We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

2

Novel Therapeutic Targets for Hepatocellular Carcinoma Treatment

Yangchao Chen and Chi Han Li
School of Biomedical Sciences, Faculty of Medicine
The Chinese University of Hong Kong
Hong Kong SAR

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Surgery is a possible curative treatment, but most symptomatic HCC cases are in advanced stage where surgical resection is not possible. For this group of patients, the prognosis after any kind of therapy remains unsatisfactory due to high relapse rate (Llovet et al., 2003). Studies were rigorously conducted to tackle various obstacles in treating HCC, putting the focuses on targeting cancer cells that either disseminated from the tumor origin, or escaped from therapeutic effects. Recently, a multikinase inhibitor sorafenib was approved by FDA for the treatment of advanced HCC patients. It marks a major advance in the field as the first efficacious targeted therapy for HCC. The primary molecular targets of sorafenib include vascular endothelial factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR) and Raf (Wilhelm et al., 2004). Although it significantly prolongs both patient survival and the time to progression, its overall survival benefit is modest (Llovet et al., 2008).

Other HCC associated targets, such as epidermal growth factor (EGF) signaling (Hampton, 2007), telomerase (Djojosubroto et al., 2005) and cyclooxygenase (Márquez-Rosado et al, 2005), were studied intensively with regard to their therapeutic effects. However, the benefits are far from satisfactory, so there is still a need to identify new therapeutic targets. The exploration of new targets against HCC involves multiple disciplines including hepatology, oncology, pathology and molecular studies. Increasing number of therapeutic targets which play crucial roles in HCC were identified. Identification of new targets not only improves the current HCC therapeutic modality, but also drives a deeper understanding of HCC that allows personalized treatment in the future. In this chapter, we will briefly review the novel molecular and cellular players that contribute to HCC tumorigenesis and progression, and evaluate their potential as additional therapeutic targets.

2. Growth receptor signaling

The studies of sorafenib administration and other growth signaling inhibitors demonstrated the prowess of targeting growth signalings such as epidermal growth factor (EGF), VEGF and PDGF pathways. In HCC, many other growth signalings were identified that markedly contributes to tumorigenesis and pathogenesis. They include insulin-like growth factor

signaling and mTOR pathway, and numerous studies suggested these pathways can be the targets against HCC.

2.1 Insulin-like growth factor signaling

The insulin-like growth factor (IGF) signaling pathway is frequently dysregulated in HCC. The activation of IGF signaling can be established in malignant cells through an autocrine route when the activated signaling is induced by an overexpressed IGF ligand in HCC cells (Nussbaum et al., 2008). Insulin-like growth factor 2 (IGF-2) is increased after an inflammatory response to liver damage or viral transactivation (Feitelson et al., 2004), and it is the major ligand contributing to the increased IGF activity in HCC. IGF-2-mediated induction of IGF signaling is prevalent in human HCC, where IGF-2 is overexpressed in 16-40%, whilst the level of competitive receptor for IGF-2 is decreased in around 80% (Whittaker et al., 2010). As such, IGF receptor-ligand binding is enhanced, and subsequent downstream signaling is activated in cancer cells. Activation of IGF signaling in HCC cells is associated with increase of cell proliferation rate (Schirmacher et al, 1992). While RNAi-mediated knockdown of IGF-2 could reduce the cell proliferation and induce apoptosis in HCC cells, small molecule inhibiting IGF-2-dependent IGF signaling was able to impair the growth of HCC cells and retard tumour growth in mice xenograft (Lund et al., 2004).

Altered IGF-2 bioavailability is another reason for the hyperactivation of IGF signaling in HCC. Normally, circulating IGF-2 is bound by IGF-binding protein (IGFBP) so that the efficiency of ligand-receptor binding is lowered. In HCC, members of IGFBPs are downregulated so that less IGF-2 is sequestrated which allow uncontrolled IGF-2-receptor interaction (Hanafusa et al, 2002). Hence, reducing the level of IGF-2 in circulation is another valid approach to abrogate the IGF signaling. Re-introduction of recombinant human IGFBP-3 was tested and showed potent effect in lowering the activity of IGF-2 (Aishima et al., 2006). IGFBP-3 was able to inhibit cancer cell growth and attenuate mitogenic activity of HCC cells. It is also reported that IGFBP-3 decreased the phosphorylation and activity of numerous pro-tumorigenic proteins such as IRS-1, MAPK, Elk-1, Akt-1 and phosphatidylinositol 3'-kinase (Huynh et al., 2002).

In addition, inhibition of IGF signaling can also be achieved by disrupting other players along the IGF signaling axis. IGF signal transduction is mediated by the Insulin receptor, IGF-IR and a hybrid of both receptors. In HCC, there is detectable level of IGF receptors ready for the signal generation stimulated by the overexpressed IGF-2. Studies showed that blocking of the receptors was able to give antitumoral effect in HCC cells (Nussbaum et al., 2008). Selective blockage of IGF-IR by monoclonal antibody effectively disrupted IGF signaling, reduced cell viability and proliferation. The inhibition of IGF-IR signal initiation was able to delay tumor growth and prolonged survival in vivo (Tovar et al., 2010). With understanding of IGF signaling mechanism in HCC, it is possible to employ various strategies to effectively inhibit IGF signaling, and in turn suppress cell proliferation and increase apoptosis in HCC.

2.2 mTOR pathway

mTOR pathway is a downstream growth signal induced by EGF and IGF signaling, and is coupled with PI3K/AKT pathway. mTOR pathway has an important role in the

pathogenesis of HCC, where aberration of mTOR pathway was seen in 15% to 41% of HCC cases ranged from 15% to 41% (Hu et al., 2003). In HCC, the commonly hyperactive EGF and IGF signaling is responsible for the induction of PI3K/AKT/mTOR pathway, promoting tumor progression. The mTOR signaling is mediated by mTOR complex 1 and 2 (mTORC1 and mTORC2). mTORC1 is comprised of mTOR, regulatory associated protein of mTOR (RAPTOR), and mammalian LST8/G-protein β-subunit–like protein. mTORC1 is a downstream signal of AKT, and has a pivotal role in regulating cell growth and proliferation. mTORC1 activates S6 kinase to regulate protein synthesis and induces cell cycle to proceed from G1 to S phase (Bjornsti and Houghton, 2004).

Besides, mTOR is also the subunit of mTORC2 which consists of a protein RAPTOR-independent companion of mTOR (RICTOR), and proline-rich protein 5/G-protein β-subunit–like protein. Unlike mTORC1 which is inducible by AKT, mTORC2 plays a critical role in the phosphorylation and activation of AKT (Sarbassov et al., 2005). The serine/threonine kinase AKT acts as a cytoplasmic regulator of numerous signals. It is shown that AKT is frequently amplified and overexpressed in various cancers, and it demonstrates significant oncogenic properties in diverse cancer types. In homeostasis condition, AKT is negatively regulated by the tumor-suppressor PTEN. However, increased activation of AKT is often observed, because PTEN is frequently lost in cancers including HCC. Other than mTORC1, AKT regulates a wide-spectrum of targets such as cyclin D1 and MDM2/p53 (Vivanco & Sawyers, 2002). In HCC, aberration of mTORC2 enhances AKT activity, induces downstream AKT targets and promotes tumorigenesis. One can see that the AKT regulating effect of mTORC2 is as important as mTORC1 within the PI3K/AKT/mTOR pathway.

Recently, it is suggested that the PI3K/AKT/mTOR pathway can be a major molecular target in cancer remedy. As a critical player in the mTOR signaling, the activity of mTOR often increases in HCC. Blockage of mTOR-mediated signaling showed antineoplastic activity in different experimental models of HCC. The use of mTOR inhibitors could reduce cell proliferation in vitro, and decrease tumor growth in xenografted mouse model (Villanueva et al., 2008). mTOR inhibitors such as sirolimus and everolimus demonstrated potent antitumor properties. Encouraging results were obtained when both mTOR inhibitors were studied in clinical trials, either as a single agent or as adjuvant. Furthermore, components in the mTOR complexes can also be the therapeutic targets. High level of RICTOR is correlated to early recurrence in HCC, and siRNA knockdown of RICTOR reduces HCC cells viability (Villanueva et al., 2008). Disruption of mTOR complexes might have additive benefit along with mTOR inhibition to abrogate mTOR pathway in treating HCC.

3. Cell-surface protein

3.1 Glypican-3

Glypican-3 (GPC3) is a protein anchored to the cell surface by a glycosyl-phosphatidylinositol link. Glypican-3 is highly expressed in HCC, and plays a role in stimulating various tumorigenic signaling pathways. GPC3 is specifically expressed in HCC, but not in cholangiocarcinoma or normal liver tissue. More than 70% of HCC tumors were observed with high GPC3 level compared to normal liver tissues (Hsu et al., 1997). Consistent with the high GPC3 protein expression found in clinical samples, numerous

HCC cell lines have high expression level of GPC3 (Midorikawa et al., 2003). In addition, GPC3 expression is correlated with the prognosis of HCC, where GPC3-positive HCC patients have a significantly lower 5-year survival rate than patients who are GPC3-negative (Shirakawa et al., 2009).

One of the GPC3 tumorigenic roles is the activation of Wnt/β-catenin signaling. It is shown that GPC3 is able to interact with Wnt ligands, and induces canonical Wnt-signaling to trigger the stabilization of β-catenin and induction of cyclin D1 (Capurro et al., 2005). The heparin sulfate chain of GPC3 is reported to bind with basic growth factors such as FGF-2. The interaction between GPC3 and FGF-2 is frequently observed in HCC cells, and is responsible for phosphorylation of ERK and AKT (Midorikawa et al., 2003). This interaction plays a role in the increase of HCC cell proliferation, and growth of tumor in nude mouse model. Additionally, GPC3 interplays with hedgehog signaling in regulating developmental growth (Capurro et al., 2008). Though yet to be elucidated, the GPC3-hedgehog signaling is suggested to contribute to HCC development.

Targeting GPC3 and its related growth signaling is a relevant approach to inhibit HCC growth. Inhibition of the interaction between GPC3 and Wnt or FGF-2 should theoretically reduce HCC growth (Capurro et al., 2005; Midorikawa et al., 2003). GPC3 is also a useful target in immunotherapy against HCC. The therapeutic monoclonal antibody against GPC3 has been developed which could induce antibody-dependent HCC cytotoxicity. Targeting GPC3 is able to inhibit tumor growth of HCC cell line xenograft (Ishiguro et al., 2008). Study also showed the concomitant treatment with GPC3 monoclonal antibody and sorafenib was more potent in preventing tumor growth than sorafenib alone in the HepG2 xenograft model (Ishiguro et al., 2008). It is likely that targeting GPC3 could provide great clinical benefit during HCC management.

3.2 Cadherin 17

Cadherins are important cell adhesion molecules strongly associated with cancer progression. Downregulation of E-cadherin (Du et al., 2009) and overexpression of P-cadherin are often observed in advanced tumor which processes crucial cellular event like epithelial-mesenchymal transition (Sun et al., 2011). Cadherin 17 (CDH17) is another adhesion molecule upregulated in HCC, and it is linked to the tumorigenesis in various gastrointestinal regions (Wang et al., 2005). The upregulation of CDH17 is capable of transforming premalignant liver progenitor cells into liver carcinomas in mice. While forced expression of CDH17 promoted tumor growth from hepatic progenitor cells, silencing of CDH17 reduced the aggressiveness of metastatic HCC cells (Liu et al., 2009). Knockdown of CDH17 by RNA-interference decreased the proliferation rate of HCC cell lines despite their metastatic potential in vitro and in vivo. It is shown that targeting CDH17 can concurrently inactivate Wnt/β-catenin signaling and reduce cyclin D1 level, leading to both growth inhibition and cell death. Inhibition of CDH17 results in the re-localization of nuclear β-catenin to the cytoplasm so as to attenuate the Wnt/β-catentin signaling (Liu et al., 2009).

Multiple isoforms of CDH17 protein are present in the HCC samples, and it is found that the isoform lacking exon 7 is the most abundant in HCC samples (Wang et al., 2005). CDH17 isoform lacking exon 7 cannot be found in normal liver tissue whereas it is present in about 50% of human HCC and 30% of premalignant tissues. Detection of this CDH17 isoform was

strongly correlated with the prognosis of HCC patients, predicting a shorter overall survival rate as well as higher relapse rate and venous infiltration after surgery (Wang et al., 2005). This CDH17 isoform, together with others that are exclusively expressed in HCC, might contribute to the pathogenesis of HCC. Strategy to target the isoforms of CDH17 allows specifically aiming malignant cells rather than the normal hepatocytes. All available evidences suggested that targeting CDH17 might be a prospective molecular-based therapy in HCC.

4. Metabolic pathway

4.1 Arginine metabolism

Arginine content is well-known to affect transplanted tumor in mice. Enhanced in vivo tumor growth is observed when mice were fed with diet rich in arginine. On the other hand, depletion of arginine from their diet inhibits the growth of metastatic tumor (Gonzalez & Byus, 1991). It is later proved that arginine is essential for the survival of cancer cells. Cancer cells are dependent on exogenous arginine for growth because most of them cannot synthesize their own and become auxotropic for arginine (Dillon et al., 2004). There are various explanations for the acquisition of arginine auxotropic phenotype in various cancer cells, but generally it is associated with the downregulation of argininosuccinate synthase (ASS) (Dillon et al., 2004). Arginine auxotrophy is also a common phenomenon in HCC cells due to their lackage of ASS (Ensor et al., 2002).

In somatic cells, deficiency of arginine puts cell cycle on hold, and cells enter the quiescence G_0 phase. They can tolerate the depletion of arginine for weeks and return to normal condition once the arginine content is resumed. On the other hand, arginine deficiency is not sustainable in cancer cells (Delage et al., 2010). Defect in cell cycle checkpoint drives continuous cell proliferation even with insufficient arginine, but arginine is necessary for metabolic and enzymatic pathways in malignant cells. In essence, cancer cells with shortage of ASS rely heavily on exogenous arginine. If the uptake of arginine is disrupted, or the stability of arginine is lowered, cell death will occur due to a loss of gross balance (Delage et al., 2010). This physiological difference between normal and cancer cell makes the arginine metabolic pathway a potent target in treatment to distinguish HCC cells from normal cells.

Reducing arginine stability is one of the strategies against malignant cells, and arginine-degrading enzyme is the major group of enzymes that can serve the purpose in depleting internal arginine. Arginase belongs to such group of enzyme which is responsible for arginine degradation in the urea cycle, and its anticancer effect is well documented (Bach et al., 1963). In addition to arginase, the enzyme arginine deiminas is proved to efficiently deplete cellular arginine in vitro and in vivo (Cheng et al., 2007). Recombinant arginine-degrading enzymes were developed, and their anticancer effect was investigated in HCC. Satisfactory result was obtained using recombinant arginase and arginine deiminas to combat ASS-deficient tumors (Izzo et al., 2004). Studies are conducted to improve the efficacy of these arginine-degrading enzymes. Modification such as pygelation can increase the half-life of the enzyme and prolong its activity. Phase III trial deploying a pegylated form of recombinant ADI is undertaken in HCC patients who have failed prior systemic treatment. It is also reported that a modified recombinant human arginase is able to inhibit ASS-positive HCC, and inhibit tumor cell growth (Cheng et al., 2007).

4.2 GLUT1-mediated anaerobic glycolysis

Due to the high proliferation rate and cell motility rate, the energy requirement of malignant cells is immense. It is suggested that malignant cells have their metabolic rate accelerated in order to accommodate the excess energy consumption, and glucose is the basic unit necessary. Like most cancers, HCC has high glucose requirement and is observed with an increase of glucose metabolism. While glucose metabolism in eukaryotic cells has multiple levels of control, transport of glucose across the cell membrane is the first rate limiting step. Indeed, accelerated glucose metabolism in cancer cells has been associated with increased expression of glucose transporter proteins. In HCC, increase uptake of glucose is mediated by glucose transporter GLUT1. GLUT1 expression is elevated in hypoxic conditions, and this elevates the rate of anaerobic glycolysis which is a metabolic event frequently observed in HCC (Amann et al., 2009). Level of GLUT1 determines the rate of anaerobic glycolysis, affects glucose uptake and utilization, and plays a role in metastasis, chemoresistance and immunity evasion.

Increased GLUT1 expression is observed in all HCC cell lines compared with primary hepatocytes, and this increase could be found in a subset of HCC patients (Amann et al., 2009). It is demonstrated that suppression of GLUT1 expression by siRNA significantly impaired the tumorigenicity of HCC cells. Inhibition of GLUT1 could decelerate anaerobic glcolysis, implied by the reduction of both glucose uptake and lactate secretion (Amann et al., 2009). RNAi-mediated targeting of GLUT1 is a potent way to combat cancer cells as shown in the study of gastric cancer and laryngeal cancer. GLUT1 is possibly a druggable target as it is shown that the ATP-binding site is important for the conformation and transporter affinity (Liu et al., 2001). Several substances have demonstrated the ability to inhibit GLUT1 and cause cancer cell death (Martin et al., 2003). To increase the GLUT1 targeting specificity, derivatives of the GLUT1 inhibitors were generated and showed promising anticancer effect (Morris et al., 1991).

Glucose analogues or glucose conjugates also serve to inhibit anaerobic glycolysis. Glucose analog such as 2-Deoxyglucose reduced the proliferation rate of many hepatoma cells (Ingram et al., 2006), and showed enhanced anticancer effects in combination with conventional chemotherapeutic drugs such as adriamycin or paclitaxel in xenografted mice (Maschek et al., 2004). The use of ketogenic diets is an alternative strategy to target the anaerobic metabolism, which is based on a high fat and low carbohydrate diet and mimic the metabolic state of fasting (Zhou et al., 2007). As a result, a reduction of carbohydrate intake occurs which allows ketones as an alternative fuel for normal tissue. All in all, disruption of critical metabolic pathways in HCC cells or targeting the main components of the pathways might become alternative therapeutic strategies.

5. Protein folding and turnover

5.1 Heat shock protein 90

Heat shock protein 90 (HSP90) belongs to a highly conserved family of molecular chaperones. It plays a role in protein homeostasis by controlling the stabilization and activation processes of different proteins (Pearl et al., 2008). HSP90 level is often increased in various tumors, which is associated with the continuous protein translation and cell proliferation during stress condition (Workman et la., 2007). Upregulation of HSP90 is often

associated with increased cyclin-dependent kinase 4 activity, and both were believed to contribute to HCC development (Pascale et al., 2005). HSP90 is involved in the folding and activity of many bona fide oncoproteins in tumor cells, maintaining their dysregulated expression and mutational status. Subsequently, tumor cells become sustainable for cell growth and survival, and equip with crucial aberrations required for metastasis (Whitesell & Lindquist, 2005).

HSP90 is proved to be an efficacious therapeutic target in HCC. Inhibition of a broad-spectrum tumorigenic mechanism is resulted when HSP90 is targeted in vitro and in vivo. Independent of the etiological background, all HCC cell lines responded to HSP90 inhibition similarly with increased cell cycle arrest and apoptosis (Breinig et al., 2009). It might due to the fact that HSP90 inhibition triggered a simultaneous degradation of various hepatocarcinogenesis driving factors. In vivo studies showed that inhibitor of HSP90 is tumor-cell specific, and is able to efficiently reduce HCC tumor growth. Newly developed HSP90 inhibitor showed a lack of significant hepatotoxicity and is more tolerated, which become more practical in therapeutic treatment (Breinig et al., 2009). HSP90 inhibition further prevents tumor growth by disruption of tumor angiogenesis, as demonstrated by blocking PDGFR-β expression in vascular smooth muscle cells and VEGF2 expression on endothelial cells (Lang et al., 2009). Moreover, the combinatory use of HSP90 inhibitor and other anticancer agents is proved to be beneficial. Blockage of HSP90 is able to enhance the antitumor effect of mTOR inhibitor rapamycin by blocking the alternative AKT signaling induced by rapamycin (Lang et al., 2009). Inhibition of HSP90 can be invaluable clinically during HCC treatment, either by targeting HSP90 alone or in combination with other anticancer agent.

5.2 Ubiquitin-proteasome system

The ubiquitin-proteasome system plays a crucial role in maintaining cellular homeostasis such as regulation of the cell cycle, apoptosis, receptor signaling and endocytosis. Aberration in different ubiquitin-proteasome systems is recognized as the fundamental cause of various human diseases including cancer. The dysregulation of NF-κB in HCC is one of the oncogenic events induced upon defect in ubiquitin-proteasome system. It is also observed proteins expressed by HBV (Hu et al., 1999) and HCV (Munakata et al., 2005) are reported to cause the alteration of different ubiquitin-proteasome systems, contributing to viral replication, hepatotumorigenesis and impairment of host immunity. These findings demonstrate the importance of an intact ubiquitin-proteasome system in preventing HCC development (Chen, 2005). In the United States, a proteasome inhibitor bortezomib is used clinically to manage late-stage multiple myeloma (Chauhan et al., 2008). Studying the mechanisms of various ubiquitin-proteasome systems not only enable a better understanding of cancers, but also help to explore new strategies to cancer management.

5.2.1 Gankyrin

In human HCC, a small proteasome regulatory subunit called gankyrin is frequently over-expressed at both mRNA and protein levels. A study showed gankyrin expression levels were highly upregulated in hepatoma cell lines, and its level was higher in HCC samples compared to normal livers, and premalignant or cirrhotic livers (Higashitsuji et al., 2000). Gankyrin is found to interact with retinoblastoma, increasing its phosphorylation level so as

to reduce cellular retinoblastoma stability (Li et al., 2005). In addition, gankyrin increases both the association and activity of MDM2 for p53. This inactivates p53 by increasing the ubiquitylation level of p53 and in turn driving proteasomal degradation of p53 (Higashitsuji et al., 2005). Gankyrin also promotes HCC growth through the activation of oncoprotein D cyclin-dependent kinase 4 (CDK4). The activity of the kinase is negatively regulated by p16 during stress condition, but this inhibitory effect is removed when gankyrin competes with p16 for the binding of CDK4 and thus allows the activation of CDK4 (Dawson et al., 2002). Other than tumor promoting effect, gankyrin contributes to cancer drug resistance. It desensitizes cancer cells to the effect of DNA-damaging chemical agents by preventing p53-dependent apoptosis (Higashitsuji et al., 2005).

The use of RNAi to knock down gankyrin in HCC resulted in a decrease of cell growth, as well as reduction in observed levels of hyperphosphorylated retinoblastoma (Li et al., 2005) and restoration of caspase 8/9-dependent apoptosis (Higashitsuji et al., 2005). Silencing of gankyrin expression also reportedly attenuated epithelial to mesenchymal transition together with cell migration and invasion. The inhibition of gankyrin also reduced the level of nuclear β-catenin (Dong et al., 2011), c-myc, cyclin D1 (Fu et al., 2011) and insulin-like growth factor binding protein 5 (Umemura et al., 2008). The close relationship with several pro-tumorgenic events makes gankyrin a rationale target during HCC treatment.

5.2.2 X-linked inhibitor of apoptosis

X-linked inhibitor of apoptosis (XIAP) belongs to the inhibitor of apoptosis (IAP) domain-containing family, and is famous of its anti-apoptotic ability. They are induced by NF-κB signaling to circumvent the pro-apoptotic effect induced by JNK pathway (Kaur et al., 2005), by inhibiting caspase-mediated apoptosis. Apart from this, XIAP participates in the regulation of transforming growth factor β (TGF-β) -induced apoptosis through an ubiqutin-proteasomal regulating machine. XIAP is able to complex with TGF-β activated kinase 1 (TAK1), as such this negatively regulates the TGF-β signaling (Chen, 2005). The RING domain of XIAP is responsible for the poly-ubiquitylation of TAK1, resulting the proteasome-mediated degradation of TAK1. Subsequently, it disrupts the activation of JNK signaling and halts apoptosis. It is speculated that the involvement of XIAP in HCC is common given that most HCCs acquire resistance to TGF-β-mediated cell killing (Chen, 2005). Moreover, TAK1 is important for the phosphorylation and activation of the IKK complex. Increased activity of IKK leads to the degradation of the IκB-α inhibitor of NF-κB and subsequent activation of classical NF-κB signaling. Activation of IKK also causes the degradation of MKK7, the upstream kinase essential for activation of JNK signaling. Reduction of MKK7 level could ablate the JNK signaling and inhibit apoptosis (Kaur et al., 2005).

Inhibition of XIAP sensitizes HCC cells to apoptotic signal owing to retaining of TAK1. In doing so, persistent activation of JNK signaling is resulted whenever the TGF-β-mediated apoptotic signal is induced. Stabilized TAK1 also potentially attenuate the influence of NF-κB signals (Chen, 2005). Besides, it is reported XIAP inhibition in HCC enhanced TRAIL-mediated cell killing. The combination of XIAP silencing shRNA and tumor-necrosis factor-related apoptosis TRAIL is reported to generate potent antitumor effect in HCC cells and tumors in animal models (Pan et al., 2008). Targeting XIAP further renders HCC cells vulnerable to other therapeutic effect by releasing the break for caspase-mediated apoptosis

(Deveraux et al., 1997). All in all, inhibition of XIAP or blockage of interaction between XIAP and TAK1 may be one of the best HCC management strategies.

6. HCC tumor microenvironment

It is gradually accepted that the progression and aggressiveness of cancer cells are defined by the tumor-stromal interaction. In HCC, the tumor microenvironment plays a pivotal role in affecting cancer development. Through paracrine and autocrine mechanisms, the stromal components communicate with the tumor, promoting the HCC cell proliferation, survival, and allowing them to invade and metastasize. In the past, majority of targeting therapies are derived from the research focusing on intracellular events of cancer cells. However, limited studies are able to be translated into effective therapies, because they ignored the influence from the surrounding components. Although the field is still in its embryonic stage waiting to be explored, targeting the interaction between tumor-stromal may be a more logical approach against HCC.

6.1 Hepatic stellate cells

Stromal remodeling occurs routinely during the development of hepatic fibrosis, cirrhosis and HCC, featured with the infiltration of activated hepatic stellate cells (HSC). Upon hepatic injury, HSCs is stimulated and transformed to acquire an activated myofibroblast-like phenotype that is responsible for the excessive hepatic matrix deposition in chronically damaged livers. They are densely located in tumor sinusoids, fibrous septa and HCC-generated capsule. Activation of HSC is recognized as a key event during hepatotumorigenesis (Zhao et al., 2011).

Activated HSCs considerably increase the activity of NF-κB and ERK in HCC. It is known that both NF-κB and MAP kinase/ERK pathways are involved in the progression of human HCC, and they induce the proliferation of HCC cells, and protect HCC cells from apoptosis (Amann et al., 2009). The paracrinal communication between HSC and HCC forms the major linkage for the induction of HCC development. Several soluble factors secreted by activated HSC are identified to be responsible for the tumorigenic effects. HSC released a substantial amount of protumorigenic factors, including the hepatic growth factor (HGF), which enhances the invasiveness of HCC cells. The growth and the migration capability of HCC were impaired once the binding of HGF to HCC cells was disrupted (Barnaeva et al., 2007). Other studies demonstrated that TGF-β secreted by HSC accelerated tumor progression in neoplastic hepatocyte (Sano et al., 2005). TGF-β was able to induce epithelial to mesenchymal transition and augment PDGF signaling in oncogenic Ras-transformed hepatocyte. It is believed that a combination of HSC-released growth factors consisting of FGF-1 and -2, PDGF and IGF are responsible for promoting HCC tumorigenesis (Bataller & Brenner, 2005). The emerging evidences support that the activated HSC/myofibroblasts in tumor microenvironment have huge impact on HCC development and progression, and this stromal components should be regarded as one of the primary targets in HCC therapy.

6.2 Heparan sulfate proteoglycan modulating enzymes

Heparan sulfate proteoglycans (HSPG) play important biological roles in both cellular and extracellular context, contributing to the proper communication between cells and their

surrounding components. While extracellular HSPGs function to maintain extracellular matrix (ECM) self assembly and integrity with other ECM molecules, cell surface HSPGs are responsible for the binding of growth factors, chemokines, cytokines and enzymes. In addition to normal biological process, HSPGs also influence a number of pathological events including inflammation, tumor growth, metastasis and angiogenesis.

6.2.1 Heparanase

Evidences suggested that the expression of heparanase, an enzyme that degrade the side chain heparin sulfate, is closely related to tumor invasion, angiogenesis and metastasis in HCC (El-Assal et al., 2001). Heparanase level is high both in HCC patient serum and tumor tissues. Heparanase level in serum is linked with the aggressiveness of HCC (Wang et al., 2010), and that in tumors is positively correlated with tumor size, staging and portal vein invasiveness (El-Assal et al., 2001). It is speculated that the major pro-tumorigenic effect of heparanase is derived from the ability to cleave HSPG, resulting in the release of HS-bound molecules such as ECM digesting enzymes and angiogenic factors. Consequent ECM degradation and angiogenic factor released combine to construct a microenvironment favorable for HCC cell migration and invasion (Zhang et al., 2007).

Extensive cleavage of heparin sulfate might release other cell surface bound factors such as growth factors and chemokines that potentially generate diverse biological effects in both autocrine and paracine manners. Upregulation of heparanase is associated with increased releasing of basic fibroblast growth factor (bFGF). bFGF released in this way contributes to tumor progression through the activation of oncogenic signaling and construction of a favourable tumor niche (Zhao et al., 2006).

Targeting heparanase provides a novel perspective in managing HCC by modulating the tumor-stromal communication. Knocking down of heparanase can significantly inhibit the invasiveness, metastasis, and angiogenesis of HCC cell both in vitro and in vivo (Zhang et al., 2007). Several molecule inhibitors of heparanase can also attenuate the progression of hepatoma cells. The antitumor effect is possibly generated by preventing the degradation of ECM and basal membrane. Another study showed inhibiting heparanase could effectively stop the release of bFGF so as to inactivate the bFGF signaling effect and suppress subsequent angiogenesis (Zhao et al., 2006). These findings have gradually switched the attention in cancer therapy research, from focusing solely in intracellular targets to the interplay between cancer cells and the surrounding microenvironment.

6.2.2 Sulfatase 2

Another important feature of heparin sulfate chains is related to its substrate binding capacity. 6-O-sulfation, a type of heparin sulfate modification, is known to play a specific role in modulating ligand binding. The enzyme SULF2 is a member of the sulfatase family that modulates critical cellular signaling pathways by the removal of 6-O-sulfation (Morimoto-Tomita et al., 2002). In contrast to another sulfatase member tumor suppressor SULF1, SULF2 has an oncogenic role in cancer, and its expression is elevated in HCC. Upregulation of SULF2 is observed in 57% HCC tissues and 73% HCC cell lines. Level of SULF2 is positively correlated with a more aggressive tumor phenotype and poorer patient survival (Lai et al., 2008). Ectopic expression of SULF2 promoted cell proliferation and

migration in various HCC cell lines, and enhanced tumor growth in vivo. The tumorigenic effect of SULF2 is partially brought by the induction of the aforementioned pro-cancerous glypican-3 expression. It was found that SULF2 enhanced the binding of FGF2 to the cancer cell and activated FGF signaling in a glypican-3 dependent manner (Lai et al., 2008). In addition, SULF2 increased cell surface glypican-3 and Wnt3a level in HCC, leading to the increase of glypican-3-dependent Wnt/β-catenin signaling (Lai et al., 2010).

SULF2 is a rational target in HCC therapy as suggested by several SULF2 knockdown studies. RNAi-induced suppression of SULF2 reduced the cell growth and migration in cell lines with high SULF2 expression (Lai et al., 2010) in vivo and in vitro. Knockdown of SULF2 was able to reduce the expression of GPC3, as well as the activity of FGF signaling by blocking FGF2 binding (Lai et al., 2008). Reduction of GPC3 also downregulates Wnt3a expression, and attenuates the Wnt/β-catenin signaling with reduced phosphorylated GSK3-β and β-catenin. Given the relationship between SULF2 and GPC3, it is worthwhile to investigate the clinical benefit in targeting SULF2 in HCC treatment. Furthemore, SULF2 protects against caspase 3 and 7 mediated apoptosis induced by PI3K, ERK and JNK inhibitor. Inhibition of SULF2 re-sensitized HCC cells to the drug-induced apoptosis by reducing phosphorylation of AKT, downregulation of cyclin D1 and anti-apoptotic BCL-2, as well as upregulation of pro-apoptotic BAD (Lai et al., 2010). The findings might have implication to develop combinatory treatment against drug-resistant HCC.

7. Epigenetic modulator

Abnormal epigenetic events are frequently observed in HCC, which can alter gene expression through modification of histone tails or DNA. The major players contributing to these aberrations such as DNA methyltransferase and histone deacetylase are under intensive investigations. In fact, there are many other players involved during the establishment of aberrant epigenetic status. Among them, polycomb repressive complexes (PRC) are catching more attention recently due to their significant roles during cancer development via suppression of various tumor suppressor genes (Steele et al., 2006). In human, there are two polycomb repressive complexes namely PRC1 and PRC2. Despite their unique gene repression mechanism, both of them are frequently involved in the oncogenesis of HCC. Targeting of epigenetic modulators in theory generates persistent effects on tumors as heritable changes are induced. Such an approach is superior to targeting other molecular players that only bring out transient effects.

7.1 BMI1

PRC aroused increasing attention recently as they are shown to contribute heavily in the maintenance of stem cell and the determination of cell fate. BMI1 is a critical component of PRC1 in mediating the ubiquitination of histone in order to regulate local gene expression. BMI1 is not detected in normal hepatocyte but is overexpressed in HCC. Dysregulation of BMI1 is speculated to promote activation of cancer stem cell in HCC. BMI1 has a higher basal level in the side-population (SP) cell where such a subgroup of cancer cells is characterized by the ability to exclude Hoechst 33342 dye via the ABC cassette transporter. This subpopulation is believed to harbor stem cell properties, and BMI1 is shown to play a crucial role in their self-renewal process (Chiba et al., 2008).

BMI1 mediates stemness features in HCC cells. In HCC, SP cells expressing BMI1 showed enhanced tumorigenic potential compared to the corresponding non-SP cells. Knockdown of BMI1 markedly abolished the tumor-initiating ability of SP cells in non-obese diabetic/severe combined immunodeficiency mice, leading to a 100 fold decrease of tumorigenic activity (Chiba et al., 2008). Such decrease in tumorigenic activity was accompanied with a reduction of SP cell number in different HCC cell lines. It is shown that BMI1 mediates the suppression of INK4A/ARF and drives self-renewal. Inhibition of BMI1 resulted in the derepression of INK4A/ARF, and in turn disrupted self-renewal in SP cells, hence suppressed SP cells survival upon long time culture. BMI1 additionally regulates diverse cellular processes including cell cycle, apoptosis and senescence by the repression of the INK4A/ARF expression (Xu et al., 2009).

Since there are numerous targets of BMI1 in human genome, it is predictable that the oncogenic effect of BMI1 should not simply depend on INK4A and ARF repression. BMI1 was able to cooperate with activated RAS to transform hepatocytes into malignant cells (Xu et al., 2009). Furthermore, BMI1 expression in HCC is significantly associated with the expression of ABC transporter B1 (ABCB1) which was consistently reported to generate the multiple drug-resistant phenotype (Effendi et al., 2010). It is possible that one of the downstream targets of BMI1 is ABCB1. The ability to eliminate cancer progenitor cell in HCC by BMI1 inhibition is a potent anticancer mediation, and potentially provides a cure for HCC patients.

7.2 EZH2

Polycomb repressive complex 2 (PRC2) is another modifier of the chromatin structure, which determines the activity of gene expression. PRC2 primarily regulates gene expression by inducing the methylation on lysine 9 and lysine 27 of histone 3, and plays important roles during development and tumorigenesis. In this complex, EZH2 is the catalytic subunit directly involves in transferring methyl-group to the histone tails (Kirmizis et al., 2004). The level of EZH2 is important in determining the PRC2 activity in cells. EZH2 regulates cell proliferation, and its expression is often augmented during tumorigenesis. EZH2 overexpression can be observed in many cancers, including prostate, breast and pancreas cancer, and most often high level of EZH2 is correlated to aggressiveness of the malignancies (Tsang et al., 2011). EZH2 is rarely detected in normal hepatocytes, but is frequently detected in HCC cell lines and HCC tissues (Chen et al., 2007).

EZH2 is involved in numerous cellular processes and signaling pathways and evidences suggested that EZH2 promotes cancer development by repressing diverse tumor-suppressors. Recently, EZH2 reportedly activated Wnt signaling in HCC. Concurrent overexpression of EZH2 and β-catenin was observed in more than 30% of human HCC, which is associated with tumor progression (Cheng et al., 2011). In HCC cells, EZH2 is found to frequently occupy the promoter of numerous Wnt pathway antagonists. As such, these antagonists are silenced, relieving the inhibitory effect on Wnt/β-catenin signaling. In immortalized hepatocytes, ectopic expression of EZH2 activated Wnt/β-catenin signaling and triggered cell proliferation (Cheng et al., 2011). Conversely, downregulation of EZH2 inhibited β-catenin signaling, resulting in the retardation of HCC cell growth. Study showed that knockdown of EZH2 by lentivirus-based shRNA inhibited tumor growth in vivo (Chen et al., 2007), demonstrating a potent effect against HCC by targeting EZH2. The significance

of EZH2 role in HCC suggested that strategies built around EZH2 is definitely advantageous.

EZH2 is theoretically suitable for pharmalogical targeting as it contains a SET domain responsible for the histone methyltransferase activity. Targeting of the enzymatic domain is proved to reduce histone methylation and de-repress expression of tumor suppressor genes. In addition to the catalytic domain, there are two N-terminal domains mediating protein-protein interactions and promoting nuclear localization within EZH protein, which are druggable targets in ablating EZH2 activity. Disruption of the PRC2 is also effective to attenuate the tumorigenic effect of EZH2. The formation of functional PRC2 requires other protein subunits such as EED and SUZ12. Report revealed that the use of agent disrupting PRC2 subunits is a relevant way to affect PRC2 function (Tan et al., 2007). Although currently there is no EZH2 specific inhibitor, but agent such as DZnep is also able to deplete the cellular EZH2, inhibit EZH2 functions and lower the H3K27 trimethylation level (Chiba et al., 2011). This fundamental knowledge surely enables researchers to design potent agents to target EZH2 in HCC.

8. Non-coding RNA

8.1 MicroRNA

MicroRNAs are small non-coding RNAs that regulate the translation of many genes. They not only regulate normal cell development but also play important roles in cancer development and progression by affecting cell survival, angiogenesis and metastasis. Many studies illustrated the potential of manipulating microRNA expression in cancer therapy. It is believed that microRNA-based remedy can have a huge impact on cancer cells, as they regulate whole programs of gene expression via suppressing hundreds of genes simultaneously (Farazi et al., 2011). In human HCC, numerous microRNAs are identified to give major contributions, either having oncogenic or tumor suppressing ability. Here, those microRNAs having great potential as HCC therapeutic targets will be discussed.

OncomiR is a novel term coined for microRNAs possessing proto-oncogenic effects in cancers. In HCC, a number of oncomiRs are identified and their roles are characterized. Among them, the roles of microRNA-21 (miR-21) in HCC development were well-documented (Liu et al., 2010). miR-21 is universally overexpressed in majority of cancers and is phenomenally involved in approximately all tumorigenic processes. miR-21 is able to induce cell transformation, mediate cancer cell growth, cell cycle and self-renewal, prevent apoptosis, promote metastasis and generate drug-resistance (Liu et al., 2010). High expression of miR-21 is correlated with advanced tumor stage, frequent metastasis and poor patient prognosis. In HCC, miR-21 is overexpressed, and has been proved to promote malignant cell growth and spreading by targeting tumor suppressor PTEN and inducing FAK phosphorylation (Meng et al., 2007). Furthermore, miR-21 induces resistance to anticancer effect of interferon-α and 5-fluorouracil in HCC (Tomimaru et al., 2010). Importantly, inhibition of miR-21 is able to reduce the aggressiveness in HCC, and relieves the suppressive effect to several tumor suppressor genes targeted. Besides miR-21, targeting other oncomiRs such as miR-29 (Xiong et al., 2010) and miR-221 (Pineau et al., 2010) is also robust in reversing the malignant phenotypes in HCC.

On the other hand, various microRNAs with tumor suppressing capacity are lost or underexpressed in HCC. Restoration of their expression in HCC is another effective approach against HCC. Previous studies suggested a strong association between low miR-26 expression and both prognosis and response to interferon therapy in patients with HCC (Ji et al., 2009). Low miR-26 expression is highly associated with tumor formation in vivo, and replenishing miR-26 in liver tumors with the use of gene therapy could generate potent antitumor effects. miR-26a in particular is substantially reduced in MYC-induced HCC (Ji et al., 2009). The replacement therapy of miR-26 is considered safe, because miR-26 is expressed by most normal cells and is unlikely to be toxic. Other than miR-26, miR-122 is significantly downregulated in liver cancer with intrahepatic metastasis. Restoration of miR-122 reduced cell migration, invasion and colony formation ability in vitro, and tumorigenesis, angiogenesis and metastasis in vivo (Coulouarn et al., 2009). Currently, more microRNAs with antitumor effect including miR-199a/b-3p were identified and potentially play a pivotal role in the combat against HCC (Hou et al., 2011).

To note, increased activity of RNA-induced silencing complex (RISC) was observed in HCC (Yoo et al., 2011). The role of RISC is critical in facilitating activity of RNAi including microRNA-mediated target silencing. The components of RISC including AEG-1 and SND1 were both overexpressed in HCC, which leads to the hyperactivity of RISC. Increased RISC activity resulted in an accelerated degradation of numerous tumor suppressor genes that are the target of various oncomiRs. Report showed that inhibition of RISC activity by knocking down SND1 abrogated cell growth in HCC cells in vitro and in vivo (Yoo et al., 2011). It not only unveils a new microRNA associated pro-tumorigenic mechanism, but also provides an additional approach to disrupt microRNA-mediated tumorigenic effect during HCC remedy.

8.2 Long non-coding RNA

In eukaryotes, there are abundant amount of transcripts which are long in length and lack any substantial open reading frame as well as protein coding capacity. Increasing evidences suggested that these long non-coding RNAs (lncRNA) play critical role in cellular processes such as development, via the modulation of chromatin structure. Some of them possess the ability to modulate cancer epigenome and contribute to different pathological conditions such as tumor invasion and metastasis. A better understanding in the oncogenic mechanisms of lncRNA will unveil a new direction in cancer therapy.

Highly upregulated in liver cancer (HULC) is an lncRNA that is frequently overexpressed in HCC. siRNA knockdown of HULC in HCC cell lines was able to alter the expression of genes described in the context of HCC (Panzitt et al., 2007). Reduction of cellular HULC upregulated genes participates in diverse biological processes including cell differentiation, cell adhesion, protein phosphorylation and tumor suppression. Another study reported that HULC was also expressed in metastasized tumor nodules in liver originated from colorectal cancer, but not in primary colorectal cancer (Matouk et al., 2009). It suggested that expression of HULC might be a pre-requisite for any tumor formed in liver. The importance of HULC in HCC is further supported by the observation that HULC expression is strongly linked to HBV infection (Matouk et al., 2009). Due to the high specificity of HULC for cancer located in liver, it is worthy of studying its potential role in managing HCC.

There are two other lncRNAs recently reported to be overexpressed in HCC cell lines and tissues, namely the metastasis associated lung adenocarcinoma transcript 1(MALAT-1) and HOX transcript antisense RNA (HOTAIR). Both of them have been previously implicated in other malignancies regarding their capacity to promote cancer metastasis. In HCC, their expression is correlated to the prognosis of the patients which predicts tumor recurrence after liver transplantation. Inhibition of MALAT-1 in vitro effectively reduced cell viability, motility, invasiveness, and HCC cells became sensitive to pro-apoptotic signal (Lai et al., 2011). Similarly, knockdown of HOTAIR decreased cell viability and cell invasiveness, as well as sensitized HCC cells to tumor necrosis factor- α induced apoptosis, and cytotoxic effect of doxorubicin and cisplatin (Yang et al., 2011). Their roles in HCC progression are important which provide a rational base to take into consideration during HCC therapy.

9. Liver cancer stem cell

Accumulating evidences support that the development of HCC is based on the cancer stem cell (CSC) model. In this hypothesis, there is only a subset of cells within a tumor or in the cell pool that sustains malignant growth. Such cellular subset is referred to as the cancer-initiating cells or cancer-propagating cells (Visvader, 2011). It provides the explanations for cancer initiation, local recurrence, metastasis and therapy resistance which raised enormous controversies in the past. CSCs have been identified in many cancer types including HCC (Mishra et al., 2009). In this regard, CSC should be the principal target of HCC therapy. However, conventional methods such as chemotherapy and radiotherapy are ineffective because of the CSC resistant properties, as well as their pro-angiogenic effect. Studies are vigorously conducted to develop effective methods to extinguish CSC in HCC.

9.1 Cancer stem cell markers

Numerous surface markers for HCC stem cells were identified, and they include CD133, CD90, CD44, CD13 and EpCAM. Although their roles in liver CSC are unclear, studies showed that targeting these markers can specifically harm CSC with high efficacy. It is reported that tumorigenicity and invasive capacity of liver CSC were impaired by targeting CSC surface marker EpCAM, leading to reduction of CSC pool (Yamashita et al., 2009). Besides, inhibition of CD44 in HCC cells could enhance apoptosis, reduce tumorigenicity and invasion. Interestingly, isoforms of CD44 are differentially expressed between HCC and normal hepatocytes. Targeting of the CD44 isoforms prevalent in HCC was able to selectively deplete HCC cells without harming normal cells (Miletti-González et al., 2005). Therefore, direct targeting of CSC-specific markers may also be a promising therapeutic strategy to eradicate liver CSC.

9.2 Stemness signaling

Cancer stem cells share various common characters with somatic and embryonic stem cells. Many signaling pathways observed exclusively in stem cells can also be detected in cancer stem cells. These signalings include Wnt/β-catenin, Hedgehog and Notch signaling (Mishra et al., 2009). Disturbing the signalings involved in normal stem cell fate reportedly decreased the self-renewal and proliferating capabilities of CSCs. For example, small molecule inhibitor of hedgehog pathway could reduce the likely CSC with progenitor

marker aldehyde dehydrogenase in pancreatic cancer (Feldmann et al., 2007); Targeting Notch pathway was able to inhibit cancer stem cell self-renewal and decreases tumor growth (Cheng et al., 2004); The Wnt pathway can be inhibited by blocking the β-catenin interaction with TCF gene, and as such there was a reduction of CSC cells and spheroid formation (Lepourcelet et al., 2004). Apart from tumor promoting effects, stem cell signalings could induce resistances and recurrences to different cancer therapies in HCC. HCC cells survived through radiation, and acquired radioresistance was found to have Wnt/β-catenin signaling activated (Woodward et al., 2007). Relapse of HCC after radiation was also associated with the induction of Notch and Hedgehog signaling pathways which sustained HCC cell self-renewal and tumorigenicity (Clement et al., 2007).

Recently, the STAT3/IL-6 signaling is revealed as another pathway activated in liver CSC and plays an important role in maintaining the liver CSC. Activation of IL-6 pathway is suggested to be a consequence of TGF-β signaling defects (Tang et al., 2008). Impaired TGF-β signaling is a piece of useful information to distinguish liver CSC from normal stem cells. Hence, targeting IL-6 pathway might be a specific way to target liver CSC without affecting somatic stem cells. STAT3/IL-6 pathway inhibition by small inhibitor is also effective in HCC with lesion of TGF-β signaling, attenuating tumorigensis of HCC (He et al., 2004).

9.3 Differentiation pathway

Like other cancer types, HCC cells are highly heterogenous. It is believed that liver cancer stem cells are the initiator in establishing the heterogenous background of the tumor, whilst liver CSC themselves remains undifferentiated (Visvader, 2011). Forced differentiation of the CSC in HCC is a relevant approach to deplete the CSC in the cancer cell pool. Differentiation of cancer cells into less aggressive forms has been a successful strategy as demonstrated in the treatment of acute promyelocytic leukemia. The application of all-trans retinoic acid after normal chemotherapy resulted in a 90% remission and 70% cure rate in acute promyelocytic leukemia. Differentiation therapy can be an appealing and effective treatment against HCC (Massard et al., 2006).

It is reported that force expression of hepatocyte nuclear factor 4-α (HNF4-α) could promote the differentiation of hepatoma cells to normal hepatocytes. Most importantly, there is a reduction of stemness genes and a decrease of $CD133^+$/$CD90^+$ subpopulation during the differentiation. HNF4-α is able to induce cell cycle arrest, cell senescense in HCC cells as well as the tumorigenic ability in mice (Yin et al., 2008). Systemic and intratumoral administration of HNF4-α carrying adenovirus could respectively prevent tumor metastasis and exhibit antitumor effect. Understanding the differentiation pathways in liver CSC allows identification of key differentiating factors (Yin et al., 2008). Identification of valid differentiation pathways in CSC enables scientists to explore a new avenue in countering liver CSC.

9.4 Cancer stem cell niche

Other novel ideas for stem cell targeting therapy include the disruption of the tumor niche essential for CSC homeostasis (Gokmen-Polar et al., 2008). The specified microenvironment where stem cells reside often dictates self-renewal and reproduction. Alteration of stem cell niche components can effectively change stem cell fate, as in the case of experimental parathyroid hormone induction. Furthermore, human embryonic stem cell–derived

fibroblast-like cells provide a supportive environment for stem cells through insulin-like growth factor 2 (Martínez-Iglesias et al., 2008). Targeting insulin like growth factor 2 therefore can manipulate the stem cell microenvironment. Apart from the molecular content surrounding liver CSC, there is accumulating evidence that the physical environment is a critical mediator of HCC tumor behaviour. The stiffness of matrix is a strong predictor of HCC development. Increasing stiffness was found to promote HCC cell proliferation. On the other hand, a soft environment induces reversible stem cell characteristics in HCC (Schrader et al., 2011). With understanding of critical factors influencing liver CSC, comprehensive approach will be developed to eradicate these primary targets in HCC.

10. References

Aishima S, Basaki Y, Oda Y, Kuroda Y, Nishihara Y, Taguchi K, Taketomi A, Maehara Y, Hosoi F, Maruyama Y, Fotovati A, Oie S, Ono M, Ueno T, Sata M, Yano H, Kojiro M, Kuwano M, Tsuneyoshi M. (2006) High expression of insulin-like growth factor binding protein-3 is correlated with lower portal invasion and better prognosis in human hepatocellular carcinoma. Cancer Sci. Nov;97(11):1182-90.

Alexia C, Fallot G, Lasfer M, Schweizer-Groyer G, Groyer A. (2004) An evaluation of the role of insulin-like growth factors (IGF) and of type-I IGF receptor signalling in hepatocarcinogenesis and in the resistance of hepatocarcinoma cells against drug-induced apoptosis. Biochem Pharmacol. Sep 15;68(6):1003-15.

Amann T, Bataille F, Spruss T, Mühlbauer M, Gäbele E, Schölmerich J, Kiefer P, Bosserhoff AK, Hellerbrand C. (2009) Activated hepatic stellate cells promote tumorigenicity of hepatocellular carcinoma. Cancer Sci. Apr;100(4):646-53.

Amann T, Maegdefrau U, Hartmann A, Agaimy A, Marienhagen J, Weiss TS, Stoeltzing O, Warnecke C, Schölmerich J, Oefner PJ, Kreutz M, Bosserhoff AK, Hellerbrand C. (2009) GLUT1 expression is increased in hepatocellular carcinoma and promotes tumorigenesis. Am J Pathol. Apr;174(4):1544-52.

Bach SJ, Hawkins RA, Swaine D. (1963) A short method for the purification of arginase from ox liver. Biochem J. Nov;89:263-5.

Barnaeva E, Nadezhda A, Hannappel E, Sjogren MH, Rojkind M. (2007) Thymosin beta4 upregulates the expression of hepatocyte growth factor and downregulates the expression of PDGF-beta receptor in human hepatic stellate cells. Ann N Y Acad Sci. Sep;1112:154-60.

Bataller R, Brenner DA. (2005) Liver fibrosis. J Clin Invest. Feb;115(2):209-18. Review

Bjornsti MA, Houghton PJ. (2004) The TOR pathway: a target for cancer therapy. Nat Rev Cancer. May;4(5):335-48.

Breinig M, Caldas-Lopes E, Goeppert B, Malz M, Rieker R, Bergmann F, Schirmacher P, Mayer M, Chiosis G, Kern MA. (2009) Targeting heat shock protein 90 with non-quinone inhibitors: a novel chemotherapeutic approach in human hepatocellular carcinoma. Hepatology. Jul;50(1):102-12.

Breuhahn K, Vreden S, Haddad R, Beckebaum S, Stippel D, Flemming P, Nussbaum T, Caselmann WH, Haab BB, Schirmacher P. (2004) Molecular profiling of human hepatocellular carcinoma defines mutually exclusive interferon regulation and insulin-like growth factor II overexpression. Cancer Res. Sep 1;64(17):6058-64.

Capurro MI, Xiang YY, Lobe C, Filmus J. (2005) Glypican-3 promotes the growth of hepatocellular carcinoma by stimulating canonical Wnt signaling. Cancer Res. Jul 15;65(14):6245-54.

Capurro MI, Xu P, Shi W, Li F, Jia A, Filmus J. (2008) Glypican-3 inhibits Hedgehog signaling during development by competing with patched for Hedgehog binding. Dev Cell. May;14(5):700-11.

Chauhan D, Hideshima T, Anderson KC. (2008) Targeting proteasomes as therapy in multiple myeloma. Adv Exp Med Biol.;615:251-60.

Cheng AS. (2011) Epigenetic regulation of signaling pathways in cancer: role of the histone methyltransferase EZH2. J Gastroenterol Hepatol. Jan;26(1):19-27.

Cheng AS, Lau SS, Chen Y, Kondo Y, Li MS, Feng H, Ching AK, Cheung KF, Wong HK, Tong JH, Jin H, Choy KW, Yu J, To KF, Wong N, Huang TH, Sung JJ. (2011) EZH2-Mediated Concordant Repression of Wnt Antagonists Promotes {beta}-Catenin-Dependent Hepatocarcinogenesis. Cancer Res. Jun 1;71(11):4028-4039.

Cheng PN, Lam TL, Lam WM, Tsui SM, Cheng AW, Lo WH, Leung YC. (2007) Pegylated recombinant human arginase (rhArg-peg5,000mw) inhibits the in vitro and in vivo proliferation of human hepatocellular carcinoma through arginine depletion. Cancer Res. Jan 1;67(1):309-17.

Cheng T. (2004) Cell cycle inhibitors in normal and tumor stem cells. Oncogene. Sep 20;23(43):7256-66. Review.

Chen Y, Lin MC, Yao H, Wang H, Zhang AQ, Yu J, Hui CK, Lau GK, He ML, Sung J, Kung HF. (2007) Lentivirus-mediated RNA interference targeting enhancer of zeste homolog 2 inhibits hepatocellular carcinoma growth through down-regulation of stathmin. Hepatology. Jul;46(1):200-8.

Chen ZJ. (2005) Ubiquitin signalling in the NF-kappaB pathway. Nat Cell Biol. Aug;7(8):758-65. Review.

Chiba T, Suzuki E, Negishi M, Saraya A, Miyagi S, Konuma T, Tanaka S, Tada M, Kanai F, Imazeki F, Iwama A, Yokosuka O. (2011) 3-deazaneplanocin A is a promising therapeutic agent for the eradication of tumor-initiating hepatocellular carcinoma cells. Int J Cancer. Jun 29.

Chiba T, Miyagi S, Saraya A, Aoki R, Seki A, Morita Y, Yonemitsu Y, Yokosuka O, Taniguchi H, Nakauchi H, Iwama A. (2008) The polycomb gene product BMI1 contributes to the maintenance of tumor-initiating side population cells in hepatocellular carcinoma. Cancer Res. Oct 1;68(19):7742-9.

Clement V, Sanchez P, de Tribolet N, Radovanovic I, Ruiz i Altaba A. (2007) HEDGEHOG-GLI1 signaling regulates human glioma growth, cancer stem cell self-renewal, and tumorigenicity. Curr Biol. Jan 23;17(2):165-72.

Coulouarn C, Factor VM, Andersen JB, Durkin ME, Thorgeirsson SS. (2009) Loss of miR-122 expression in liver cancer correlates with suppression of the hepatic phenotype and gain of metastatic properties. Oncogene. Oct 8;28(40):3526-36. Epub 2009 Jul 20.

Dawson S, Apcher S, Mee M, Higashitsuji H, Baker R, Uhle S, Dubiel W, Fujita J, Mayer RJ. (2002) Gankyrin is an ankyrin-repeat oncoprotein that interacts with CDK4 kinase and the S6 ATPase of the 26 S proteasome. J Biol Chem. Mar 29;277(13):10893-902.

Delage B, Fennell DA, Nicholson L, McNeish I, Lemoine NR, Crook T, Szlosarek PW. (2010) Arginine deprivation and argininosuccinate synthetase expression in the treatment of cancer. Int J Cancer. Jun 15;126(12):2762-72. Review.

Deveraux QL, Takahashi R, Salvesen GS, Reed JC. (1997) X-linked IAP is a direct inhibitor of cell-death proteases. Nature. Jul 17;388(6639):300-4.

Dillon BJ, Prieto VG, Curley SA, Ensor CM, Holtsberg FW, Bomalaski JS, Clark MA. (2004) Incidence and distribution of argininosuccinate synthetase deficiency in human cancers: a method for identifying cancers sensitive to arginine deprivation. Cancer. Feb 15;100(4):826-33.

Djojosubroto MW, Chin AC, Go N, Schaetzlein S, Manns MP, Gryaznov S, Harley CB, Rudolph KL. (2005) Telomerase antagonists GRN163 and GRN163L inhibit tumor growth and increase chemosensitivity of human hepatoma. Hepatology. Nov;42(5):1127-36.

Dong LW, Yang GZ, Pan YF, Chen Y, Tan YX, Dai RY, Ren YB, Fu J, Wang HY. (2011) The oncoprotein p28(GANK) establishes a positive feedback loop in β-catenin signaling. Cell Res. Jun 21.

Dong S, Wu XZ. (2010) Heparanase and hepatocellular carcinoma: promoter or inhibitor? World J Gastroenterol. Jan 21;16(3):306-11.

Du GS, Wang JM, Lu JX, Li Q, Ma CQ, Du JT, Zou SQ. (2009) Expression of P-aPKC-iota, E-cadherin, and beta-catenin related to invasion and metastasis in hepatocellular carcinoma. Ann Surg Oncol. Jun;16(6):1578-86.

Effendi K, Mori T, Komuta M, Masugi Y, Du W, Sakamoto M. (2010) Bmi-1 gene is upregulated in early-stage hepatocellular carcinoma and correlates with ATP-binding cassette transporter B1 expression. Cancer Sci. Mar;101(3):666-72.

El-Assal ON, Yamanoi A, Ono T, Kohno H, Nagasue N. (2001) The clinicopathological significance of heparanase and basic fibroblast growth factor expressions in hepatocellular carcinoma. Clin Cancer Res. May;7(5):1299-305.

Ensor CM, Holtsberg FW, Bomalaski JS, Clark MA. (2002) Pegylated arginine deiminase (ADI-SS PEG20,000 mw) inhibits human melanomas and hepatocellular carcinomas in vitro and in vivo. Cancer Res. Oct 1;62(19):5443-50.

Farazi TA, Spitzer JI, Morozov P, Tuschl T. (2011) miRNAs in human cancer. J Pathol. Jan;223(2):102-15.

Feldmann G, Dhara S, Fendrich V, Bedja D, Beaty R, Mullendore M, Karikari C, Alvarez H, Iacobuzio-Donahue C, Jimeno A, Gabrielson KL, Matsui W, Maitra A. (2007) Blockade of hedgehog signaling inhibits pancreatic cancer invasion and metastases: a new paradigm for combination therapy in solid cancers. Cancer Res. Mar 1;67(5):2187-96.

Feitelson MA, Pan J, Lian Z. (2004) Early molecular and genetic determinants of primary liver malignancy. Surg Clin North Am. Apr;84(2):339-54. Review.

Fu J, Chen Y, Cao J, Luo T, Qian YW, Yang W, Ren YB, Su B, Cao GW, Yang Y, Yan YQ, Shen F, Wu MC, Feng GS, Wang HY. (2011) p28GANK overexpression accelerates hepatocellular carcinoma invasiveness and metastasis via phosphoinositol 3-kinase/AKT/hypoxia-inducible factor-1α pathways. Hepatology. Jan;53(1):181-92.

Gokmen-Polar Y, Miller KD. (2008) Redefining the target again: chemotherapeutics as vascular disrupting agents? Cancer Cell. Sep 9;14(3):195-6.

Gonzalez GG, Byus CV. (1991) Effect of dietary arginine restriction upon ornithine and polyamine metabolism during two-stage epidermal carcinogenesis in the mouse. Cancer Res. Jun 1;51(11):2932-9.

Hampton T. (2007)Cancer drug trials show modest benefit: drugs target liver, gastric, head and neck cancers. JAMA. Jul 18;298(3):273-5.

Hanafusa T, Yumoto Y, Nouso K, Nakatsukasa H, Onishi T, Fujikawa T, Taniyama M, Nakamura S, Uemura M, Takuma Y, Yumoto E, Higashi T, Tsuji T. (2002) Reduced expression of insulin-like growth factor binding protein-3 and its promoter hypermethylation in human hepatocellular carcinoma. Cancer Lett. Feb 25;176(2):149-58.

He XC, Zhang J, Tong WG, Tawfik O, Ross J, Scoville DH, Tian Q, Zeng X, He X, Wiedemann LM, Mishina Y, Li L. (2004) BMP signaling inhibits intestinal stem cell self-renewal through suppression of Wnt-beta-catenin signaling. Nat Genet. Oct;36(10):1117-21.

Higashitsuji H, Itoh K, Nagao T, Dawson S, Nonoguchi K, Kido T, Mayer RJ, Arii S, Fujita J. (2000) Reduced stability of retinoblastoma protein by gankyrin, an oncogenic ankyrin-repeat protein overexpressed in hepatomas. Nat Med. Jan;6(1):96-9.

Higashitsuji H, Higashitsuji H, Itoh K, Sakurai T, Nagao T, Sumitomo Y, Masuda T, Dawson S, Shimada Y, Mayer RJ, Fujita J. (2005)The oncoprotein gankyrin binds to MDM2/HDM2, enhancing ubiquitylation and degradation of p53. Cancer Cell. Jul;8(1):75-87.

Hou J, Lin L, Zhou W, Wang Z, Ding G, Dong Q, Qin L, Wu X, Zheng Y, Yang Y, Tian W, Zhang Q, Wang C, Zhang Q, Zhuang SM, Zheng L, Liang A, Tao W, Cao X. (2011) Identification of miRNomes in human liver and hepatocellular carcinoma reveals miR-199a/b-3p as therapeutic target for hepatocellular carcinoma. Cancer Cell. Feb 15;19(2):232-43.

Hsu HC, Cheng W, Lai PL. (1997) Cloning and expression of a developmentally regulated transcript MXR7 in hepatocellular carcinoma: biological significance and temporospatial distribution. Cancer Res. Nov 15;57(22):5179-84

Hu TH, Huang CC, Lin PR, Chang HW, Ger LP, Lin YW, Changchien CS, Lee CM, Tai MH. (2003) Expression and prognostic role of tumor suppressor gene PTEN/MMAC1/TEP1 in hepatocellular carcinoma. Cancer. Apr 15;97(8):1929-40.

Hu Z, Zhang Z, Doo E, Coux O, Goldberg AL, Liang TJ. (1999) Hepatitis B virus X protein is both a substrate and a potential inhibitor of the proteasome complex. J Virol. Sep;73(9):7231-40.

Huynh H, Chow PK, Ooi LL, Soo KC. (2002) A possible role for insulin-like growth factor-binding protein-3 autocrine/paracrine loops in controlling hepatocellular carcinoma cell proliferation. Cell Growth Differ. Mar;13(3):115-22.

Ingram DK, Zhu M, Mamczarz J, Zou S, Lane MA, Roth GS, deCabo R. (2006) Calorie restriction mimetics: an emerging research field. Aging Cell. Apr;5(2):97-108. Review.

Ishiguro T, Sugimoto M, Kinoshita Y, Miyazaki Y, Nakano K, Tsunoda H, Sugo I, Ohizumi I, Aburatani H, Hamakubo T, Kodama T, Tsuchiya M, Yamada-Okabe H. (2008) Anti-glypican 3 antibody as a potential antitumor agent for human liver cancer. Cancer Res. Dec 1;68(23):9832-8.

Izzo F, Marra P, Beneduce G, Castello G, Vallone P, De Rosa V, Cremona F, Ensor CM, Holtsberg FW, Bomalaski JS, Clark MA, Ng C, Curley SA. (2004) Pegylated arginine deiminase treatment of patients with unresectable hepatocellular carcinoma: results from phase I/II studies. J Clin Oncol. May 15;22(10):1815-22.

Ji J, Shi J, Budhu A, Yu Z, Forgues M, Roessler S, Ambs S, Chen Y, Meltzer PS, Croce CM, Qin LX, Man K, Lo CM, Lee J, Ng IO, Fan J, Tang ZY, Sun HC, Wang XW. (2009) MicroRNA expression, survival, and response to interferon in liver cancer. N Engl J Med. Oct 8;361(15):1437-47.

Kaur S, Wang F, Venkatraman M, Arsura M. (2005) X-linked inhibitor of apoptosis (XIAP) inhibits c-Jun N-terminal kinase 1 (JNK1) activation by transforming growth factor beta1 (TGF-beta1) through ubiquitin-mediated proteosomal degradation of the TGF-beta1-activated kinase 1 (TAK1). J Biol Chem. Nov 18;280(46):38599-608.

Kirmizis A, Bartley SM, Kuzmichev A, Margueron R, Reinberg D, Green R, Farnham PJ. (2004) Silencing of human polycomb target genes is associated with methylation of histone H3 Lys 27. Genes Dev. Jul 1;18(13):1592-605.

Lai JP, Sandhu DS, Yu C, Han T, Moser CD, Jackson KK, Guerrero RB, Aderca I, Isomoto H, Garrity-Park MM, Zou H, Shire AM, Nagorney DM, Sanderson SO, Adjei AA, Lee JS, Thorgeirsson SS, Roberts LR. (2008) Sulfatase 2 up-regulates glypican 3, promotes fibroblast growth factor signaling, and decreases survival in hepatocellular carcinoma. Hepatology. Apr;47(4):1211-22.

Lai JP, Oseini AM, Moser CD, Yu C, Elsawa SF, Hu C, Nakamura I, Han T, Aderca I, Isomoto H, Garrity-Park MM, Shire AM, Li J, Sanderson SO, Adjei AA, Fernandez-Zapico ME, Roberts LR. (2010) The oncogenic effect of sulfatase 2 in human hepatocellular carcinoma is mediated in part by glypican 3-dependent Wnt activation. Hepatology. Nov;52(5):1680-9.

Lai JP, Sandhu DS, Yu C, Moser CD, Hu C, Shire AM, Aderca I, Murphy LM, Adjei AA, Sanderson S, Roberts LR. (2010) Sulfatase 2 protects hepatocellular carcinoma cells against apoptosis induced by the PI3K inhibitor LY294002 and ERK and JNK kinase inhibitors. Liver Int. Nov;30(10):1522-8.

Lai MC, Yang Z, Zhou L, Zhu QQ, Xie HY, Zhang F, Wu LM, Chen LM, Zheng SS. (2011) Long non-coding RNA MALAT-1 overexpression predicts tumor recurrence of hepatocellular carcinoma after liver transplantation. Med Oncol. Jun 16.

Lang SA, Moser C, Fichnter-Feigl S, Schachtschneider P, Hellerbrand C, Schmitz V, Schlitt HJ, Geissler EK, Stoeltzing O. (2009) Targeting heat-shock protein 90 improves efficacy of rapamycin in a model of hepatocellular carcinoma in mice. Hepatology. Feb;49(2):523-32.

Lepourcelet M, Chen YN, France DS, Wang H, Crews P, Petersen F, Bruseo C, Wood AW, Shivdasani RA. (2004) Small-molecule antagonists of the oncogenic Tcf/beta-catenin protein complex. Cancer Cell. Jan;5(1):91-102.

Li H, Fu X, Chen Y, Hong Y, Tan Y, Cao H, Wu M, Wang H. (2005) Use of adenovirus-delivered siRNA to target oncoprotein p28GANK in hepatocellular carcinoma. Gastroenterology. Jun;128(7):2029-41.

Liu C, Yu J, Yu S, Lavker RM, Cai L, Liu W, Yang K, He X, Chen S. (2010) MicroRNA-21 acts as an oncomir through multiple targets in human hepatocellular carcinoma. J Hepatol. Jul;53(1):98-107.

Liu LX, Lee NP, Chan VW, Xue W, Zender L, Zhang C, Mao M, Dai H, Wang XL, Xu MZ, Lee TK, Ng IO, Chen Y, Kung HF, Lowe SW, Poon RT, Wang JH, Luk JM. (2009) Targeting cadherin-17 inactivates Wnt signaling and inhibits tumor growth in liver carcinoma. Hepatology. Nov;50(5):1453-63.

Liu Q, Vera JC, Peng H, Golde DW. (2001) The predicted ATP-binding domains in the hexose transporter GLUT1 critically affect transporter activity. Biochemistry. Jul 3;40(26):7874-81.

Llovet JM, Burroughs A, Bruix J. (2003) Hepatocellular carcinoma. Lancet. Dec 6;362(9399):1907-17. Review.

Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. Jul 24;359(4):378-90.

Lund P, Schubert D, Niketeghad F, Schirmacher P. (2004) Autocrine inhibition of chemotherapy response in human liver tumor cells by insulin-like growth factor-II. Cancer Lett. Mar 31;206(1):85-96.

Márquez-Rosado L, Trejo-Solís MC, García-Cuéllar CM, Villa-Treviño S. (2005) Celecoxib, a cyclooxygenase-2 inhibitor, prevents induction of liver preneoplastic lesions in rats. J Hepatol. Oct;43(4):653-60.

Martin HJ, Kornmann F, Fuhrmann GF. (2003) The inhibitory effects of flavonoids and antiestrogens on the Glut1 glucose transporter in human erythrocytes. Chem Biol Interact. Dec 15;146(3):225-35. PubMed PMID: 14642735.

Martínez-Iglesias O, Ruiz-Llorente L, Sánchez-Martínez R, García L, Zambrano A, Aranda A. (2008) Histone deacetylase inhibitors: mechanism of action and therapeutic use in cancer. Clin Transl Oncol. Jul;10(7):395-8. Review.

Maschek G, Savaraj N, Priebe W, Braunschweiger P, Hamilton K, Tidmarsh GF, De Young LR, Lampidis TJ. (2004) 2-deoxy-D-glucose increases the efficacy of adriamycin and paclitaxel in human osteosarcoma and non-small cell lung cancers in vivo. Cancer Res. Jan 1;64(1):31-4.

Massard C, Deutsch E, Soria JC. (2006) Tumour stem cell-targeted treatment: elimination or differentiation. Ann Oncol. Nov;17(11):1620-4. Review.

Matouk IJ, Abbasi I, Hochberg A, Galun E, Dweik H, Akkawi M. (2009) Highly upregulated in liver cancer noncoding RNA is overexpressed in hepatic colorectal metastasis. Eur J Gastroenterol Hepatol. Jun;21(6):688-92.

Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T. (2007) MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. Gastroenterology. Aug;133(2):647-58. Epub 2007 May 21.

Midorikawa Y, Ishikawa S, Iwanari H, Imamura T, Sakamoto H, Miyazono K, Kodama T, Makuuchi M, Aburatani H. (2003) Glypican-3, overexpressed in hepatocellular carcinoma, modulates FGF2 and BMP-7 signaling. Int J Cancer. Feb 10;103(4):455-65.

Miletti-González KE, Chen S, Muthukumaran N, Saglimbeni GN, Wu X, Yang J, Apolito K, Shih WJ, Hait WN, Rodríguez-Rodríguez L. (2005) The CD44 receptor interacts with P-glycoprotein to promote cell migration and invasion in cancer. Cancer Res. Aug 1;65(15):6660-7.

Mishra L, Banker T, Murray J, Byers S, Thenappan A, He AR, Shetty K, Johnson L, Reddy EP. (2009) Liver stem cells and hepatocellular carcinoma. Hepatology. Jan;49(1):318-29.

Morimoto-Tomita M, Uchimura K, Werb Z, Hemmerich S, Rosen SD. (2002) Cloning and characterization of two extracellular heparin-degrading endosulfatases in mice and humans. J Biol Chem. Dec 20;277(51):49175-85. Epub 2002 Oct 3.

Morris DI, Robbins JD, Ruoho AE, Sutkowski EM, Seamon KB. (1991) Forskolin photoaffinity labels with specificity for adenylyl cyclase and the glucose transporter. J Biol Chem. Jul 15;266(20):13377-84.

Munakata T, Nakamura M, Liang Y, Li K, Lemon SM. (2005) Down-regulation of the retinoblastoma tumor suppressor by the hepatitis C virus NS5B RNA-dependent RNA polymerase. Proc Natl Acad Sci U S A. Dec 13;102(50):18159-64.

Nussbaum T, Samarin J, Ehemann V, Bissinger M, Ryschich E, Khamidjanov A, Yu X, Gretz N, Schirmacher P, Breuhahn K. (2008) Autocrine insulin-like growth factor-II stimulation of tumor cell migration is a progression step in human hepatocarcinogenesis. Hepatology. Jul;48(1):146-56.

Pan Q, Liu B, Liu J, Cai R, Liu X, Qian C. (2008) Synergistic antitumor activity of XIAP-shRNA and TRAIL expressed by oncolytic adenoviruses in experimental HCC. Acta Oncol. 47(1):135-44.

Panzitt K, Tschernatsch MM, Guelly C, Moustafa T, Stradner M, Strohmaier HM, Buck CR, Denk H, Schroeder R, Trauner M, Zatloukal K. (2007) Characterization of HULC, a novel gene with striking up-regulation in hepatocellular carcinoma, as noncoding RNA. Gastroenterology. Jan;132(1):330-42.

Pascale RM, Simile MM, Calvisi DF, Frau M, Muroni MR, Seddaiu MA, Daino L, Muntoni MD, De Miglio MR, Thorgeirsson SS, Feo F. (2005) Role of HSP90, CDC37, and CRM1 as modulators of P16(INK4A) activity in rat liver carcinogenesis and human liver cancer. Hepatology. Dec;42(6):1310-9.

Pearl LH, Prodromou C, Workman P. (2008) The Hsp90 molecular chaperone: an open and shut case for treatment. Biochem J. Mar 15;410(3):439-53.

Pineau P, Volinia S, McJunkin K, Marchio A, Battiston C, Terris B, Mazzaferro V, Lowe SW, Croce CM, Dejean A. (2010) miR-221 overexpression contributes to liver tumorigenesis. Proc Natl Acad Sci U S A. Jan 5;107(1):264-9.

Sano T, Kagawa M, Okuno M, Ishibashi N, Hashimoto M, Yamamoto M, Suzuki R, Kohno H, Matsushima-Nishiwaki R, Takano Y, Tsurumi H, Kojima S, Friedman SL, Moriwaki H, Tanaka T. (2005) Prevention of rat hepatocarcinogenesis by acyclic retinoid is accompanied by reduction in emergence of both TGF-alpha-expressing oval-like cells and activated hepatic stellate cells. Nutr Cancer. 51(2):197-206.

Sarbassov DD, Guertin DA, Ali SM, Sabatini DM. (2005) Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science. Feb 18;307(5712):1098-101.

Scharf JG, Braulke T. (2003) The role of the IGF axis in hepatocarcinogenesis. Horm Metab Res. Nov-Dec;35(11-12):685-93.

Schirmacher P, Held WA, Yang D, Chisari FV, Rustum Y, Rogler CE. (1992) Reactivation of insulin-like growth factor II during hepatocarcinogenesis in transgenic mice suggests a role in malignant growth. Cancer Res. May 1;52(9):2549-56.

Schrader J, Gordon-Walker TT, Aucott RL, van Deemter M, Quaas A, Walsh S, Benten D, Forbes SJ, Wells RG, Iredale JP. (2011) Matrix stiffness modulates proliferation, chemotherapeutic response, and dormancy in hepatocellular carcinoma cells. Hepatology. Apr;53(4):1192-205.

Shirakawa H, Suzuki H, Shimomura M, Kojima M, Gotohda N, Takahashi S, Nakagohri T, Konishi M, Kobayashi N, Kinoshita T, Nakatsura T. (2009) Glypican-3 expression is correlated with poor prognosis in hepatocellular carcinoma. Cancer Sci. Aug;100(8):1403-7.

Steele JC, Torr EE, Noakes KL, Kalk E, Moss PA, Reynolds GM, Hubscher SG, van Lohuizen M, Adams DH, Young LS. (2006) The polycomb group proteins, BMI-1 and EZH2, are tumour-associated antigens. Br J Cancer. Nov 6;95(9):1202-11.

Sun L, Hu H, Peng L, Zhou Z, Zhao X, Pan J, Sun L, Yang Z, Ran Y. (2011) P-cadherin promotes liver metastasis and is associated with poor prognosis in colon cancer. Am J Pathol. Jul;179(1):380-90.

Tan J, Yang X, Zhuang L, Jiang X, Chen W, Lee PL, Karuturi RK, Tan PB, Liu ET, Yu Q. (2007) Pharmacologic disruption of Polycomb-repressive complex 2-mediated gene repression selectively induces apoptosis in cancer cells. Genes Dev. May 1;21(9):1050-63.

Tang Y, Kitisin K, Jogunoori W, Li C, Deng CX, Mueller SC, Ressom HW, Rashid A, He AR, Mendelson JS, Jessup JM, Shetty K, Zasloff M, Mishra B, Reddy EP, Johnson L, Mishra L. (2008) Progenitor/stem cells give rise to liver cancer due to aberrant TGF-beta and IL-6 signaling. Proc Natl Acad Sci U S A. Feb 19;105(7):2445-50.

Tomimaru Y, Eguchi H, Nagano H, Wada H, Tomokuni A, Kobayashi S, Marubashi S, Takeda Y, Tanemura M, Umeshita K, Doki Y, Mori M. (2010) MicroRNA-21 induces resistance to the anti-tumour effect of interferon-α/5-fluorouracil in hepatocellular carcinoma cells. Br J Cancer. Nov 9;103(10):1617-26.

Tovar V, Alsinet C, Villanueva A, Hoshida Y, Chiang DY, Solé M, Thung S, Moyano S, Toffanin S, Mínguez B, Cabellos L, Peix J, Schwartz M, Mazzaferro V, Bruix J, Llovet JM. (2010) IGF activation in a molecular subclass of hepatocellular carcinoma and pre-clinical efficacy of IGF-1R blockage. J Hepatol. Apr;52(4):550-9. Tsang DP,

Umemura A, Itoh Y, Itoh K, Yamaguchi K, Nakajima T, Higashitsuji H, Onoue H, Fukumoto M, Okanoue T, Fujita J. (2008) Association of gankyrin protein expression with early clinical stages and insulin-like growth factor-binding protein 5 expression in human hepatocellular carcinoma. Hepatology. Feb;47(2):493-502.

Villanueva A, Chiang DY, Newell P, Peix J, Thung S, Alsinet C, Tovar V, Roayaie S, Minguez B, Sole M, Battiston C, Van Laarhoven S, Fiel MI, Di Feo A, Hoshida Y, Yea S, Toffanin S, Ramos A, Martignetti JA, Mazzaferro V, Bruix J, Waxman S, Schwartz M, Meyerson M, Friedman SL, Llovet JM. (2008) Pivotal role of mTOR signaling in hepatocellular carcinoma. Gastroenterology. Dec;135(6):1972-83, 1983.e1-11.

Visvader JE. (2011) Cells of origin in cancer. Nature. Jan 20;469(7330):314-22.

Vivanco I, Sawyers CL. (2002) The phosphatidylinositol 3-Kinase AKT pathway in human cancer. Nat Rev Cancer. Jul;2(7):489-501.

Wang GB, Zhou XY, Wang XQ. (2010) Relationship between serum heparanase and microscopic venous invasion in patients with hepatocellular carcinoma. Am J Clin Pathol. Aug;134(2):242-8.

Wang XQ, Luk JM, Leung PP, Wong BW, Stanbridge EJ, Fan ST. (2005) Alternative mRNA splicing of liver intestine-cadherin in hepatocellular carcinoma. Clin Cancer Res. Jan 15;11(2 Pt 1):483-9.

Whitesell L, Lindquist SL. (2005) HSP90 and the chaperoning of cancer. Nat Rev Cancer. Oct;5(10):761-72.

Whittaker S, Marais R, Zhu AX. (2010) The role of signaling pathways in the development and treatment of hepatocellular carcinoma. Oncogene. Sep 9;29(36):4989-5005.

Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M, Cao Y, Shujath J, Gawlak S, Eveleigh D, Rowley B, Liu L, Adnane L, Lynch M, Auclair D, Taylor I, Gedrich R, Voznesensky A, Riedl B, Post LE, Bollag G, Trail PA. (2004) BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. Oct 1;64(19):7099-109

Woodward WA, Chen MS, Behbod F, Alfaro MP, Buchholz TA, Rosen JM. (2007) WNT/beta-catenin mediates radiation resistance of mouse mammary progenitor cells. Proc Natl Acad Sci U S A. Jan 9;104(2):618-23.

Workman P, Burrows F, Neckers L, Rosen N. (2007) Drugging the cancer chaperone HSP90: combinatorial therapeutic exploitation of oncogene addiction and tumor stress. Ann N Y Acad Sci. Oct;1113:202-16.

Xiong Y, Fang JH, Yun JP, Yang J, Zhang Y, Jia WH, Zhuang SM. (2010) Effects of microRNA-29 on apoptosis, tumorigenicity, and prognosis of hepatocellular carcinoma. Hepatology. Mar;51(3):836-45.

Xu CR, Lee S, Ho C, Bommi P, Huang SA, Cheung ST, Dimri GP, Chen X. (2009) Bmi1 functions as an oncogene independent of Ink4A/Arf repression in hepatic carcinogenesis. Mol Cancer Res. Dec;7(12):1937-45.

Yamashita T, Ji J, Budhu A, Forgues M, Yang W, Wang HY, Jia H, Ye Q, Qin LX, Wauthier E, Reid LM, Minato H, Honda M, Kaneko S, Tang ZY, Wang XW. (2009) EpCAM-positive hepatocellular carcinoma cells are tumor-initiating cells with stem/progenitor cell features. Gastroenterology. Mar;136(3):1012-24.

Yang Z, Zhou L, Wu LM, Lai MC, Xie HY, Zhang F, Zheng SS. (2011) Overexpression of long non-coding RNA HOTAIR predicts tumor recurrence in hepatocellular carcinoma patients following liver transplantation. Ann Surg Oncol. May;18(5):1243-50.

Yin C, Lin Y, Zhang X, Chen YX, Zeng X, Yue HY, Hou JL, Deng X, Zhang JP, Han ZG, Xie WF. (2008) Differentiation therapy of hepatocellular carcinoma in mice with recombinant adenovirus carrying hepatocyte nuclear factor-4alpha gene. Hepatology. Nov;48(5):1528-39.

Yoo BK, Santhekadur PK, Gredler R, Chen D, Emdad L, Bhutia S, Pannell L, Fisher PB, Sarkar D. (2011) Increased RNA-induced silencing complex (RISC) activity contributes to hepatocellular carcinoma. Hepatology. May;53(5):1538-48.

Zhang Y, Li L, Wang Y, Zhang J, Wei G, Sun Y, Shen F. (2007) Downregulating the expression of heparanase inhibits the invasion, angiogenesis and metastasis of human hepatocellular carcinoma. Biochem Biophys Res Commun. Jun 22;358(1):124-9..

Zhou W, Mukherjee P, Kiebish MA, Markis WT, Mantis JG, Seyfried TN. (2007) The calorically restricted ketogenic diet, an effective alternative therapy for malignant brain cancer. Nutr Metab (Lond). Feb 21;4:5.

Zimmerman RL, Fogt F, Burke M, Murakata LA. (2002)Assessment of Glut-1 expression in cholangiocarcinoma, benign biliary lesions and hepatocellular carcinoma. Oncol Rep. Jul-Aug;9(4):689-92.

Zhao W, Zhang L, Yin Z, Su W, Ren G, Zhou C, You J, Fan J, Wang X. (2011) Activated hepatic stellate cells promote hepatocellular carcinoma development in immunocompetent mice. Int J Cancer. Jan 6.

Zhao H, Liu H, Chen Y, Xin X, Li J, Hou Y, Zhang Z, Zhang X, Xie C, Geng M, Ding J. (2006) Oligomannurarate sulfate, a novel heparanase inhibitor simultaneously targeting basic fibroblast growth factor, combats tumor angiogenesis and metastasis. Cancer Res. Sep 1;66(17):8779-87.
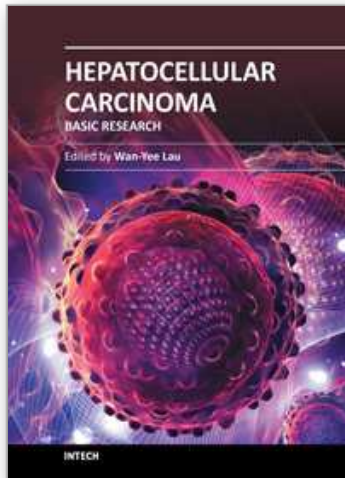
Hepatocellular Carcinoma - Basic Research

Edited by Dr. Joseph W.Y. Lau

Hepatocellular Carcinoma represents a leading cause of cancer death and a major health problem in developing countries where hepatitis B infection is prevalent. It has also become increasingly important with the increase in hepatitis C infection in developed countries. Knowledge of hepatocellular carcinoma has progressed rapidly. This book is a compendium of papers written by experts to present the most up-to-date knowledge on hepatocellular carcinoma. This book deals mainly with the basic research aspect of hepatocellular carcinoma. The book is divided into three sections: (I) Biomarkers / Therapeutic Target; (II) Carcinogenesis / Invasion / Metastasis; and (III) Detection / Prevention / Prevalence. There are 18 chapters in this book. This book is an important contribution to the basic research of hepatocellular carcinoma. The intended readers of this book are scientists and clinicians who are interested in research on hepatocellular carcinoma. Epidemiologists, pathologists, hospital administrators and drug manufacturers will also find this book useful.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Yangchao Chen and Chi Han Li (2012). Novel Therapeutic Targets for Hepatocellular Carcinoma Treatment, Hepatocellular Carcinoma - Basic Research, Dr. Joseph W.Y. Lau (Ed.), ISBN: 978-953-51-0023-2, InTech, Available from: http://www.intechopen.com/books/hepatocellular-carcinoma-basic-research/novel-therapeutic-targets-for-hepatocellular-carcinoma-treatment

INTECH
open science | open minds