Mini-Review

Current perspectives of recurrence and progression in hepatocellular carcinoma

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Abstract: There has been great progress in understanding the molecular biology of hepatocellular carcinoma (HCC) and in the development of new therapies, and cures are now possible in some patients. Nonetheless, the high rates of recurrence and metastasis remain significant clinical challenges. In this article, a PubMed database search was performed to identify the articles relevant to recurrence and progression of HCC. Many recent studies have examined mechanisms of HCC and potential targets for therapy of HCC in efforts to reduce postoperative recurrence. The invasion and metastasis of HCC are complex processes that involve multiple steps, including liver cancer stem cells, cancer biology, matrix metalloproteinases (MMP) and their regulatory factors, and tumor angiogenesis. With the deep going of understanding for HCC, and it seems that the new feasible strategies for cancer treatment will require a better understanding of the molecular mechanism of development and progression of HCC.

Keywords: Hepatocellular carcinoma (HCC); recurrence; progression

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Introduction

Hepatocellular carcinoma (HCC) accounts for the second place of cancer deaths, and is responsible for about 746,000 deaths per year worldwide (1). Five-year recurrence rates after liver transplantation in HCC patients meeting Milan or University of California San Francisco criteria were 5.8% and 14.3%, respectively (2). As shown in *Table 1*, several recent studies showed significant relationship between high Edmondson-Steiner grades (III–IV) and occurrence of recurrence, which increased the risk of development of tumor recurrence in patients with HCC (3-7). Despite extensive clinical as well as basic research efforts, the invasion and metastasis of HCC are the main reason of operative failure and the main factor affecting survival rate. Therefore, understanding mechanisms of HCC are even more important. In this review, we assessed these mechanisms that promote the recurrence and progression of HCC.

Liver cancer stem cells

As previously reported, liver cancer stem cells have been identified by several biomarkers such as EpCAM (8), CD24 (9), CD90 (10), and CD133 (11), and these liver cancer stem cells are relatively resistant to chemotherapy and capable of self-renewal. CD24 overexpression is associated with increased risk for tumor recurrence in HCC, and shorter disease-free survival. It is thought that CD24+ HCC cells functioned to initiate tumor self-renewal and growth by Stat3-mediated Nanog up-regulation (9).

Table 1 Relationship between Edmondson-Steiner grade and disease-free survival of HCC patients

Reference	Edmondson-Steiner grade	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Xiao *et al.* (3)	Low grade (I–II) *vs.* high grade (III–IV)	1.75 (0.88–2.36)	0.021	1.66 (0.71–3.15)	Non-significant
Lee K *et al.* (4)	Low grade (I–II) *vs.* high grade (III–IV)	–	–	1.265 (1.017–1.573)	0.034
Zhou *et al.* (5)	Low grade (I–II) *vs.* high grade (III–IV)	5.440 (3.337–8.867)	<0.001		
Perea Del Pozo *et al.* (6)	Low grade (I–II) *vs.* high grade (III–IV)	not determined (0.759–8.777)	0.129		
Zhu *et al.* (7)	Low grade (I–II) *vs.* high grade (III–IV)	1.866 (1.125–3.096)	0.016		

CD133+ liver cancer stem cell was promoted to self-renewal and growth by miR-130b, in part, through silencing p53-inducible nuclear protein (11).

Biological activity of liver cancer cells

Almost 32% of all human liver tumor cases show somatic mutation of p53, suggesting that tumor suppressor p53 has important roles in hepatocarcinogenesis (12). MDM2 overexpression is associated with increased risk for damaged cells to escape the cell-cycle checkpoint and become carcinogenic through Inhibiting p53 (13). Furthermore, the combination of p53 and MDM2 polymorphisms correlates with tumor progression and poor prognosis in postoperative patients with clinically (14). Human miR-146a is embedded on chromosome 5q34, which is a region that is often deleted in liver cancer (15), and miR-146a expression was negative correlated with increased HAb18G, vascular endothelial growth factor (*VEGF*), NF-κB p65 and beneficial prognosis of HCC (16).

Both β-catenin mutations and activation of H-ras signaling pathways, such as overexpression of insulin-like growth factor II or transforming growth factor α, occurs in human HCC (17) and β-catenin accumulation has been correlated with HCC progression (18). Moreover, Wnt-transforming growth factor-β-class plays a critical role in transforming growth factor-β activation, vascular invasion, and postoperative recurrence in patients with HCC (19). We previously investigated the expression of multiple genes in hepatitis B virus-related liver cancer and adjacent normal tissues by use of a cDNA microarray assay to establish the gene profile, and RT-PCR to measure expression of candidate genes. We found that normal liver tissues had low expression of Transmembrane 4 superfamily member 1 (*TM4SF1*), but liver cancer had high expression of *TM4SF1*, and suggest that *TM4SF1* overexpression correlates with tumor progression and poor prognosis in patients with HCC (20,21).

Cyclin D1 can form complexes with cyclin-dependent kinase 4 and cyclin-dependent kinase 6. These complexes have protein kinase activity and regulate the transcription of genes related to DNA replication in a positive feedback loop. This promotes cell progression from the G1 phase to S phase and leads cell proliferation (22). In HCC, numerous studies have reported *cyclin D1* overexpression, and a relationship of this overexpression with cell differentiation, invasive growth, and metastasis (23,24). *Cyclin D1* is overexpressed in liver cancer, and promotes the metastasis of liver cancer (25). Thus, the upregulation of *Cyclin D1* might play an important role in cancer cell invasion (26,27).

Proliferating cell nuclear antigen (*PCNA*) is necessary for DNA synthesis in eukaryotic cells. *PCNA* is an accessory protein of DNA polymerase, which is indispensable for DNA synthesis whose expression is correlative with cell proliferation and progression of the cell cycle. Thus, previous studies have used *PCNA* as a marker of cell proliferation (28). *PCNA* is not expressed in the G0 phase, first appears late in the G1 phase, reaches a peak in the S phase, and declines in the M phase. Malignancies are characterized by aberrant cell proliferation and thus *PCNA* may be used as an indicator of cell proliferation and biological activity of liver cancer cells (29). In liver cancer patients, *PCNA* overexpression is correlated with poor prognosis in postoperative patients (30). Moreover, *PCNA* expression is significantly higher in involved than in uninvolved vessels, and may be related to poor cell differentiation, high malignancy, and susceptibility to vascular involvement (31,32).

Studies of nude mice showed that a heterozygous mutation of the *Beclin-1* gene increased cell proliferation and

reduced autophagy, and that these *Beclin-1*$^{+/-}$ mice had a high incidence of liver cancer (33). In addition, after introduction of *Beclin-1* into nude mice, liver cancer cells exhibited increased autophagy, loss of the malignant phenotype, reduced cell proliferation, decreased colony formation rate, and reduced susceptibility to tumorigenesis (34).

Autophagy also plays important role in tumorigenesis. In particular, cancer cells with deficient apoptosis may counteract the incipient necrosis and inflammation via autophagy, and deficient autophagy is positively associated with malignant proliferation of cancers (35). Microtubule-associated proteins 1A/1B light chain 3A (LC3) is widely expressed in different types of cells, and may be a specific marker of autophagy (36). After surgery of liver cancer patients, elevated LC3 expression is associated with longer survival (37).

On the other side, autophagy also promotes the survival of cancer cells (38). Thus, autophagy is a double-edged sword: it inhibits tumorigenesis in the early phase of tumorigenesis, but it also allows cancer cells to adapt to their adverse metabolic environment and thereby improves their survival. In other words, autophagy has different roles in the different phases of tumorigenesis and in different cancers.

miR-122 overexpression in HCC cells stimulates the expression of E-cadherin, occluding, and α-catenin, and inhibits the expression of mesenchymal proteins (fibronectin and vimentin), RhoA/Rock pathway inactivation, and invasion of HCC cells (39). Loss of miR-1258 contributes to carcinogenesis and progression of HCC through targeting CDC28 protein kinase regulatory subunit 1B and associated with poor patients' survival (40). Recent studies showed that MTHFR C677T polymorphism was significantly associated with susceptibility to HCC in Chinese population, and MTHFR A1298C polymorphism was conversely associated with liver cancer risk in Chinese population (41). Decreased expression of fructose-1,6-bisphosphatase in HCC contributed to tumor progression and poor prognosis by altering glucose metabolism (42). HBx expression in liver cancer region of HCC is accompanied by the specific synthesis of sialyl lewis A and induced expression of N-acetylglucosamine-β1-3 galactosyltransferase V gene associated with the initial synthesis of sialyl lewis A, and N-acetylglucosamine-β1-3 galactosyltransferase V silencing suppressed hematogenous cancer cell adhesion to endothelial cells for cancer metastasis (43). Intercellular adhesion molecule-1 has the capability to induce the adhesion between cancer cells, and overexpression of intercellular adhesion molecule-1 correlates with HCC clinical tumor-node-metastasis stage, portal vein tumor thrombus, distant metastasis, and recurrence (44).

Vascular endothelial growth factor and its receptor in HCC

Proteins in the *VEGF* family, which are synthesized and secreted by normal cells and cancer cells, are important pro-angiogenic factors (45). *VEGF* binds to their receptors and promote the proliferation and metastasis of cancer cells by several mechanisms: mediation of the adhesion of cancer cells to endothelial cells and migration of cancer cells across endothelial cells; promotion of angiogenesis; phosphorylation and inactivation of pro-apoptotic proteins, leading to inhibition of apoptosis in cancer cells; and promotion of the differentiation and proliferation of cancer cells (46-49). *VEGF* significantly increases the activities of matrix metalloproteinase 2 (*MMP-2*) and *MMP-9* in liver cancer cells, and inhibition of *VEGF* almost completely blocks activation of these *MMP*s in liver cancer cells (50). In addition, *VEGF* may induce expression of *MMP-9* and act synergistically with *MMP-9* to induce angiogenesis in cancer, leading to cancer progression and metastasis. These findings suggest that proteins in the *VEGF* family play key roles in the recurrence and metastasis of liver cancer (51).

Urokinase-type plasminogen activator (uPA) and its regulatory factors

The extracellular matrix (ECM) also has a role in the angiogenesis and metastasis of cancers. In particular, degradation of the vascular basement membrane and the ECM is required for cancer angiogenesis (52). *uPA* and its inhibitor (PAI), and *MMP*s and their inhibitors (tissue inhibitors of metalloproteinases, *TIMP*s) play important roles in degradation of the ECM and basement membrane (53). *uPA* is a serine protease that binds to specific receptors on the cell membrane and activates plasminogen to plasmin; it also promotes the degradation of ECM (including laminin, fibronectin, proteoglycans, and type IV collagen) and the vascular basement membrane, leading to invasion and metastasis of cancer cells. *uPA* and plasminogen activator inhibitor-1 (*PAI-1*) have high expression in liver cancers. In particular, liver cancer patients with portal vein tumor thrombi and metastasis have significantly higher expression of *uPA* and *PAI-1* in tumor cells than in adjacent normal tissues and controls. Liver cancers that are positive for *uPA*, *uPA* receptor, and *PAI-1* are more susceptible to invasion and metastasis (*Figure 1*) (54).

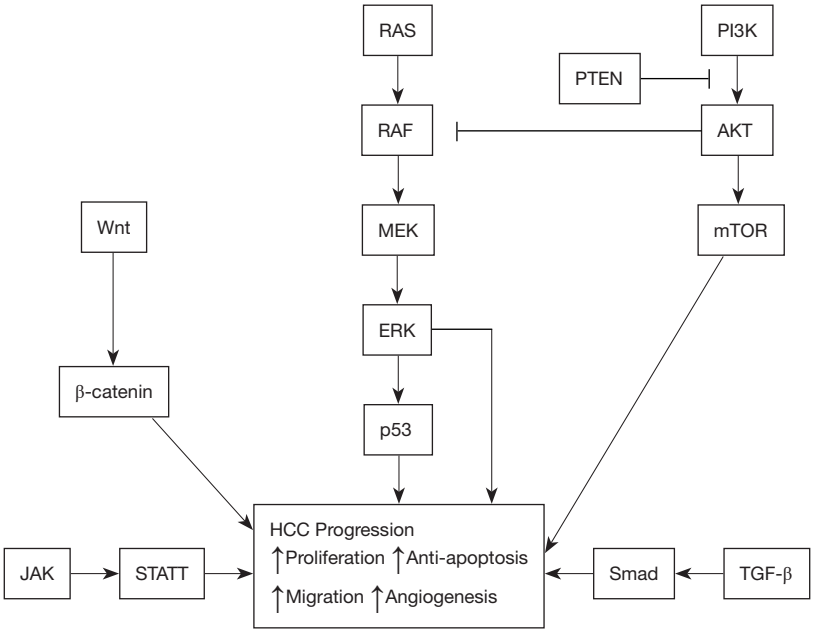

Figure 1 Potential mechanisms in HCC development and progression. Multiple steps and factors, including liver cancer stem cells, cancer biology, matrix metalloproteinases and their regulatory factors, and tumor angiogenesis, are recognized as the potential mechanisms involved in HCC cell invasion and metastasis.

Conclusions

In summary, the invasion and metastasis of HCC is a complex process involving multiple steps and factors. For new therapeutic strategies, a better understanding of the molecular mechanisms of development and progression of HCC is required. Characterizing the molecular mechanisms underlying HCC invasion and metastasis would help to improve the strategies for liver cancer therapy.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jxym.2017.09.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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