha$ , IL-6, and GM-CSF, than conventional CAR-T cells. When injected into immune-deficient mice inoculated subcutaneously with HepG2 cells, the split anti-hGPC3 CAR-T cells could suppress HCC growth, but released significantly lower levels of cytokines than conventional CAR-T cells. The split anti-hGPC3 CAR-T cells reduced the level of cytokine release, and represent a more versatile and safer alternative to conventional CAR-T cells for HCC treatment[35,36]. The most recent data indicate novel combination strategies and targets, and a future role for molecular therapies in the treatment of advanced HCC. Current barriers in CAR-T therapy include its high production cost and the need to identify validated extracellular HCC-specific antigens[33,37].

## WNT3a

Several signaling pathways involved in HCC have been studied, including STAT3- NF $\kappa$ B, JAK-STAT, RAS MAPK, PI3K-AKT-mTOR and Wnt- $\beta$ -catenin. Of these, cascades involving mitogen-activated protein kinase (MAPK) emerge as key regulators of HCC. Both HBV and HCV infection can induce activation of the Wnt/ $\beta$ -catenin signal pathway and participate in HCC progression[38,39]. Oncogenic HBx of HBV can activate Src kinase to inhibit GSK3 activity and induce intracellular  $\beta$ -catenin accumulation, promote DNA methyl-transferase I expression and Wnt3a to bind and silence secreted frizzled related protein 1 and 5[40]. HBx can reduce the inhibitory role of deacetylase 1 to  $\beta$ -catenin, and activation of the Wnt pathway promotes HCC development[41]. Also, the core protein of HCV can promote Wnt3a expression, induce TCF dependent transcription, inhibit GSK3, increase and stabilize intracellular  $\beta$ -catenin to nucleus transport, and up-regulate the expression of cyclinD1, c-myc, WISP2, Wnt3a, Wnt1 and CTGF to promote HCC growth, and DNA synthesis for HCC progression[42]. Wnt3a is a critical signal molecule among the 19 mammalian Wnt proteins. A higher level of Wnt3a expression was only found in the sera or tissues of HCC patients from a cohort of cases with chronic liver diseases [43,44], and it is the first report of Wnt3a as a novel specific marker for HCC diagnosis and prognosis[45, 46].

Abnormal Wnt3a expression is involved in the development and metastasis of HCC[47], and may be a novel strategy for HBV or HCV-related HCC therapy. High hepatic LINC00662 correlated with poor survival of HCC patients[48,49], and might up-regulate Wnt3a expression by competitively binding miR-15a, miR-16 and miR-107, with tumor-associated macrophages as a major component of the HCC microenvironment, and they have been revealed to have associations with Wnt3a signaling and cancer initiation, tumor growth, metastasis, dormancy, immunity and tumor stem cell maintenance[40]. Wnt3a

is one of HCC-related Wnt signals exhibiting numerous genetic abnormalities as well as epigenetic alterations including modulation of DNA methylation. Targeted *Wnt3a* gene transcription might be an effective molecule-targeted therapy. The novel Crispr/Cas9-gsRNA lentiviral vector system with the advantages of higher targeting accuracy has been successfully used to inhibit *Wnt3a* in liver cancer cell lines at the mRNA level *in vitro* and confirmed at the protein level *in vivo* in transplanted tumor studies [44,50].

The inhibitory effect of *Wnt3a* on the proliferation of HCC cells or HCC xenograft growth has been demonstrated and interfering with *Wnt3a* could significantly inhibit the expression of down-stream  $\beta$ -catenin and related-signal molecules[51]. The xenograft model of knockout *Wnt3a* in HepG2 cells resulted in slower growth, and a significant reduction in tumor size or loss of weight. The molecular mechanism of the *Wnt3a* cascade reaction involving multiple targets, can block upstream GPC-3 signals and downstream  $\beta$ -catenin to nucleus transport[52,53], and inhibiting or delaying HCC progression can be carried out using specific antibodies (OMP-54F28, OTSA101)[54] and small size peptide SAH-BCL-9 [55]. The abnormal liver or circulating *Wnt3a* in HCC has provided initial evidence, and the tumor volume after intervening in *Wnt3a* mRNA transcription with specific shRNA was  $355.0 \pm 99.9 \text{ mm}^3$  in the intervention group which was significantly lower than that ( $869.4 \pm 222.5 \text{ mm}^3$ ) in the negative group, and the time to tumor formation in the intervention group was longer than that in the negative group; the tumor weight ( $0.35 \pm 0.11 \text{ g}$ ) in the intervention group was markedly lower than that ( $0.88 \pm 0.20 \text{ g}$ ) in the negative group. Immunohistochemistry confirmed that *Wnt3a* was strongly inhibited in the intervention group[56], and indicated that targeted-*Wnt3a* signaling could result in effective inhibition of HCC growth.

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## CLUSTERIN

Secretory clusterin (sCLU) is a stress-induced heterodimer sulfated glycoprotein, located on chromosome 8q21-q12, which is highly conserved between species and has a cytoprotective effect. Its biological function as a small molecule partner is almost similar to that of heat shock protein[57]. Basic and clinical studies have shown that sCLU expression was low in normal liver tissues and its activation during the malignant transformation of hepatocytes was progressively over-expressed[58,59], which was closely associated with HCC progression by contributing to angiogenesis, chemo-resistance, cell survival, and metastasis[60]. The positive rate of hepatic sCLU expression was up to 73.3% in stage I HCC by immunohistochemical analysis. Its expression at the mRNA or protein level was increased with clinical staging of HCC, which indicated that sCLU could be a biomarker for differentiating benign from malignant liver diseases[61].

Recurrence and metastasis after hepatectomy are the main causes of poor prognosis of HCC[62]. Hepatic sCLU plays an important role in the proliferation, multidrug resistance, invasion and metastasis of HCC cells[63,64]. sCLU mediated the expression of MMP-2, p-AKT and E-cadherin in HCC BEL-7402 or SMMC-7721 cell lines, and down-regulating sCLU expression can significantly reduce the invasive ability of HCC cells by the selective COX-2 inhibitor meloxicam plus specific sCLU-shRNA plasmids[65, 66]. These data indicated that sCLU is a new effective target for the occurrence, invasion and metastasis of HCC, and should have a bright future in HCC immunotherapy.

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## INSULIN-LIKE GROWTH FACTOR AXIS

The hepatic insulin-like growth factor (IGF) axis contains ligands, receptors, substrates, and ligand binding proteins. Accumulating data have demonstrated that aberrant IGF signaling might lead to malignant transformation of hepatocytes or HCC progression, in particular, IGF-II or IGF-I receptor (IGF-IR) are key molecules in hepatocarcinogenesis[67] or rat xenograft models[68], and affect the molecular pathogenesis of HCC, thus providing the rationale for targeting the IGF axis in HCC[69]. The biological activities of IGF-II or IGF-IR not only promote HCC cell proliferation or xenograft growth, but also confer resistance to standard treatments[70]. Several strategies targeting this system including monoclonal antibodies against IGF-1R or small molecule inhibitors of the tyrosine kinase function of IGF-1R are under active investigation. For example, DX-2647, a recombinant human antibody, potently neutralizes the action of IGF-II, which is overexpressed in HCC[71] and impairs xenograft growth of the Hep3B but not HepG2 cell line with high p-STAT3 levels, suggesting that STAT3 activation is one pathway that mediates resistance to IGF-II-targeted therapy in HCC[72].

The over-expression of hepatic IGF-IR in human HCC promotes HCC cell proliferation, and attaching importance to IGF-IR might improve the prognostic or therapy of HCC[73]. Enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) is a regulator of promoted IGF-IR induced sorafenib resistance of HCC *in vitro* by directly transcriptionally repressing a set of microRNAs including miR-101, miR-122, miR-125b, and miR-139[74-76]. A model of an EZH2-miRNAs-IGF-IR regulatory axis might provide insights into how to reverse sorafenib resistance in HCC. Silencing the IGF-IR gene by a specific shRNA to induce inhibition of cell proliferation *in vitro* or rat xenograft growth *in vivo* may be a

novel molecular-targeted therapy for HCC. Several strategies targeting this system including monoclonal antibodies against IGF-IR and inhibitors of the tyrosine kinase function of IGF-IR are under active investigation. Gene-specific shRNA against IGF-signaling molecules as well as IGF-IR selective receptor tyrosine kinase (RTK)-inhibitors (tyrphostins) may therefore offer new therapeutic options[77, 78]. However, as a specific shRNA is currently not applicable in HCC therapy, selective RTK-inhibitors represent the most promising approach for future therapeutic strategies.

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## SYNERGY OF NON-CODING RNAS

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While immunotherapy holds great promise for combating cancer, its limited efficacy due to an immunosuppressive tumor microenvironment and systemic toxicity hinder the broader application of immunotherapy[79,80]. Combinatorial immunotherapy approaches that use a highly efficient and tumor-selective gene carrier can improve anticancer efficacy and circumvent the systemic toxicity. HCC is one of the multi-genetic diseases, and multiple studies have highlighted the key roles of noncoding RNAs (ncRNAs) in the chemo-resistance of HCC such as biomarkers and functional modulation of the cellular response to sorafenib[81-83]. Targeted chemotherapeutic agent, sorafenib, is known to show a statistically significant but limited OS advantage in advanced HCC, linked with the modulation of several intracellular signaling pathways through diverse operating biomolecules including ncRNAs[84-86]. Accumulated evidence has demonstrated that ncRNAs (miRNAs, long ncRNAs or lncRNAs, and circular RNA or circRNA) could serve as biomarkers in the diagnosis, prognosis, and treatment of HCC [87,88] and have been well-documented to participate in HCC progression with promoting or inhibiting roles[89,90].

Interestingly, varied responses to miRNAs have been linked with the modulation of several intracellular signaling pathways[91]. An abnormality of miR-218 expression was investigated in human HCC tissues or HCC cell lines to evaluate its function and the underlying mechanisms of HCC. Gain-of-function and loss-of-function assays indicated forced expression of miR-218 by inhibited HCC cell migration/invasion and reversed epithelial-mesenchymal transition to mesenchymal-epithelial transition. Serpine mRNA binding protein 1 (SERBP1) is a target gene of miR-218, and targeting the miR-218/SERBP1 signal pathway that inhibits malignant phenotype formation might be a potential novel strategy for HCC therapeutics, as miR-218 functions as a HCC suppressor and is involved in many biological processes such as tumor initiation, development, and metastasis[92]. Nanotechnology-enabled dual delivery of siRNA and plasmid DNA that selectively targets and reprograms the immunosuppressive tumor microenvironment has been shown to improve HCC immunotherapy[93-95].

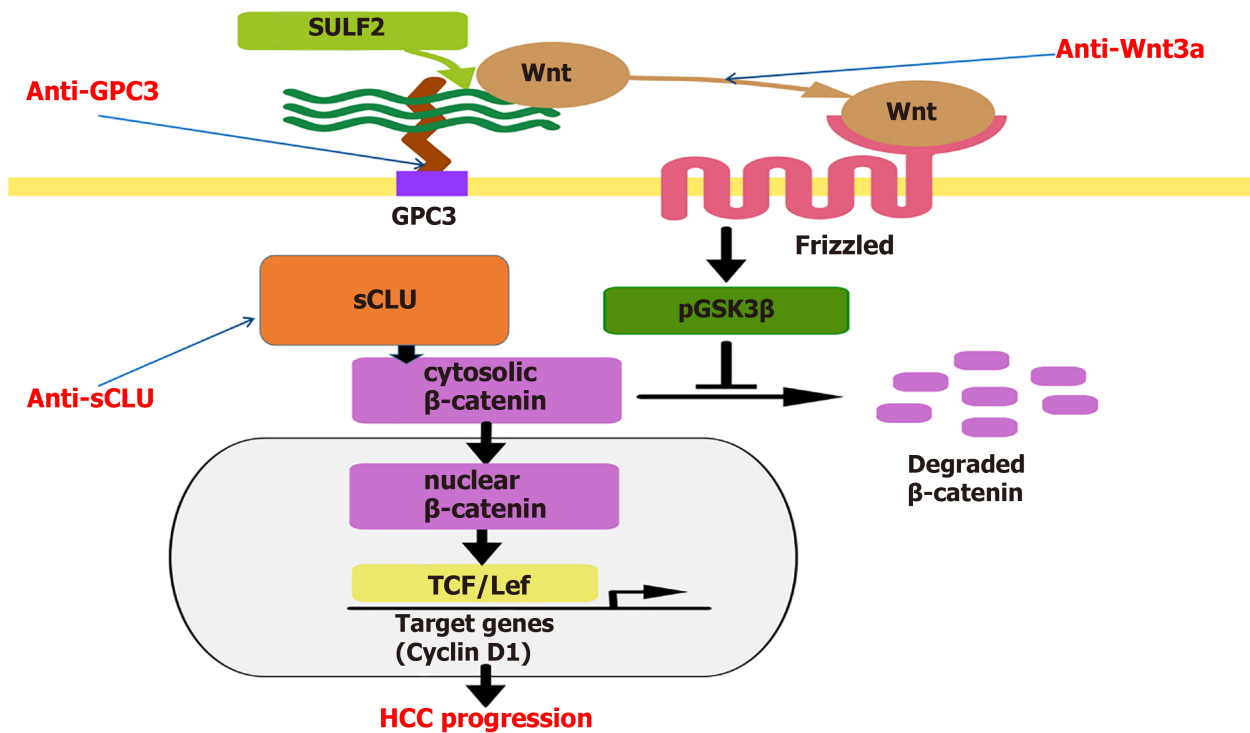
HCC-associated circRNAs are abundant, and their over/low expression might promote/inhibit HCC cell proliferation or tumor growth[96-98]. An abnormality of circ-homer1 in HCC cells or tissues was related to tumor size, lymph node metastasis, high clinical staging and poor prognosis. The mechanism of circ-homer1 over-expression promoted HCC growth or invasiveness *via* the mir-1322/cxc16 axis[99]; conversely, interfering with circ-homer1 activation inhibited the proliferation, migration and invasion of liver cancer cells *via* apoptosis. The circ-0051443 from circulating exosomes or HCC tissues regulated BAK1 expression by combining with mir-331-3p to promote cell apoptosis or cell cycle arrest in HCC, and inhibit the biological behavior of HCC cells *in vivo* or nude mice HCC xenografts[100]. Another interesting study also showed that has\_circ\_0008450 expression in HCC tissues or cells might inhibit HCC progression by regulating the mir-214-3p/ezh2 axis[101,102]. These data suggested that specific ncRNAs were useful molecular targets for HCC therapy.

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## CONCLUSION

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In conclusion, HCC is a multi-gene variant malignant tumor with DNA methylation, microRNA, lncRNA expression and immune response[103]. Immunotherapy for HCC has begun to produce better results, and HCC-specific molecules may be combined with comprehensive interventions such as surgery, interventional therapy, radiotherapy, and chemotherapy to improve the efficacy and prolong the survival time of HCC patients[104]. Despite the rapid development of genomics and proteomics, advances in molecular pathology, pharmacology and genetic engineering, DNA splicing, gene silencing, transcription interference, and monoclonal antibodies for more specific and less side effects immune therapy techniques[105] that can directly block the signaling molecules involved in HCC growth related signaling pathways (Figure 1) or serve as molecular targets such as radionuclide, drug carriers, and immunotherapy play a unique role in the specific or comprehensive treatment of HCC.



**Figure 1** Some signals in the Wnt/ $\beta$ -catenin pathway by anti-signaling antibodies or intervening in their gene transcription to inhibit hepatocellular carcinoma growth. Using anti-signaling molecule antibodies or intervening in their gene transcription to inhibit Wnt/ $\beta$ -catenin pathway activation could suppress proliferation of hepatocellular carcinoma (HCC) cells or HCC growth. GPC-3: Glypican-3; HCC: Hepatocellular carcinoma; sCLU: Secretory clusterin; TCF: T-cell factor; SULF2: Sulfatase 2; pGSK3 $\beta$ : Phosphorylated glycogen synthase kinase 3 $\beta$ .

## FOOTNOTES

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