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ABOUT COVER

Editorial board member of *World Journal of Clinical Oncology*, Dr. Takura is a Project Professor in the Department of Healthcare Economics and Health Policy, Graduate School of Medicine, University of Tokyo, Japan. He is part-time Research Fellow of the Cabinet Office and Chairman of the Specialized Agency of Cost-effectiveness Evaluation, Ministry of Health, Labour and Welfare. Dr. Takura also serves as a Guest Professor at Osaka University Graduate School of Medicine. Dr. Takura's research has focused on socioeconomic evaluation of cancer treatments and renal transplantation, and cost effectiveness analysis of revascularization for ischemic heart disease. His current approach to this work involves integrating big data from various sources. (L-Editor: Filipodia)

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REVIEW

Novel molecular targets in hepatocellular carcinoma

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Abstract

Globally, hepatocellular carcinoma (HCC) is a leading cause of cancer and cancer-related deaths. The therapeutic efficacy of locoregional and systemic treatment in patients with advanced HCC remains low, which results in a poor prognosis. The development of sorafenib for the treatment of HCC has resulted in a new era of molecular targeted therapy for this disease. However, the median overall survival was reported to be barely higher in the sorafenib treatment group than in the control group. Hence, in this review we describe the importance of developing more effective targeted therapies for the management of advanced HCC. Recent investigations of molecular signaling pathways in several cancers have provided some insights into developing molecular therapies that target critical members of these signaling pathways. Proteins involved in the Hedgehog and Notch signaling pathways, Polo-like kinase 1, arginine, histone deacetylases and Glypican-3 can be potential targets in the treatment of HCC. Monotherapy has limited therapeutic efficacy due to the development of inhibitory feedback mechanisms and induction of chemoresistance. Thus, emphasis is now on the development of personalized and combination molecular targeted therapies that can serve as ideal therapeutic strategies for improved management of HCC.

Key words: Hepatocellular carcinoma; Prognosis; Arginine deprivation; Cancer stem cells; Glypican-3; Hedgehog signaling pathway; Histone deacetylases; Personalized medicine; Molecular targeted therapy; Notch signaling pathway; Polo-like kinase 1; Tumour-associated antigens

Core tip: Hepatocellular carcinoma (HCC) remains a critical concern worldwide due to the severity of disease outcome. The primary cause is the low efficacy of current therapeutic

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regimens available to treat advanced HCC. This review provides details on novel potentially vulnerable targets in the oncogenic signaling pathways associated with HCC development and progression, which should be targeted to develop molecular combination therapies to improve disease management. Moreover, the identification and establishment of novel biomarkers would complement this process in assisting timely management of the disease *via* powerful personalized drug regimens.

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INTRODUCTION

Cancer of the liver is the sixth most commonly diagnosed cancer worldwide, and is responsible for 4.7% of all new cancer cases and 8.2% of all cancer-related deaths[1]. Although the five-year survival rate of liver cancer have improved from an abysmal 3% four decades ago to 18%, it is still significantly lower than the survival rates observed in many other solid cancers with a high global incidence, including breast (90%), colorectal (65%), and prostate (98%) cancers[2]. Three quarters of liver cancer patients present with hepatocellular carcinoma (HCC); while the other subtypes include cholangiocarcinoma, angiosarcoma, hepatoblastoma, and other non-cancerous liver diseases. The most common cause of HCC is hepatitis B virus (HBV) or hepatitis C virus (HCV) infection which is responsible for more than 90% of HCC cases in developing countries and nearly half the number of cases in developed countries[3]. Other risk factors include aflatoxin B_1 consumption, alcoholic liver disease, non-alcoholic fatty liver disease, smoking, autoimmune hepatitis, hemochromatosis, obesity, and diabetes. Importantly, in countries endemic for HBV, the introduction of a new universal vaccination program aided by mass screening has been shown to significantly reduce the rate of HBV-induced HCC in children and young adults[4,5]. Nevertheless, patients with early HCC are always asymptomatic or develop nonspecific complaints such as abdominal pain, enlarged abdomen, jaundice, and weight loss which results in HCC being initially undetected. Consequently, the management of high risk groups using routine serum α-fetoprotein monitoring and abdominal ultrasonography is important for better control over disease progression[6]. For the management of early and intermediate HCC, liver resection, orthotopic liver transplantation, thermal ablation including radiofrequency ablation and microwave ablation, transarterial therapies including, radioembolization with yttrium-90 and transarterial embolization with chemotherapeutic agents, and selective internal radiotherapy are potentially curative[6-8]. Although a 5-year survival rate of 50%-75% can be achieved, these curative therapies are only applicable for HCC patients with a smaller tumour size and adequate liver function[7,9-13]. Moreover, for patients presenting with advanced HCC, neoadjuvant and adjuvant systemic therapies are prescribed to reduce the rate of recurrence or the development of extrahepatic metastases; however, systemic chemotherapy has been reported to have a low tumour response rate and is commonly associated with the development of chemoresistance in advanced HCC[14-17].

The most actively used first-line systemic therapeutic agent approved for patients with nonresectable advanced HCC is sorafenib, an oral multikinase inhibitor targeting Raf, epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), FMS-like tyrosine kinase-3 and c-kit[18,19]. At least two large-scale, randomized, placebo-controlled drug trials independently confirmed the effectiveness of sorafenib treatment in inhibiting tumour growth and angiogenesis in advanced HCC; although, the median increase in the overall survival period of HCC patients treated with sorafenib was just under 3 mo as compared to the placebo group[20,21]. Moreover, prolonged exposure of HCC cells to sorafenib has been shown to induce resistance, caused by activation of the phosphoinositide 3-kinase (PI3K)/AKT pathway, resulting in enhanced tumour growth and the development of distant metastases[22,23]. Considering this predicament in managing HCC using sorafenib alone, it is essential to explore alternative options such as investigating potentially druggable molecular targets or the administration of alternative drug regimens, to achieve an improved disease outcome. Recently, the

FDA approved lenvatinib (Lenvima) as an alternate first-line therapeutic agent demonstrated a non-inferior role in improving the overall survival of HCC patients relative to sorafenib[19,24]. Furthermore, for HCC patients not benefitting from sorafenib, regorafenib or nivolumab and ipilimumab are the approved second-line therapeutic agents[25,26]. Treatment with lenvatinib was found to have improved secondary endpoints including a higher objective response rate, longer progression-free survival and longer time to progression than patients treated with sorafenib alone[19], HCC patients not responding to first-line sorafenib treatment were found to have a better overall survival following the administration of second-line drugs[25,27,28]. Due to the limited options available for the systemic treatment of HCC patients, there is an immediate requirement to develop novel therapeutic compounds with high efficacy to improve disease management. In this review, we explore some of the novel molecular targets currently known in HCC. Emphasis will also be paid to the development and clinical application of personalized molecular targeted therapies as powerful therapeutic strategies to improve prognosis in HCC.

POTENTIAL DRUGGABLE MOLECULAR TARGETS IN HCC

An important aspect of cancer therapeutics is the development of targeted therapy that makes use of chemical compounds designed to regulate the activity of specific molecular targets involved in critical oncogenic signaling pathways that ultimately govern the proliferation, growth, survival and distant metastatic dissemination of cancer cells. Consequently, targeted therapy has the advantage of delivering focussed and powerful suppression of cancer development and progression, albeit with a lower toxicity to non-malignant cells; which is a common pitfall associated with systemic chemotherapy and radiotherapy. With an increase in our understanding of the molecular biology of HCC, many such druggable molecular targets associated with HCC genesis and progression have been identified. Key targets include: (1) Intracellular signaling proteins such as those involved in the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway, ras/raf/mitogen-activated protein kinase (MAPK) pathway, Janus kinase (JAK)/Signal transducer and activator of transcription (STAT) pathway and Wnt/β-catenin pathway; (2) Angiogenic factors such as VEGF, fibroblast growth factor (FGF), angiopoietins, platelet-derived endothelial cell growth factor (PD-ECGF), heparanase, matrix metalloproteinases (MMPs), PDGFR, and COX-2; (3) Peptide growth factors and their receptors such as EGF and its receptor (EGFR), hepatocyte growth factor (HGF) and its receptor (c-Met), insulin-like growth factor (IGF) and its receptor (IGFR) and transforming growth factor-alpha (TGF-α); (4) Cell cycle regulators such as cyclins and cyclin-dependent kinases (CDKs); and (5) Transcription factors such as nuclear factor-kappa B and activator protein 2. The details of these targets have been comprehensively reviewed elsewhere[29-36]. Examples of the therapeutic agents against these molecular targets, currently in phase II/III clinical trials for the treatment of HCC are summarized in Table 1. However, the anti-tumour activity as well as the primary outcome measures, such as time to progression and overall response rate and safety level, exhibited by most of these compounds are either equivalent or significantly less than the effectiveness of sorafenib in HCC[37-40]. Consequently, it is important to identify novel molecular targets that are druggable in HCC. Table 2 summarizes potential pipeline compounds targeting novel targets that are a part of oncogenic signaling pathways in several cancers, including HCC. Given the importance of these oncogenic pathways in HCC development, these pipeline compounds hold promise as novel therapeutic strategies in HCC treatment. Hence, the following section specifically focuses on these targets to understand their role in HCC pathogenesis.

Hedgehog signaling pathway

The Hedgehog (Hh) pathway is an evolutionarily conserved signaling cascade that plays a critical role in early embryonic development and adult tissue homeostasis. Under normal circumstances, the adult liver does not manufacture the Hh protein unless the organ is undergoing regeneration after a partial hepatectomy[41]. However, recent evidence suggests that dysregulation of Hh signaling contributes to the development of HCC[42-44]. In its oncogenic role, the Hh protein impairs the inhibitory activity of patched homolog-1 (Ptch), resulting in the release of the proto-oncoprotein smoothened (Smo) from Ptch[42]. The released Smo subsequently induces the nuclear translocation of glioma-associated oncogene homolog (GLI) transcription factor, resulting in increased transcription of regulatory genes such as, cyclins and β-catenin

Table 1 Summary of current molecular targeted compounds under phase II/III clinical studies for the treatment of hepatocellular carcinoma

Drug	Targets	Descriptions	Ref./ClinicalTrials.gov identifier
Phase II			
Bevacizumab	VEGF	Monoclonal antibody Inhibits tumour growth of HCC cell line or patient-derived HCC xenografts Shows significant antitumour activity in patients with non-metastatic HCC, but serious bleeding complications occurs in 11% of patients.	[116-118]
Cediranib	VEGFR	Tyrosine kinase inhibitor Shows high toxicity and ineffective for patients with unresectable or metastatic HCC	[119]
Cetuximab	EGFR	Human-mouse chimeric monoclonal antibody Shows no obvious response in patients with advanced HCC	[120]
Dovitinib	c-KIT, Flt-3, FGFR, VEGFR	Multikinase inhibitor Significantly prolongs survival and inhibits primary tumour growth and lung metastasis in HCC xenograft models Shows less antitumour activity than sorafenib as a frontline systemic therapy for HCC	[38,121]
Erlotinib	EGFR	Tyrosine kinase inhibitor Shows modest prolonged progression-free survival and overall survival in patients with unresectable HCC	[122,123]
Gefitinib	EGFR	Tyrosine kinase inhibitor Inhibits tumour growth of HCC xenografts in mouse model	NCT00071994, [124]
Selumetinib	MEK1	Tyrosine kinase inhibitor Suppresses tumour growth of HCC xenografts in mouse model Shows inadequate antitumour activity with no radiographic response and short progression-free survival in patients with locally advanced or metastatic HCC	[125,126]
Phase III			
Brivanib	FGFR, VEGFR	Tyrosine kinase inhibitor Inhibits tumour growth of patient-derived HCC xenografts by increasing apoptosis, reducing microvessel density and decreasing VEGFR phosphorylation Shows promising antitumour activity in patients with advanced HCC	[127-129]
Linifanib	PDGFR, VEGFR	Receptor tyrosine kinase inhibitor Inhibits tumour growth of HCC xenografts in mouse model Shows similar overall survival in patients with advanced HCC as compared with sorafenib	[39,130,131]
Sunitinib	c-Kit, Flt-3, PDGFP, VEGFR	Multi-targeted receptor tyrosine kinase inhibitor Inhibits tumour growth of patient-derived HCC xenografts by increasing apoptosis and reducing microvessel density Shows significantly poorer overall survival than sorafenib in patients with advanced HCC, and shows more frequent and severe toxicity in treated patients	[132-134]
TSU-68 (Orantinib)	FGFR, PDGFR, VEGFR	Tyrosine kinase inhibitor Suppresses the tumour growth of subcutaneously co-injected HCC cell lines (Huh7/WI-38) xenografts	[135-137]

	Orantinib combined with TACE shows no improvement in overall survival in patients with unresectable HCC

EGFR: Epidermal growth factor receptor; FGFR: Fibroblast growth factor receptor; Flt-3: FMS-like tyrosine kinase-3; HCC: Hepatocellular carcinoma; MEK1: Mitogen-activated protein kinase (MAPK) kinase; PDGFR: Platelet-derived growth factor receptor; TACE: Transcatheter arterial chemoembolization; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.

which promote cell cycle progression, a higher rate of cell proliferation and an associated tumour growth in HCC. Moreover, activation of the Hh signaling pathway also enhances the metastatic potential of HCC cells through focal adhesion kinase (FAK)/AKT and ERK-mediated production and activation of MMP-2 and MMP-9[45,46]. In addition to the Hh protein, mRNA levels of Ptch and GLI were found to be over-expressed in HCC and have been reported to serve as potential biomarkers to determine disease recurrence and overall survival following curative surgery[47]. In addition, blocking of the Hh signaling pathway by a Smo inhibitor (Vismodegib) has been found to exert anti-proliferative effects in HCC cells[42,48], suggesting that targeting the Hh signaling pathway is a potential therapeutic option for HCC patients.

Notch pathway

The Notch cell-cell signaling cascade is highly conserved and regulates cell fate, cell proliferation and cell death in several developmental and physiological processes[49]. Four Notch proteins are found in mammals and they are transmembrane proteins composed of a large extracellular domain for ligand binding and a cytoplasmic Notch intracellular domain (Nicd) for signal transduction. Mammalian Notch ligands include Delta-like ligand (DLL)1, DLL3, DLL4, Jagged1 and Jagged2 which are also membrane-bound. Therefore, activation of the Notch signaling pathway is mediated by ligand-receptor interaction between adjacent cells which leads to a conformational change in Notch receptors. After γ-secretase-induced cleavage of the Notch receptor, cytoplasmic Nicd is released and then translocated to the nucleus. Nuclear Nicd functions as a transcription factor to cause the transcription of its target genes including, HES-family members p21 and c-Myc[50].

Dysregulation of the Notch signaling pathway is observed in several types of cancers, including HCC. Aberrant expression of Notch receptors and its ligand Jagged1 has been detected in HCC tissues when compared with the adjacent non-malignant mucosae[51-54]. Activation of Notch signaling has also been reported to induce HCC tumour formation in mice[55]. Moreover, Notch signaling also contributes to enhancement of the oncogenic effects of HBV and HCV in HCC pathogenesis[56-58]. Several studies have verified that targeting critical members of the Notch signaling pathway represents a potential therapeutic avenue for HCC treatment. Giovannini *et al*[59] demonstrated that selective ablation of the Notch protein in combination with chemotherapeutics such as doxorubicin results in increased DNA damage, cellular apoptosis, and a concurrent decrease in cell cycle progression in HCC cells. Treatment with γ-secretase inhibitors (GSI) was found to inhibit growth of HCC cells *in vitro*[60,61]. Zhou and colleagues inhibited the Notch signaling pathway using DAPT which suppressed the invasion of HCC cells by impacting signaling of the extracellular signal-regulated kinases 1 and 2 (ERK1/2), thereby repressing the activity of MMP2, MMP9 and VEGF[62]. Active clinical studies on the use of GSIs such as MK-0752 and RO4929097 demonstrated a significant anti-tumour effect in different cancer models[63-66], which suggests its therapeutic potential in treating HCC.

Polo-like kinase 1

Polo-like kinase 1 (Plk1) is a serine/threonine kinase with peak expression during the mitotic phase of the cell cycle[67]. Plk1 functions as a cell cycle regulator promoting mitosis by modulating the activities of cell division cycle 25 homolog C (Cdc25C) and CDK1/Cyclin B[68,69]. Overexpression of Plk1 overrides the mitotic checkpoint which results in immature cell division and genetic instability leading to aneuploidies and tumour development[70]. In HCC, activation of Plk1 by HBx, a hepatitis B viral protein, was found to impair the DNA damage checkpoint and DNA repair pathways causing increased genetic instability and malignant transformation[71]. Consequently, Plk1 has been reported to be upregulated in numerous cancers, including HCC. In addition, a higher expression of Plk1 was found to predict poor prognosis in HCC[72-74]. Silencing Plk1 inhibited proliferation of HCC cells *in vitro* and *in vivo* by inducing G2/M arrest and enhanced apoptosis[75-77], suggesting that targeting Plk1 with small molecule inhibitors is a potential strategy for the treatment of HCC. Gilmartin *et al*[78] described a

Table 2 Summary of potential pipeline compounds targeting novel molecular targets in several cancers

Drug	Descriptions	Phase	Type of tumour	Ref./ClinicalTrials.gov identifier
Hh signaling pathway				
Erismodegib, (LDE-225)	Smo antagonist	0	Pancreatic cancer	NCT01694589
	In vitro and *in vivo* test results on HCC cells are not available	I	Advanced solid tumours	NCT00880308
		I	SCLC	NCT01579929
		II	Advanced or metastatic basal cell carcinoma	NCT01327053
		I/II	Medulloblastoma	NCT01125800
Vismodegib	Smo antagonist	I	HCC and lymphoma	NCT01546519
	Promotes regression of liver fibrosis and HCC tumour growth in a murine model of primary liver cancer[138]	I	Advanced or metastatic basal cell carcinoma	
	Shows no obvious response in patients with hepatic impairment[139]	II	Ovarian cancer	NCT00739661
Notch signaling pathway				
MK-0752	γ-secretase inhibitor	I	Advanced solid tumour	[63]
	In vitro and *in vivo* test results on HCC cells are not available	I	Brain and central nervous system tumours	[64]
RO4929097	γ-secretase inhibitor	I	Refractory metastatic or locally advanced solid tumours	[65]
	Prevents tumour development and decreases liver fibrosis in mouse model[141]	II	Metastatic colorectal cancer	[66]
Plk1				
HMN-214	Stilbene derivative interferes with the subcellular spatial distribution of Plk1 at centrosomes	I	Advanced solid tumours	[79]
	In vitro and *in vivo* test results on HCC cells are not available			
GSK461364	Reversible ATP-competitive Plk1 inhibitor	I	Advanced solid tumours and non-Hodgkin's lymphoma	[81]
	In vitro and *in vivo* test results on HCC cells are not available			
Arginine deprivation				
ADI-PEG-20	Arginine deiminase	I	Pediatric ASS-deficient tumour	NCT01528384
	Shows its safe and efficacious in stabilizing the progression of advanced HCC in an Asian population	II	SCLC	[142], NCT01266018
	Shows no overall survival benefit in second line setting for patients with advanced HCC	II	Advanced melanoma	[143]
		II	Malignant pleural mesothelioma	NCT01279967
		II/III	Advanced HCC	[87,144]
BCT100/ Peg-rhArg1	Recombinant human arginase I	I	Leukemia and lymphoma	NCT01551628
	Inhibits tumour growth of HCC xenografts in mouse model[85]	I/II	Advanced HCC	[90], NCT01092091
HDACs				
Resminostat	HDACs (1, 3 & 6) inhibitor[145]	I/II	Advanced HCC	[146]
	Combined with sorafenib shows no significant efficacy advantage over sorafenib monotherapy in patients with advanced HCC in East Asian populations	II	Hodgkin's lymphoma	NCT01037478
		I/II	Advanced colorectal carcinoma	NCT01277406
Chidamide	HDACs inhibitor (1, 2, 3 & 10)[147]	I	Advanced solid tumours and lymphomas	[148]
	Inhibits proliferation of HCC cells *in vitro*[95]			

Panobinostat,(LBH-589)	Pan-HDAC inhibitor Inhibits tumour growth and lung metastasis of HCC xenografts in mouse model[149]	I	Prostate carcinoma	[150]
		I	Advanced solid tumours	[151]
		II	Refractory metastatic renal cell carcinoma	[152]
Glypican-3				
Codrituzumab (GC33)	Anti-GPC3 monoclonal antibody Inhibits tumour growth of HCC xenografts in mouse model[102] Shows no clinical benefit in advanced HCC patients who has failed prior systemic therapy	I	Advanced or metastatic HCC	[153]

HCC: Hepatocellular carcinoma; HDAC: Histone deacetylase; Plk1: Polo-like kinase-1; SCLC: Small cell lung cancer; Smo: Proto-oncoprotein smoothened.

reversible ATP-competitive Plk1 inhibitor with a very high selectivity for Plk1 relative to other Plk subtypes or a panel of 48 other kinases that included CDK2/Cyclin A, MEK and serine/threonine kinase NEK2. Moreover, the authors demonstrate that the inhibition of Plk1 resulted in a dose-dependent arrest of cell cycle progression, leading to cell culture growth inhibition and tumour regression in xenograft models; while the toxicity of the drug in slow dividing non-cancerous cells was minimal. Therefore, GSK461364 offers the feasibility to overcome the limitation of traditional chemotherapy. Other phase I/II clinical studies of Plk1 inhibitors also demonstrated an anti-tumour effect by causing tumour regression and inhibition of tumour growth[79-82]. These studies suggest that Plk1 may be a potential therapeutic target in the treatment of HCC.

Arginine deprivation in arginine-driven HCC

Arginine is a semi-essential amino acid biosynthesized from citrulline in the urea cycle through the action of argininosuccinate synthetase (ASS-1), argininosuccinate lyase (ASL) and ornithine transcarbamylase (OTC)[83]. HCC is auxotrophic for arginine as it lacks the expression of ASS-1, ASL and/or OTC[84,85]. Therefore, enzymes capable of removing arginine can function as potential therapeutic agents in HCC. ADI-PEG-20 is an arginine deiminase (ADI) which has been shown to induce HCC regression through arginine depletion in ASS-deficient tumours[86,87]. For ASS-positive but OTC-deficient HCC, a recombinant human arginase I (rhArg1) has been shown to be potent in inhibiting HCC tumour growth[84,88-90]. A recent study by our group demonstrated that treatment with a pegylated rhArg1, BCT100, inhibits proliferation of HCC cells through an enhanced caspase-dependent apoptosis and induction of S-phase cell cycle arrest[85]. Moreover, the drug also inhibited xenograft tumour growth in a dose-dependent manner. At the molecular level, arginine deprivation was observed to inhibit the Wnt/β-catenin and Akt/mTOR signaling pathways with a concurrent downregulation of survivin and X-linked inhibitor of apoptosis (XIAP) expression[85]. Therefore, human recombinant arginase may be a potential agent in arginine-driven tumours such as HCC.

Histone deacetylases

One of the key regulatory mechanisms of gene expression is *via* epigenetic post-translational modifications of histone proteins. Among other covalent modifications, acetylation of the histones is a critical physiological process that is regulated by a balance between the activities of histone acetyltransferases and histone deacetylases (HDACs). Contrary to the acetyltransferases, HDACs work by removing acetyl groups from the lysine amino acid on the histone protein to increase the net positive charge on the histone tails, resulting in high-affinity binding between the histones and the DNA backbone. High HDAC activity results in a condensed and a transcriptionally inactive chromatin[91]. Moreover, aberrant expression of HDAC family members has been observed in multiple steps of cancer development including, cell proliferation, autophagy and cell cycle progression (HDAC 1, 2, 3 and 8), apoptosis (HDAC 1 and 2), differentiation (HDAC 3, 4, 5, and 8), angiogenesis (HDAC 4, 6, 7 and 10), migration (HDAC 6), and chemosensitivity (HDAC 1). The functional roles played by each family member of HDACs have been reviewed elsewhere in greater detail[92]. Dysregulated expression of HDACs has been found to correlate with a poor disease outcome in several cancers including HCC[92-94]. Specifically, upregulation of HDAC 3

and 5 mRNA expression was observed to be associated with DNA copy number gains in HCC[93]. Several HDAC inhibitors (HDACi) have been shown to have an anti-proliferative effect on HCC cells *in vitro* and *in vivo*. Panobinostat, a pan-HDAC inhibitor, has been found to enhance apoptosis and inhibit tumour growth in HCC cells through down-regulation of the anti-apoptotic protein survivin[93]. Chidamide, a benzamide type inhibitor of HDAC 1, 2, 3 and 10 subtypes, inhibits HCC cell growth by inducing cell cycle arrest at G0/1 phase by the up-regulation of p21[95]. Although most of the studies of HDACi in HCC are still at the pre-clinical stage, HDACi in HCC therapy has great potential.

Glypican-3

The glypican (GPC) family represents a group of cell-surface heparan sulphate proteoglycans which interact with growth factors, act as a co-receptor and modulate growth factor activity. Glypican-3 (GPC3), a carcinoembryonic antigen, promotes cell proliferation by modulating fibroblast growth factor 2 (FGF2) activity[96] and canonical Wnt signaling[97]. Interestingly, GPC3 is a transcriptional target of c-Myc, while the expression of c-Myc is under the regulation of GPC3[98]. This positive feedback loop between GPC3 and c-Myc also determines the oncogenic behaviour of GPC3. GPC3 is a diagnostic marker for HCC which is over-expressed in 70% of cases, while its expression is correlated with a poor outcome[99,100]. Silencing GPC3 in HCC cells induced apoptosis *via* the Bax/Bcl-2/cytochrome c/caspase-3 signaling pathway[101]. An antibody against GPC3 has also been developed, and it has been shown to cause antibody-dependent cell-mediated cytotoxicity in HCC cells[102]. In addition, due to its highly specific expression in HCC tumours, but not in the normal hepatocytes or benign hepatocellular mass lesions[103], GPC3 serves as a tumour-associated antigen which is an ideal target for immunotherapy. Tumour immunotherapy is the use of the host tumour-specific immune response to selectively target the tumour-associated antigens present on tumour cells. A phase I trial of a GPC3-derived peptide vaccine demonstrated measurable immune response and antitumor efficacy which correlated with overall survival in advanced stage HCC patients[104].

CANCER STEM CELLS AS THERAPEUTIC TARGETS FOR HCC TREATMENT

Cancer stem cells (CSCs) are a subpopulation of cancer cells possessing stem cell-like properties. Briefly, CSCs are tumour-initiating cells in the bulk of tumours that are capable of self-renewal and can divide and differentiate into multiple cell lineages. Markers of CSCs in HCC include ALDH, CD13, CD44, CD90, CD133, CD326 (EpCAM), and OV6, and a side population (SP) determined through an adenosine triphosphate (ATP)-binding cassette (ABC) membrane transporter[105,106]. CSCs also play a crucial role in tumour recurrence, metastasis and chemoresistance. A recent study reported that circulating $CD45^{-}CD90^{+}CD44^{+}$ CSCs can predict post-hepatectomy HCC recurrence[107]. Importantly, while systemic chemotherapy is effective in killing differentiated, fast-growing cancer cells, it induces chemoresistance and enriches the population of CSCs which significantly increases the risk of disease recurrence and metastasis. Ma *et al*[108] reported a CSC population in HCC characterized by their CD133 phenotype which were shown to survive chemotherapy of doxorubicin and fluorouracil with preferential expression of survival proteins involved in the AKT and Bcl-2 pathway. The authors further demonstrated that treatment with an AKT1 inhibitor significantly reduced the expression of these survival proteins, thereby enhancing the chemosensitivity of $CD133^{+}$ CSCs. In a different study, CD133+ cells were also observed to contribute to radio-resistance in HCC in a mouse xenograft model[109]. Other molecular pathways including TGF-β, Wnt, Notch and Hh, that are deregulated in HCC were also found in CSCs[105,110,111]. Therefore, molecular therapy that is targeted towards CSCs can assist in preventing tumour-initiation, recurrence, metastasis or even chemoresistance in HCC.

PERSONALIZED AND COMBINED MOLECULAR TARGETED THERAPIES IN HCC

Development of HCC is a multi-step process and the mechanisms involved in the initiation, progression and metastasis are not completely understood. Recent studies

have demonstrated the role of multiple signaling pathways that contribute to the pathogenesis of HCC. Although no single pathway is deemed dominant, the inhibition of a single pathway may induce a feedback mechanism within an alternate pathway resulting in a low response rate to monotherapy. For example, rapamycin up-regulates the expression and phosphorylation of PDGFRβ and the subsequent activation of the AKT and MAPK pathway through the PDGFRβ-dependent feedback loop results in rapamycin resistance[112]. Therefore, emphasis is focussed on a personalized and combined molecular targeted therapy as an ideal therapeutic strategy for HCC.

An *in vitro* study demonstrated that the level of EGFR expression predicts the cell line response to sorafenib treatment and the addition of gefitinib or erlotinib (EGFR inhibitors) or cetuximab (a monoclonal antibody against EGFR) significantly enhances the efficacy of sorafenib and a synergistic anti-proliferative effect is also demonstrated[113]. Therefore, by screening the EGFR status, we can predict the tumour's response to sorafenib treatment, and the addition of an EGFR inhibitor may help sensitize the tumour's response to sorafenib. However, an *in vivo* orthotopic model failed to demonstrate a synergistic anti-tumour effect of combination treatment with erlotinib and sorafenib[114]. A recent press release also reported that a large scale phase III clinical trial on the efficacy of combining erlotinib with sorafenib treatment in HCC (SEARCH trial, NCT00901901) failed to demonstrate any additional benefit on the overall survival of patients with unresectable HCC over sorafenib treatment alone[115]. Although these studies failed to show a clinical impact of one combined treatment in HCC, presently several clinical studies are evaluating alternate combination based molecular targeted therapies, examples of which are summarized in Table 3. Importantly, the success of personalized therapies in HCC heavily depends on the identification of novel biomarkers that provide critical information pertaining to the progress of the disease. As small tissue biopsy or fine-needle aspiration biopsy specimens are easily obtained, evaluation of biomarkers associated with crucial signaling pathways within these specimens can provide indications for treatment of these patients with drug combinations with/without locoregional therapies to maximize tumour response and survival rates.

CONCLUSION

HCC has been a cause of concern for a long time owing to a high rate of mortality and an overall poor outcome associated with the disease. Molecular investigations have indicated the dysregulation of several critical signaling pathways that contribute to the genesis and progression of HCC. Hence, the role of molecular therapy targeting pivotal members within these signaling pathways is undisputed. While monotherapy is frequently associated with a low tumor response rate and chemoresistance events, there is a need to explore and develop personalized and combined molecular targeted therapies as a powerful therapeutic strategy in HCC. Additionally, an increase in the discovery and clinical application of novel biomarkers that can speak volumes about the developing tumor would provide important information for guiding the clinician on the usage of appropriate personalized therapies in HCC.

Table 3 Clinical study of combined molecular targeted therapy based on sorafenib treatment for hepatocellular carcinoma

Drug + Sorafenib	Phase	Ref./ClinicalTrials.gov identifier
VEGF inhibitors		
Bevacizumab	I/II	NCT00867321
Lenvatinib	I/II (HCC)	NCT01271504
mTOR inhibitor		
Everolimus (RAD001)	II	NCT01005199
	I/II	[154]
Temsirolimus	I/II	NCT01335074, NCT01687673, NCT01008917
HDAC inhibitors		
Resminostat	II (Advanced HCC)	NCT00943449
Panobinostat	I (HCC)	NCT00823290
Anti-GPC3 antibody		
GC33	I	NCT00976170
MEK1 inhibitor		
Selumetinib (AZD6244)	I/II	NCT01029418
HGFR inhibitor		
Tivantinib (ARQ197)	I	NCT00827177
TNF-a secretion inhibitor		
Lenalidomide	I	NCT01348503
TRAIL receptor 1 antibody		
Mapatumumab	I/II	NCT00712855, NCT01258608

HGFR: Hepatocyte growth factor receptor; TNF-α: Tumour necrosis factor-α; TRAIL: Anti-TNF-related apoptosis-inducing ligand; HCC: Hepatocellular carcinoma; VEGF: Vascular endothelial growth factor; mTOR: Mammalian target of rapamycin.

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