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TOPIC HIGHLIGHT

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Hepatitis C virus-mediated angiogenesis: Molecular mechanisms and therapeutic strategies

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Abstract

Angiogenesis is an essential process for organ growth and repair. Thus, an imbalance in this process can lead to several diseases including malignancy. Angiogenesis is a critical step in vascular remodeling, tissue damage and wound healing besides being required for invasive tumor growth and metastasis. Because angiogenesis sets an important point in the control of tumor progression, its inhibition is considered a valuable therapeutic approach for tumor treatment. Chronic liver disease including hepatitis C virus (HCV) infection is one of the main cause for the development of hepatic angiogenesis and thereby plays a critical role in the modulation of hepatic angiogenesis that finally leads to hepatocellular carcinoma progression and invasion. Thus, understanding of the molecular mechanisms of HCV-mediated hepatic angiogenesis will help design a therapeutic protocol for the intervention of HCV-mediated angiogenesis and subsequently its outcome. In this review, we will focus on the molecular mechanisms of HCV-mediated hepatic angiogenesis and the related signaling pathways that can be target for current and under development therapeutic approaches.

Key words: Hepatitis C virus; Hepatocellular carcinoma; Angiogenesis; Signaling pathway; Therapy

Core tip: This editorial elaborate the molecular mechanisms of hepatitis C virus (HCV)-mediated angiogenesis and its mechanisms, and the potential of angiogenic pathways as target for hepatocellular carcinoma therapy. We summarized the current knowledge of HCV-mediated angiogenesis and the possible therapeutic strategies.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is considered one of the most common cancers worldwide. Therefore, the limited treatment options and poor prognosis of HCC patients emphasize the importance of the development of a new therapeutic strategy. Chronic liver diseases including hepatitis C virus (HCV) infection are the major risk factors for developing HCC[1,2]. Although the molecular mechanisms that link HCV infections to the development and progression of HCC are not entirely characterized, increasing evidence indicates the involvement of hepatic angiogenesis in the modulation of HCV viral proteins-induced HCC malignancy[3-5]. Therefore, targeting the angiogenic signaling pathways is thought to be a relevant therapeutic strategy for tumor treatment. Accordingly, understanding the mechanistic role of HCV infection in the modulation of the imbalance of hepatic angiogenesis may help to develop novel therapeutic options for HCC treatment.

ANGIOGENESIS

Angiogenesis is a dynamic, hypoxia stimulated and growth factor-dependent process that is responsible for the formation of new vascular structures from preexisting vessels[6,7]. Angiogenesis occurs in several organs in response to a pathophysiological alteration, and thereby is one of the most thoroughly studied pathophysiological phenomena. Besides its role in promotion of the etiopathogenesis of several diseases, angiogenesis is considered a potential therapeutic target for tumor treatment[8,9].

Hypoxia and inflammation are the main inducers of angiogenesis in liver and other organs[10-13]. Under hypoxia conditions angiogenesis is regulated through a mechanism mediated by hypoxia inducing factor (HIF)[14,15], where as its induction during the course of inflammation is regulated through a mechanism mediated by angiogenic cytokines and growth factors[11,16]. Thus, the formation of new functional vessels from preexisting vessels is mediated by tightly regulated mechanism, in which HIF plays a central role[17,18].

Although neo-angiogenesis is common for most chronic inflammatory and fibrogenic disorders, the processes of hepatic angiogenesis differ from homologous processes in other organs or tissues. This may be due to the unique phenotypic profile as well as to the functional role of both activated hepatic stellate cells and other liver myofibroblasts[19,20].

REGULATION OF ANGIOGENESIS

The regulation of angiogenesis is mediated by a mechanism regulated through the balance between the angiogenic growth factors and their inhibitors. These angiogenic growth factors can be released from different cell types including endothelial cells (ECs), monocytes, platelets, and smooth muscle as well as tumor cells[21]. Under normal physiological condition, the inhibitors of neovascularization is in excess in solid organs, and thereby can overcome the reservoir of growth factors that are essential for the initiation of the angiogenic process, a mechanism for the inhibition of neovascularization in solid organs[22-24]. Whereas, in tumors, the release of growth factors are in excess. Accordingly, the excess of the resleased growth factors has the ability to overcome the inhibitor of angiogenesis, and thereby contributes to the promotion of tumor progression. Thus, the initiation of the angiogenic process is an important mechanism for tumor development and progression. A model for the regulation of angiogenesis by hepatocyte growth factor *via* mechanism mediated by either vascular endothelial growth factor (VEGF) or thrombospondin 1 is shown (Figure 1)

MOLECULAR MECHANISMS OF HCV-INDUCED ANGIOGENESIS

The role of HCV infection in the regulation of hepatic angiogenesis is reported in several studies[5,25]. Also, the microvessel density in liver biopsies of patients with HCV chronic infection is significantly high when compared to those of patients with hepatitis B virus (HBV) infection[26]. Accordingly, *in vitro* analysis of HCV positive sera were found to stimulate the migration and the proliferation of human ECs[27]. These enhanced migration and proliferation of ECs are attributed to the HCV-induced production of VEGF[27]. There are two different types of microvascular structures in the liver including the large vessels that are mainly covered by a continuous endothelium, and the sinusoids that are lined by a fenestrated endothelium[28]. Sinusoidal capillarization identified by CD34-positive ECs that mainly reported in most HCCs[29,30]. Moreover, CD34-positive ECs have also been observed in the sinusoid of both higher-grade and lower-grade dysplastic nodules[31,32], as well as in HCV-associated HCC[33]. Also, the elevation of CD34 in response to the stimulation of ECs together with the detection of CD34 in liver biopsies of HCV infected patients provide evidence for the mechanistic role of HCV infection in the regulation of hepatic angiogenesis[5]. Although the direct relation between HCV infection and angiogenesis has been reported *in vitro* and *in vivo*, little is known about the molecular mechanisms, which are responsible for the modulation of HCV-promoted hepatic angiogenesis.

Accordingly, the infection of the liver derived cell line Huh7 with HCV subgenomic replicon was found to stabilize HIF-1α under normoxic conditions[34], an evidence for the involvement of HCV viral proteins in the regulation of HIF-1α, an essential factor for the regulation of angiogenesis. Further analysis of HCV proteins (structural or non-structural proteins) using several molecular biological techniques in combination with inhibitory experiments demonstrated that the oxidative stress, signal transducer and activator of transcription 3, nuclear transcription factor NF-κB, mitogen activated protein kinase (MAPK), phosphatidylinositol 3-kinases

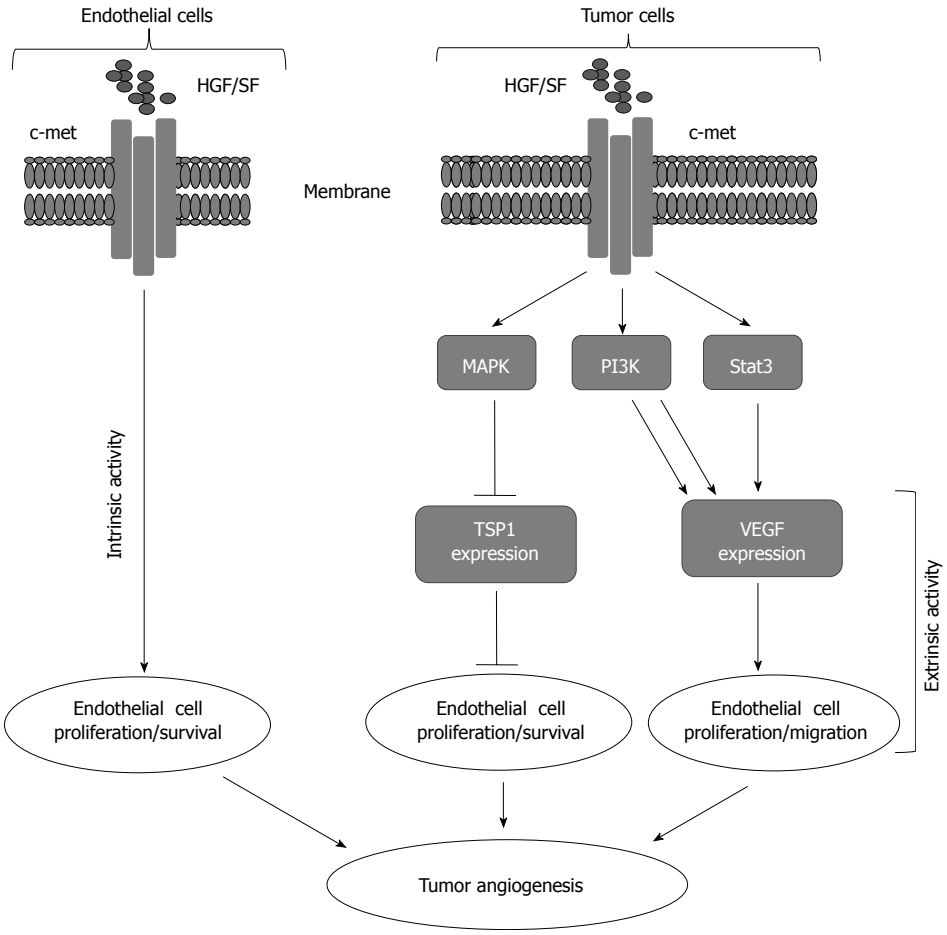

Figure 1 Representative model for tumor angiogenesis induced by hepatocytes growth factor/Scater factor-Met signaling. Intrinsically hepatocytes growth factor/Scater factor (HGF/SF) activates Met receptor on the surface of host endothelial cells leading to cell proliferation and migration. Extrinsically, HGF/SF-Met signaling turns on the angiogenic switch by simultaneous upregulation of pro-angiogenic vascular endothelial growth factors (VEGF) expression and down regulation of thrombospondin 1 (TSP-1) expression from the tumor cells.

(PI3-kinases) play an essential role in the stabilization of HIF-1α[5,25]. Also, the role of HCV nonstructural proteins NS3 and NS4A-induced reactive oxygen species[35,36] seems to be essential for the stabilization of HIF-1α, that in turn, leads to the upregulation of VEGF and other angiogenic factors[5,37]. Also, the elevation of VEGF secretion in patient's sera, in subgenomic replicon, and in HCV core-expressing Huh7 reveals an important role for HCV infection in the promotion of hepatic angiogenesis[5]. Moreover, HCV-induced VEGF, and subsequently the activation of endothelial have been reported to be regulated *via* mechanism mediated by multiple pathways including c-Jun-N-terminal kinase, p38 and extracellular regulated kinase (ERK)[5].

Although the several studies dealing with mechanistic role of HCV infection in the context of angiogenesis are limited, the induction of several angiogenic factors by HCV proteins has been demonstrated[5,38,39]. For example, elevation of Ang-2 in the sera of HCV-infected patients[39,40], as well as the upregulation of MMP-2 in response to expression of HCV viral proteins[41-43]. Furthermore, the enhancement of MMP-9 by HCV core protein is also reported[42,44-46]. Moreover, the overexpression of cyclooxygenase (COX)-2 in response to the expression of HCV core or NS5A in hepatocytes has been demonstrated in several studies[47-49]. The mechanism, by which HCV induces COX-2 has been investigated, and thought to be regulated *via* a mechanism mediated by HCV-induced oxidative stress[50].

The findings mentioned above are supported by a set of clinical investigations. For example, patients with HCV chronic infection revealed significant elevation of intrahepatic COX-2, MMP-2 and MMP-9[44]. These intrahepatic COX-2, MMP-2, and 9 along with VEGF and Ang-2 are thought to play an important role in the stimulation of angiogenesis in the context of HCV-associated HCC. A proposed model for the possible mechanisms demonstrating the pathways, which are involved in the modulation of HCV-induced hepatic angiogenesis is outlined in Figure 2.

ANGIOGENESIS AS THERAPEUTIC TARGET FOR HCC TREATMENT

The inhibition of angiogenesis is thought to be a relevant therapeutic strategy for HCC treatment. Despite

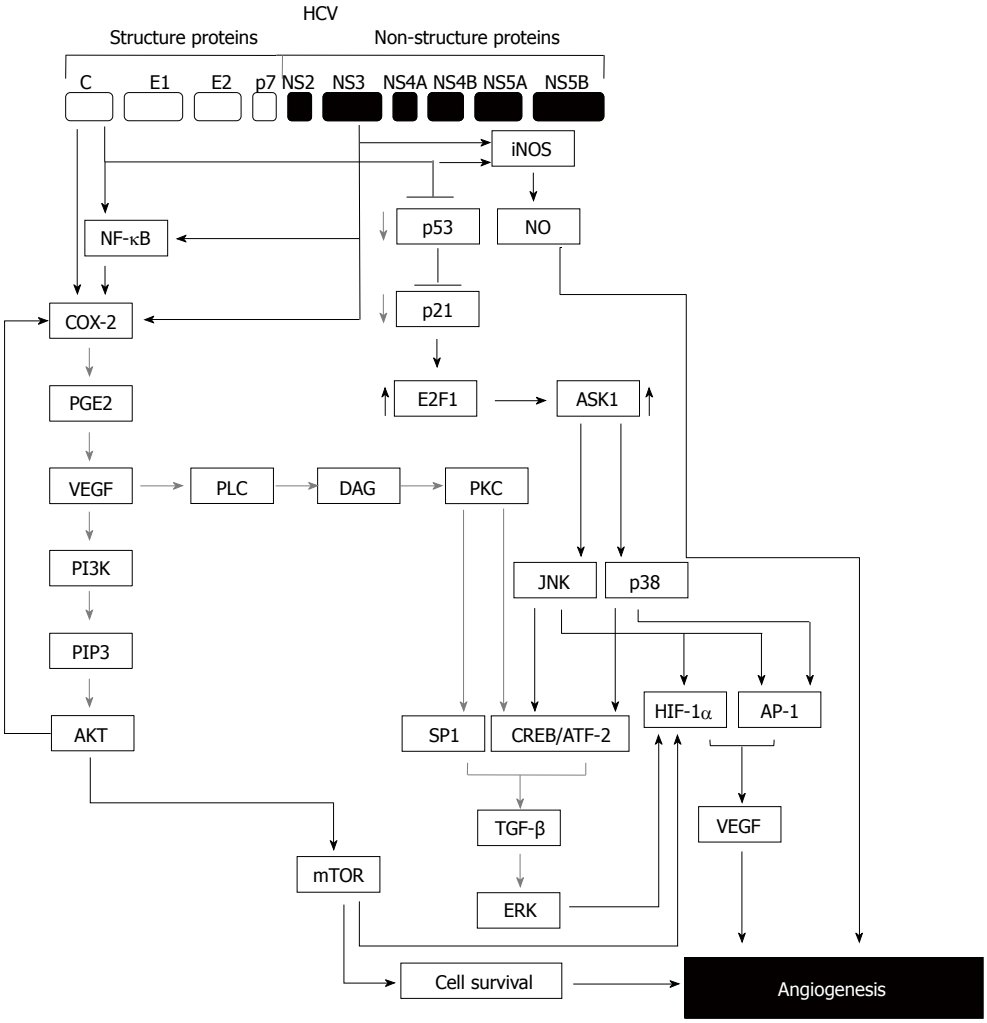

Figure 2 Model for hepatitis C virus-mediated hepatic angiogenesis. During the infection with hepatitis C virus (HCV), normal angiogenesis process can be malignant through the deregulation of genes involved in the angiogenic pathway by viral proteins such as core and non-structural protein NS3. HCV infection can enhance angiogenic process *via* multiple pathways. One of these pathways is initiated by HCV core or NS3 *via* NF-κB and, cyclooxygenase (COX-2) leading to the activation of vascular endothelial growth factor (VEGF)/PI3K/AKT/mTOR axis. The other pathway is initiated by core and NS3-induced iNOS/NO axis leading to angiogenesis. Further pathway is initiated by HCV-induced suppression of p53-p21 axis leading to the induction of E2F1 that subsequently mediates the activation of ASK1-JNK/p38 that results in the induction of TGF-β leading to the activation of extracellular regulated kinase (ERK) pathway. ERK pathway together with c-Jun-N-terminal kinase (JNK), p38 will be able to trigger the expression of VEGF and subsequently to the promotion of hepatic angiogenesis.

of there has been poor efficacy with treatment using single-agents as anti-angiogenic approaches in advanced solid cancers[51,52], many molecular-targeted drugs have been proofed for their reliability in HCC treatment[53,54]. Although the multi-tyrosine kinase inhibitor sorafenib demonstrated an overall survival benefit for patients with HCC, the efficacy of anti-angiogenic agents, including sorafenib in HCC is limited[55]. This may due to that most of anti-angiogenic agents including sorafenib, can only target newly formed blood vessels rather than the matured one. As a consequence the vascular remodeling can substitute the eliminated newly formed vessels[56,57]. Apart from their ability to block the cell cycle of tumor cells, most anti-angiogenic agents fail to induce tumor death, a further limitation for their anti-tumor efficacy. Hence, the design of an anti-angiogenic approach for HCC treatment must be taken into account that targeting a unique signaling pathway by a small-molecule inhibitor is not sufficient to abrogate or even to block tumor development and progression. Thus, the combination of inhibitors of different angiogenic pathways may be more efficient.

Tumor angiogenesis has received more attention as a potential target for therapeutic intervention. Although many of the research studies have focused on the inhibition of vascular endothelial growth factor receptor (VEGFR) or its ligand, VEGF[58,59], the VEGF/VEGFR axis, an important mediator of tumor angiogenesis, is only one of several angiogenic pathways that are essential for initiation and progression of angiogenesis[60-62]. Thus, recent evidence suggests that Src may be a mediator for the expression of multiple pro-angiogenic molecules[63,64]. Src is membrane-associated non-receptor protein tyrosine kinases, and is overexpressed and/or aberrantly activated in a variety of human tumors[65], therefore targeting of this pathway may be a relevant strategy for HCC treatment.

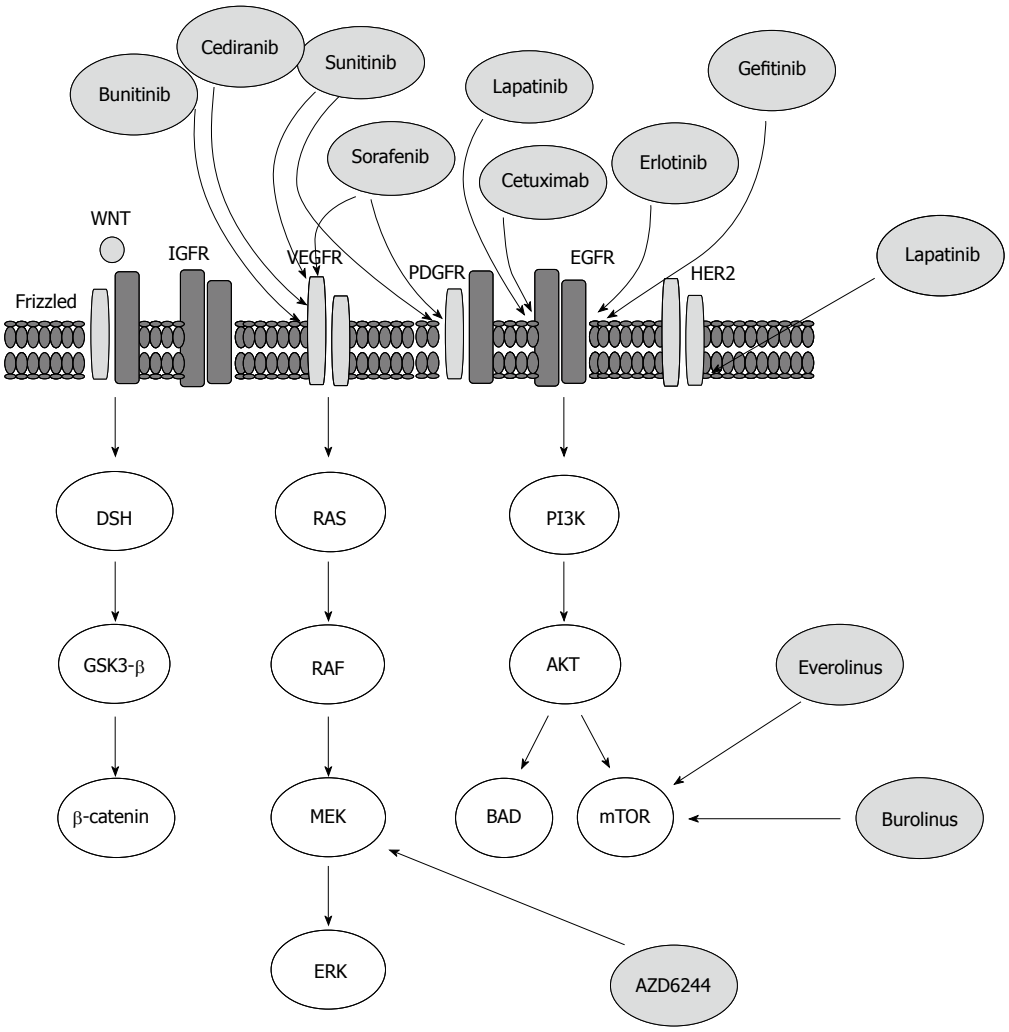

Figure 3 Outline of the targeted therapies, which are currently available or under development for the treatment of hepatocellular carcinoma, and the molecular targets on which they are believed to act upon. AKT: A protein kinase family of genes involved in regulation of cell survival, Bcl-2-associated agonist of cell death promoter (BAD), Bcl-2-associated death promoter; Disheveled (DSH) protein, downstream effector Disheveled; EGF: Epidermal growth factor; EGFR: EGF receptor; ERK: Extracellular signal-regulated kinase; Frizzled: A family of G-protein coupled receptor proteins that serve as receptors in the WNT/β-catenin signaling pathway; once activated: Frizzled leads to activation of Disheveled in the cytoplasm; GSK-3β: Glycogen synthase kinase 3β; HER2/neu: Human epidermal growth factor receptor 2, a cell membrane surface-bound receptor tyrosine kinase that is involved in the signal transduction pathways leading to cell growth and differentiation; MEK: Kinases that phosphorylate mitogen activated protein (MAP) kinase (MAPK); mTOR: Mammalian target of rapamycin; PDGFR: Platelet-derived growth factor receptor; PI3K: Phosphatidylinositol-3-kinase; PTEN: Phosphatase and tensin homolog, regulates cell-survival pathway; RAF: A MAP kinase kinase kinase (MAP3K) that functions in the MAPK/ERK signal transduction pathway; a serine/threonine-specific kinase; RAS: Prototypical member of the RAS superfamily of proteins; activation of RAS signaling causes cell growth, differentiation and survival; the dysregulation of RAS signaling can lead to oncogenesis and cancer.

Although some studies focused mainly on the ability of Src family kinase inhibitor that is acting directly on tumor cells through a mechanism mediated by the reduction of pro-angiogenic factors[66], the anti-angiogenic effect of Src family kinase inhibitors was found to be more efficient *in vivo*[61,67,68]. Thus, the inhibition of Src family kinase activity by highly potent and selective small-molecule inhibitor(s) may be a relevant therapeutic strategy for the treatment of human solid tumors.

Moreover, the ERK/MAP kinase also known as RAF/MEK/ERK pathway is a ubiquitous signal transduction pathway that is involved in the regulation of crucial cellular functions such as angiogenesis is thought to be a promising target for anti-angiogenic agents[69-71]. The activation of this pathway through the overexpression or activation of its components contributes to the regulation of angiogenesis that, in turn, leads to tumor progression and metastasis[5,71]. The ERK/MAPK pathway is a downstream pathway of various growth factors such as insulin growth factor receptor, endothelial growth factor (EGFR), VEGFR, and platelet-derived growth factor receptor (PDGFR), consequently the ERK/MAPK pathway is thought to be a valid therapeutic target for the treatment of HCC[72-76].

Furthermore, constitutive activation of the PI3K/AKT/mTOR signaling pathway has been established as determinant of cell growth and survival in solid tumors including HCC[77]. The activation of PI3K/AKT/mTOR signaling pathway can be mediated by the enhanced activation of tyrosine kinases receptors such as those of

IGF and EGF[78]. The expression of both EGF and IGF receptors is upregulated in HCC and cirrhotic liver[79]. Accordingly, PI3K/AKT/mTOR signaling pathway may be a potential target for the development of therapeutic approaches for HCC treatment. Also, WNT/β-catenin pathway is considered a promised therapeutic target of HCC treatment, based on its potential role in the regulation of major and early carcinogenic processes of HCC[80].

Ligands that bind to the EGFR, such as EGF, play a central role both in tumor angiogenesis and proliferation, *via* mechanism mediated by the activation of RAF/MEK/ERK and PI3/AKT/mTOR pathways[81]. Thus, based on their efficacy in the treatment of most solid tumors, targeting of EGF/EGFR signaling pathway may be beneficial for HCC treatment[82]. As a result, variable therapeutic targets have been developed based on the reliability of this pathway as a relevant therapeutic target for tumor treatment. Thus, the current agents targeting EGFR in HCC includes erlotinib, lapatinip and gefitinib, as well as the monoclonal antibody cetuximab[83].

Based on the fact that the activation of IGF signaling pathway induced potent proliferative effects in hepatocytes and thereby promotes the development and progression of HCC, the targeting of this signaling pathway offers a relevant therapeutic intervention for HCC treatment. Thus, the inactivation of IGF-1R can induce growth inhibition, apoptosis or cell cycle arrest[84,85]. Also, the blockade of IGF-1R consequently leads to inhibition of its downstream signaling pathways in solid tumors[86]. Therefore, the development of a small-molecule inhibitor for IGF-1R may be relevant for HCC treatment. The targeted therapies currently available or those under the development for HCC treatment together with their possible molecular targets are outlined (Figure 3).

CONCLUSION

Hepatic angiogenesis sets an important point in the control of HCC progression, its inhibition is considered a valuable therapeutic approach for HCC treatment. In recent years, several studies focused on the investigation of cellular signaling mechanisms underlying HCC development, progression and invasion. In addition to the genetic alterations, chronic liver diseases including HCV infection clearly has a major role in the development and progression of HCC. Because chronic HCV infection is implicated in the modulation of abnormalities in several critical molecular signaling pathways, the attention of clinicians and researchers has focused on the mechanistic role of HCV infection in the regulation of HCC-associated signaling pathways. These pathways include both extra and intracellular-mediated mechanisms, which among them are the MAPK, PI3K/mTOR, WNT/β-catenin and IGF, and growth factor associated angiogenic signaling. Although a direct link between HCV infection and angiogenesis has been suggested in several studies, it is not clear, which factors actually drive the angiogenesis during the course of HCV infection. Further analysis is needed to address, in detail, the molecular mechanisms of HCV-induced hepatic angiogenesis. The investigation of these mechanisms may help to improve current therapies and in the design of an efficient alternative approach for HCC treatment. Thus, targeting signaling pathways that are directly involved in the regulation of hepatic angiogenesis may be a powerful strategy for HCC treatment.

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