Hepatocellular Carcinoma: Insights from the Centrosome Abnormalities

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1. Introduction

Hepatocellular carcinoma (HCC) ranks the third in cancer-related death in the world. In Africa and Asia, the incidence of HCC, and death rate in particular, is even higher than other types of cancer. Chronic inflammation, mainly caused by viruses such as hepatitis B virus (HBV) and hepatitis C virus (HCV), has long been regarded as the major player in HCC development. However, increasing genes and/or tremendous epigenetic factors, and interactions thereof, have appeared to be involed in HCC development (Beasley & Lin, 1978; Arbuthnot & Kew, 2001). Although great efforts have been made in the past, early diagnosis and effective treatment to the patients in the late stage are still difficult. Centrosome amplification, a distinct feature in most cancer cells, has been widely studied recently in leukemia and increasing types of solid tumors. In HCC, however, there are few studies reported. What roles may centrosome play in hepatocellular carcinoma? What insights may it shine in guiding cancer therapies? And so on. We, in this chapter, would like to discuss the relations between centrosome and HCC development, through which, hopefully, novel therapeutic approaches are developed based on targeting the centrosome as a whole instead of just some proteins on it.

2. Centrosome in cancer

Centrosomes are tiny complex organelles, near the nucleus of an interphase cell, serving as microtubule organizing center (MTOC) involved in fundamental cellular activities such as cell polarity, cellular adhesion, mobility, signal and molecule transport. These cellular processes are inseparable with important cellular events, such as cell cycle, DNA synthesis, DNA repair, apoptosis regulation, signal transduction, and carcinogenesis (Whitehead & Salisbury, 1999; Rieder et al., 2001; Palazzo et al., 2000). When cell enters into M phase, two newly duplicated centrosomes move to the opposing sites and form the poles of the mitosis spindle. Mitosis spindle play key roles in maintaining genetic stability, with the roles of centrosome in carcinogenesis having long been noticed by Theodor Boveri (Boveri T, 1914). Recently the centrosome was even described as a core part of "cell brain" (Kong et al., 2002).

2.1 The roles of centrioles in centrosome duplication

The important roles that centrosome plays in carcinogenesis should be understood together with the understanding of the centrioles embedded in the centrosome. Normal structure and/or function of centrosome requires the exactly controlled centrioles cycle. In fact, in most cells the reproductive capacity of centrosome does depend on its centriole contents, and centrosome would not duplicate if centrosome lacks centrioles. Therefore, strictly controlled mechanisms to regulate the centriole duplication in one cell cycle, appear to particularly important, as abnormality of centrioles may promote genetic instability, centrosome mis-segregation and/or apoptosis (Schatten et al., 2000).

As known, centrioles embedded in a cloud of electron-dense materials called pericentriolar material (PCM), which is responsible for formation of centrosome leading to bipolar mitosis, which, in turn, results in genetic stabilities. In cell cycle, centrosome cycle can be divided into centriole disorientation and disengagement, centriole duplication, centrosome maturation, centrosome separation, and procentriole assembly (Azimzadeh & Bornens, 2007). In G1 phase, the orthogonal arrangement of the two centrioles is lost and the distance between the two centrioles increased. Then, the amorphous central tube forms perpendicular to mother centriole, subsequently, nine individual microtubules around it assemble to procentriole. S and G2 phase trigger the newly generated daughter centrioles elongation until they reach to the same size of their mothers. Once cells enter into M phase, the two parental centrioles disconnect fully and finally lose their orthogonal relationship. In the end, PCM separates to give rise to each own cloud of PCM.

However, these two centrioles are not identical in cell since centriole only originated from a pre-existing one called the mother centriole. The new one, being about 80% of the length of the mother centriole, is called the daughter centriole (Azimzadeh & Bornens, 2007). Only mother centriole has external appendages functioning as docking site for microtubules and mediating centriole attachment to plasma membrane. PCM also plays important roles in directing microtubule nucleation by minus ends at proteinaceous complexes around mother centriole. Therefore, the mother centriole may be a major player in "licensing" event to ensure that one cell contains only one newly duplicated centriole in rigorous centriole duplication cycle. Support of this idea came from the finding that once daughter centriole formed from mother centriole, the centriole duplication process would have been inhibited, even though the cell was in a permissive condition (Tsou & Stearns, 2006a). In other words, the centriole duplication was determined by the mother centriole. Does this mean that in M phase, the separated duplication centriole each can be as a template to give rise to a new centriole? The prevailing view is that cytoplasm symaptic with mother centriole controls the centriole duplication. In S phase, even if the newly synthesized centriole has been ablated by laser, centriole duplication cycle cannot restart (Balczon et al., 1995; Loncarek et al., 2008). It is noteworthy that in S phase arrested CHO, HeLa and U2OS cells, mother centriole generates more than one daughter centriole, indicating mother centriole must have a mechanism to count the number of newly formed centriole (Loncarek et al., 2008; Jones & Winey, 2006; Tsou & Stearns, 2006b). Once this mechanism attenuated, the number of daughter centriole is out of the control of mother one. Today, we know that some mother centrole proteins may be the major players in this process, such as PLK4, SAS-6, and pericentrin. Support of this further came from the experiment that HIV-16 E7 oncoprotein can induce multiple daughter centriole at single mother centriole by cyclin E/CDK2 and

PLK4 over-expression both in normal primary cells and in tumor cell lines (Kleylein-Sohn et al., 2007; Duensing et al., 2007; Strnad et al., 2007). These findings may help to explain why supernumerary centrosomes are found in most cancer cells. However, there may be other ways to form newly synthesized centriole. De novo assembly of centriole has been found in the centriole that lacks of oocyte in most species (Manandhar et al., 2005; Riparbelli & Callaini, 2003; Szollosi & Ozil, 1991). *De novo* centriole assembly can be activated only in somatic cells with the centrioles removed either by microsurgery or by laser ablation in spite of the cell is transformed or not (Khodjakov et al., 2002; La Terra et al., 2005). Under this circumstance, the *de novo* assembled centriole is usually supernumerary, displacement, and malformed. In addition, the minimal pericentriolar material, lower microtubule nucleation capacity, and disjoin centriole pairs are the common features. Obviously, *de novo* assembly centriole is deleterious consequences in somatic cells, so *de novo* assembly pathway always inhibited by canonical centriole duplication cycle as a well-defined cloud of PCM (Young et al., 2000). Thus the elegant centriole duplication mechanism ensures that only one centrosome is in interphase cells unless two in M phase.

2.2 Centrosome abnormalities in cancer

Given that centrosome abnormalities, including increased number and centrosome structural abnormalities, is a hallmark in most, if not all, cancer cells, some questions remain to be elucidated: why supernumerary centrosomes are common features in cancer cell; how do they arise; and are they the causes or consequences of tumorigenesis (Lingle et al., 1998; Pihan et al., 1998). Recent studies showed that centrosome abnormalities in cancers can originate either by centrosome overduplication or by *de novo* synthesis of centrosomes (Duensing, 2005). Several centriole maturity markers, including ODF2/cenexin, ε-tubulin, ninein, ninein-like protein, adenomatous polyposis coli, EB1, centriolin, and Cep170, which only located in the mother centriole, can be used to distinguish the centriole duplication either from centrosome supernumerary or vice versa (Huber et al., 2008; Chang et al., 2003; Ibi et al., 2011; Louie et al., 2004; Hinchcliffe, 2003; Guarguaglini et al., 2005). No matter what is causal factor in inducing centosome overduplication, the extra centrosome can form multipolar mitosis, which leads to unequal chromosomes separation, therefore, promoting tumorigenesis. In addition, only centrosome amplification has been recently shown to initiate tumorigenesis in flies (Basto et al., 2008). Although the relation between centrosome abnormalities and chromosome instability (CIN) has long been regarded as a hen-and-egg problem, increasing studies intent to support the findings that extra centrosomes are major players in directly inducing chromosome missegregation, which, in turn, facilitates the evolution of more malignant phenotypes (Ganem et al., 2009).

As known that centrosome supernumerary and CIN are deleterious to cancer cells, the question is then how cancer cells survive. If the number of tumor cell having abnormal centrosome is less, the negative effects on the cell fates can be neglected. However, if most of the tumor cells have extra centrosomes, then there must be some mechanism to limit the detrimental consequences of supernumerary centrosome and CIN. Based on the findings that not all of extra centrosomes are activated to form MTOC and the normal cells harboring extra centrosome can survive, to date, bipolar spindle has been regarded as the major mechanism to prevent multipolar mitosis in supernumerary centrosomal tumor cells (Godinho et al., 2009). In principle, bipolar division is an effective way to

eliminate extra centrosome. In fact, several research groups have found that some cell lines, which contain extra centrosomes, undergo bipolar divisions by clustering extra centrosomes. Interestingly, this phenomenon has been observed in some non-transformed cells that harbor extra centrosomes. Why is the centrosome clustering such a so popular event in supernumerary centrosome cells? It is highly possible that bipolar mitoses may be the best way to reduce the selective pressure. Although the exact mechanisms through which centrosome clustering is coordinated are not fully elucidate, recent studies have indicated that SAC, some MT motor proteins, such as Ncd/HEST, a kinesin family, and dynein, may be major players (Godinho et al., 2009).

Centrosome amplification has long been regarded as a distinct feature in most cancer cells. Abnormal centrosome biology, either centrosome amplification or structural abnormalities, frequently occur in most types of tumors including testicular germ cell, liposarcoma, adrenocortical, bronchial, bladder, cerebral primitive neuroectodermal, cervical, prostate, breast, squamous cell carcinomas of the head and neck, myeloma, and T-cell leukemia (Pihan et al., 1998; Duensing, 2005; Kramer et al., 2005; Nigg, 2002; Nigg, 2007; Giehl et al., 2005). Recent proteomic studies showed that abnormal centrosome may be the consequences of centrosome protein dysregulation. Up to now, More than 500 proteins have been identified and localized in centrosome, suggesting that centrosome may function as a central docking platform, where regulatory complexes converge and cross-talk by signaling pathway through microtubule network (Andersen et al., 2003). These centrosome localized proteins are generally divided into two classes: 1) structure proteins, including alpha tubulin, beta tubulin, gamma-tubulin, gamma-tubulin complex components 1–6, centrin 2 and 3, AKAP450, pericentrin/kendrin, ninein, pericentriolar material 1 (PCM1), ch-TOG protein, C-Nap1, Cep250, Cep2, centriole-associated protein CEP110, Cep1, centriolin, centrosomal P4.1 associated protein (CPAP), CLIP-associating proteins CLASP1 and CLASP 2, ODF2, cenexin, Lis1, Nudel, EB1, centractin, myomegalin; 2) temporary proteins, including oncogenes, tumor suppressor genes, ubiquitination and degradation related proteins, DNA damage checkpoint proteins, cell cycle regulated proteins, such as Survivin, Ras, Rad6, HER2/neu, p53, Rb, p21, APC, Gadd4, including APC/C, brca1, Cdc20, Cdh1, ATM, ATR, BRCA1, Chk1, including cyclin B1, Cdks, Chks, Plks, aurora kinases, and Neks. Over-expression of these centrosome proteins, mainly temporary proteins, has been demonstrated to induce tumor-like features. Since more and more known and yet-to-be known key proteins are found to be docked to centrosome, regarding centrosome together with centrioles and microtubules as the center of cell or called cell brain appears to be reasonable.

2.3 Roles of the centrosome in HBV virus infection

About 15% of all human cancers were caused by tumor viruses, mainly including human T-cell leukemia virus (HTLV-I), HBV, HCV, human papillomavirus (HPV), Epstein–Barr virus (EBV), Kaposi's sarcoma herpesvirus (KSHV) (Parkin, 2006). Whether virus need to entry into the cell or out from the cell, the cytoplasm is a very viscous milieu to preclude efficient directional movements by free diffusion (Suzuki & Craigie, 2007). What can they do to cope with this problem? Intracellular viral pathogens has evolved numerous mechanisms to hijack the host for their own profit during their life cycles. As centrosome is a perinuclear

organelle and functions as an MTOC, which, in turn, is responsible for MT assembly and mediates MT-dependent trafficking due to MTs minus ends anchoring to the PCM and the plus ends extending towards the cell periphery, it is reasonable to believe that centrosome is the most appropriate candidate (Afonso et al., 2007). In fact, centrosome, particularly the pericentriole may act as progeny virus assembly site because of the high local concentration of chaperons, and play as a transfer station controlling virus cytoplasm - nuclear transport through MTs (Brown et al., 1996a, 1996b). The evidence stems from that microtubule depolymerizing agents can affect the ability of incoming viruses to reach to their replication site and viral protein assembly. This is why viruses such as HBV and HCV exploit the host cell's centrosomal capabilities and recruit centrosomal material for their own survival within host cells (Scaplehorn & Way, 2004; Coppens et al., 2006).

As for HCC, more than 85% of the cases are attributed to HBV infections (World Health Organization Scientific Group on Prevention and Control of Hepatocellular Carcinoma, 1983; Goncalves et al., 1998; Brechot et al., 2000). HBV is a DNA virus, which can lead to centrosome abnormalities, either supernumerary or dysfunction. Among HBV virus encoded proteins, only X proteins (HBx) is an oncoprotein associated with dysregulated cell division and cell death mainly caused by centrosome abnormal. Among HBx binding partners, HBXIP, a centrosome associated protein in mitotic cells, controls the virus cellular movement by binding to the motor protein, dynein (Chisari & Ferrari, 1995). HBXIP is a cytosolic survivin adaptor belonging to BIR-family chromosome passenger protein involved in cell apoptosis and division controlling. In Reed group, it is reported that HBXIP functions as a regulator in prometaphase and at telophase through centrosome duplication and cytokinesis pathway (Fujii et al., 2006). In HBV virus infected cells, the functions of cellular HBXIP may be dysregulated by HBx oncoprotein, which promote amplification of centrosomes, multipolar mitotic spindle formation, and CIN, and eventually creating tumorigenesis. Over-expression of HBXIP can trigger formation of extra centrosomes, which results in tripolar and multipolar spindles formation in premetaphase, whereas down-regulation of HBXIP may lead to monopolar spindle formation, regardless of p53 status. This may partly explain the contradictory findings that the centrosome abnormalities were caused by p53 and vice versa. Interestingly, pericentrin , the primary signal, transports signal to HBx and HBXIP to regulate centrosome functions (Wen et al., 2008). These findings explain why pericentriole is an assembly site for most virus infection and centrosome is a major hijacking target in virus entry and out process. Besides, 20 kDa centrin 2 has been found only in the cell expressiong HBx. Chromosome region maintenance 1 (CRM1), which is a transport receptor that mediates nuclear export of proteins, was found to mediates HBx nuclear export through Crm1/Ran GTPase-mediated pathway (Rousselet, 2009). Once exported from the nuclear by Crm1, HBx can be transported to pericentriole to assembly and budding sites. And pericentrin, main component of pericentriole, identified as five novel nuclear export signals (NESs) could bind to Crm1 (Forgues et al., 2003). Any disruption of specific nuclear cytoplasm transport pathways is crucial for the productive life cycle of some viruses. Clearly, centrosome and associated MTs plays pivotal roles in virus life cycle (Greber & Way, 2006).

2.3.1 The roles of centrosome-associated proteins in HBV induced HCC

More recently, a growing list of centrosome located proteins associated with carcinogenesis have been identified, such as PLK4, Aurora-A/STK 15/ BTAK, p53, NF-κB, and so on. In

normal cells, the balance of apoptosis and proliferation must maintain at a stable level, whereas viruses usually hamper the host apoptosis to facilitate virus reproduction. The proteins involved in this process include p53, NF-κB, MAPK (Pang et al., 2006). HBx may influence apoptosis by interacting with the NF-κB signaling cascade or p53 (Wang et al., 1995; Becker et al., 1998; Livezey et al., 2002), whereas stimulate cell proliferation through the activation of cyclin-dependent kinase activities (Bouchard et al., 2001). p53, the tumor suppressor and key surveillance factor, has recently been detected to be mutated in HCC. In HCC, HBx inactivates p53 and p53-mediated activation of p21 (Ogden et al., 2000; Park et al., 2009), which, in turn, do not act as the "stop signal" for cell division. On the other hand, inactivated p53 no longer binds DNA in an effective way and acts as the negative signal for cell division, inducing an uncontrolled cell cycle-specific manner, which, in turn, leads to multiple copies of centrosome duplication in cell cycle. p53 mutation accompanied with centrosome aberration can induce genetic instability and this defective surveillance checkpoint mechanism ensures cancer cell reentering the cell cycle, thereby leading to series of catastrophic cascade, such as uncontrolled cell growth, pro-oncogenes activation, and tumors formation. NF-κB, the oncogene, promotes cell division, which can be augmented by mutant p53 through activation IKKα and IKKβ and enhancing NF-κB activity, therefore promoting cancer cell utilization of aerobic glycolysis preferentially for energy provision. Studies found in HBx expression cells, NF-κB was highly up-regulated and accompanied with extending life span, which indicated that cells enhance endogenous NF-κB transcriptional activity, harboring p53 mutations through a selective survival advantage in inflammatory microenvironments, and that p53 mutations may promote cancer under conditions of chronic inflammation (Park et al., 2006). More recently, the studies showed that HBx, but not export-defective mutant, can bind to and sequester Crm1 in the cytoplasm, thereby altering Crm1/Ran GTPase-dependent nuclear export of the NF-κB/IκBα complex (Forgues et al., 2003). In addition, all these findings suggested that HBx may act as several centrosome associated proteins to regulate cell apoptosis and proliferation benefitting for virus reproduction.

In addition, several centrosome associated kinases have been shown to induce chromosomal instability, leading to aneuploidy and cell transformation, such as Aurora-A, PLK4. Frequently occurred over-expression and amplification of Aurora-A, which can promote tumor formation and progression by causing unbalanced chromosomal segregation and centrosome aberrations in human cancer, lately have been detected in HCC (Benten et al., 2009). Centrosomal proteins such as Aurora-A and p53 may regulate each other in carcinogenesis. p53 protein could suppress the Aurora-A induced centrosome amplification and cellular transformation in a trans-activation-independent manner in HCC. Aurora-A over-expression was found to be correlated with p53 mutation, and tumors with both Aurora-A over-expression and p53 mutation usually have worse prognosis than that with p53 mutation alone (Jeng et al., 2004). This indicates that both of p53 and Aurora-A contribute to tumor progression and poor prognosis. Similar results have been found in PLK abnormal expression cells. Polo-like kinases (Plks), potential regulators of M phase, functions in mitotic entry, spindle pole activities and cytokinesis, which are broadly conserved despite physical and molecular differences in these processes in disparate organisms (de Carcer et al., 2011). PLK1-4 proteins are aberrantly regulated and possess different roles in human HCC, with PLK1 acting as an oncogene and PLK2-4 being

presumably tumor suppressor genes. Plk4, major risk factor for primary liver cancer, localizes to centrioles throughout the cell cycle and is essential for centriole duplication (Pellegrino et al, 2010). In Plk4 down expression HCC cells, cell cycle progression was impaired with delay in M phase completion by dysregulation of cyclins D1, E, and B1, and of cdk1, whereas multipolar spindle formation was increased 6-fold and p53 activation and p21 expression were suppressed (Pellegrino et al., 2010; Ward et al, 2011).

2.3.2 The roles of centrosome in signaling pathway in HBV-induced HCC

Network of signaling pathway provides a robust mechanism for cells to respond to various biological stimuli. Although little is known about the roles of centrosome in signal transduction, a growing body of evidence has demonstrated that many signaling proteins localize at centrosome, being the targets of HBx. For example, protein kinase C (PKC) and its major substrate MARCKS (myristoylated alanine-rich C-kinase substrate), exerting multiple roles, such as controlling microtubule organization, spindle function, and cytokinesis, were found to colocalize to pericentrin and gamma-tubulin within MTOCs (Kim et al., 2008; Michaut et al., 2005). HBx activates PKC, which is transient and differs from activation of PKC by the ras oncogene product or phorbol ester in that it does not lead to rapid down-regulation of the enzyme subsequent to the activation. Previous studies have implicated protein kinase C (PKC) as upstream regulators of the MAPK. Interestingly, both of PKC and MAPK are required for phosphorylation of HBx, which, in turn, alters its subcellular localization and dysregulation of cell cycle progression, leading to hepatocarcinogenesis in HBV-infected cells. Besides, phosphoinositide 3-kinase (PI3K), a family of enzymes linked to extraordinarily diverse group of cellular functions, are involved in cancer (Lee et al., 2001; Yun et al., 2004, Wang et al., 2011). In HBV-infected cells, PI3K/Akt pathway can be activated through Akt phosphorylation by HBXIP, which also induce up-regulate cyclin D and down-regulate p21 and p53 expression, promoting cell proliferation (Wang, et al., 2011).

Cell adhesion to the extracellular matrix (ECM) is an important process that controls cell morphology, migration, proliferation, and so on. Integrin bridges cell and ECM, enduring pulling forces to promote cell migration. Otherwise, cell attachment to ECM is a basic requirement to build a multicellular organism, during this process integrin transmits surrounding signals into cytoplasm. The cytoplasmic domain of β1 integrin acts as a proximal receptor kinase to phosphorylate downstream targets regulating integrin-mediated signal transduction. If β1 integrin cytoplasmic domain mutation occurs, it will inhibit MT nucleation from the centrosomes and also disrupts cytokinesis, most likely due to spindle defects such as multipolar spindles (Reverte et al., 2006). In addition, cell migration also requires the orientation of the spindle during asymmetric cell division. Integrin linked kinase (ILK), a serine/threonine protein kinase, has also been shown to localize to the centrosome and to play a role in spindle assembly (Fielding et al., 2008). Interestingly, ILK signaling effectors such as Akt, GSK3 and β-catenin have also been found at the centrosome and mitotic spindles, indicating that centrosome associated proteins play important roles in spindle assembly. Recent evidence suggests that β-catenin involves in two signaling transduction pathways, cell-adhesion signaling and Wnt signaling pathway in which process β-catenin–T-cell factor (TCF) complex transcriptionally regulates gene expression

(Nelson & Nusse, 2004). No matter which way β-catenin involves, the intracellular β-catenin level is critical to its functions, therefore, HBx can regulate β-catenin, which plays an important role in various aspects of liver biology including cancer development, either by GSK-3, which directly suppress its activation via Src, or indirectly inhibit its activation by ERK signaling, or by p53, in which process HBx stabilize p53 expression leading to β-catenin degeneration (Hsieh et al., 2011; Wu et al., 2008; Jung et al., 2007). Importantly, β-catenin, a component of centrosome, interacts with centrosomal proteins to regulate mitotic centrosome separation (Bahmanyar, 2010) by forming a complex with the centrosomal proteins Nek2, C-Nap1 and Rootletin (Bahmanyar et al., 2008; Hadjihannas et al., 2010). Depletion of β-catenin in asynchronous cells results in monopolar spindles with unseparated centrosomes (Bahmanyar et al., 2008), whereas expression of mutation β-catenin causes increased centriole splitting in G1-S (Bahmanyar et al., 2008; Hadjihannas et al., 2010). These findings suggest that cell adhesion is a major target for HBx both on cell migration and on signaling transduction.

3. Centrosome abnormalities in the development of drug resistance

As signaling center, centrosome plays important roles in the development of drug resistance. Many centrosome-associated proteins are involved in chemo-resistance process, such as Her-2/neu, bcl-2, c-myc, ras, c-jun, MDM2, p210 BCR-abl, or mutant p53. In fact, abnormal centrosome itself may lead to formation of poly- or monopolarity spindle resulting in chromatin mis-segregation, which further result in or accelerate inactivation of tumor suppressor genes and/or activation of tumor genes, thereby leading to the development of chemoresistance. Support of this idea comes from the recent finding that p53 status determines tumor response to anti-angiogenic therapy and heat shock proteins (HSPs) varies with tumor progressions (Chen & Kong, 2009; Ciocca & Calderwood, 2005).

3.1 Centrosome clustering pathway as a target in cancer therapy

Centrosome clustering pathway is indispensable in cells with supernumerary centrosomes ensuring the success of cell division. Interference in this process could be lethal to tumor cells containing extra centrosomes (Kwon et al., 2008). Therefore, proper interference centrosome clustering pathway may raise the possibility of developing a new therapeutic strategy. HSET, the human homologue of the KAR3 family of minus end-directed kinesin-like motors, may be one of the most appropriate such candidates, as HSET depletion destroys centrosome clustering pathway and induces multipolar divisions and hence abnormal chromosome segregation or aneuploidy. Besides, HEST is essential only for clustering extra centrosomes in cancer cell but not in normal cells, by bundling the minus end of MT in acentrosomal spindles (Mountain et al., 1999). These results indicate that inhibition of HSET can selectively kill cells with extra centrosomes without affecting the viability of cells that contain normal centrosome numbers. In addition, HEST has been found to be involved in cell-cell adhesion by influencing the cells shape, then inducing low integrin -1 expression, and eventually resulting in tumor environment changes (Amendola et al., 2001). Taken together, HSET inhibitor may have a relative low toxicity compared with other mitosis-blocking agents involving centrosme, including checkpoint

with forkhead and ring finger domains (CHFR), Aurora A, B, and C, Polo-like kinases (Plk1-4), and Nek kinases (NIMA1-11).

3.2 Targeting the centrosome as a whole in HCC therapy

As stated above, most of the key proteins are associated with cancer development. Selective inhibitors of these proteins such as p53, kinase C (PKC), proteasome, Aurora, NEDD1, and centrosome-associated regulators, therefore, have recently been tried in drug development (Graff et al., 2005; Montagut et al., 2005; Godl et al., 2005; Warner et al., 2006; Wang et la., 2009; Tillement et al., 2009). Since most of the key cellular proteins are localized to the centrosome, and centrosome abnormalities has long been found to be one of the most common features in a variety of human cancers and to be one of the earliest events in cancer development, as compared to p53 mutation and telomerase up-regulation that have been long regarded as the major factors contributing to the development of carcinogenesis. Centrosome is naturally becoming a candidate target in cancer therapy. In addition, chromosome instability (CIN) may be the fundamental cause in the development of drug resistance, and centrosome together with centrioles abnormalities are closely associated CIN, the whole complex consisting of the centrosome and centrioles may be a most promising candidate in cancer therapy.

Since increasing key proteins are found to be localized on centrosome and/or centrioles. And each protein exerts its yet unknown functions alone or through centrosome and/or centrioles. Selective targeting centrosome as a whole like mentioned previously (Kong, 2003a, 2003b, 2003c) or through combination of chemotherapeutic drugs that work through different mechanisms is expected to be reasonable and promising. Kong proposed that centrosome can be crystallized with tetrazolium salts (Kong et al., 2002). Although there is no further evidence to affirm whether it works or not in clinic, it seems to be reasonable that the crystallized centrosome may not function as the centre of the cell to mediate important cellular events. In other words, all key enzymes located in the centrosome will not function normally, and the cellular structures that are rich in the enzymes will be functionally and structurally frozen or restrained (Kong et al., 2002; Chen & Kong, 2006). Therefore, selective targeting centrosome as a whole unlike traditional approaches aiming at single protein or pathway is worthy of trying.

4. Conclusion

Centrosome works as an integrated complex in regulating important cellular events. Disrupting centrosome structurally and functionally may trigger malignant transformation. Although the roles of centrosome in carcinogenesis have been elucidated in some types of cancer, the roles of the centrosome in HCC development, particularly in cancer therapy, are largely uncovered. As discussed above, centrosome serves as a platform for HBV virus infection through centrosome-associated proteins, then transforming cell to immortalization. It is reasonable to believe that the drugs targeting centrosome-associated proteins should be developed to stop cancer cells proliferation and exert their efficacy when combined with conventional therapeutic agents. However, centrosome is an open prison, where proteins can bind and release in a precisely time-dependent manner in different cell cycle. Selective

targeting centrosome as a whole, instead of a single protein or pathway, is, therefore, particularly worthy of trying.

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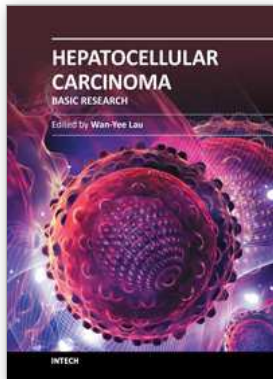
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Hepatocellular Carcinoma represents a leading cause of cancer death and a major health problem in developing countries where hepatitis B infection is prevalent. It has also become increasingly important with the increase in hepatitis C infection in 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.

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