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Targets and Approaches to Control Hepatocellular Carcinoma in Future

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1. Introduction

Cancer is uncontrolled proliferation of cells, which results from the loss of proper balance between cell death and cell growth. The transformed phenotypes of cancer cells are caused by the accumulation of mutations in a variety of genes, products of which normally play a role in the biochemical pathways that regulate cell death and cell proliferation. Cancer is a broad term used to define a group of more than 250 different diseases (Roncalli et al. 2010). It is a slow multi-stage, multi-step process (Cammà et al. 2008; Calvisi et al. 2009; Sherman 2011). In the first instance, these cells, derived initially from a normal cell, form a primary tumor which comprises a growth-transformed population of cells. The cells acquire a set of mutations to a set of genes which allow them to divide repeatedly in a way that normal cells cannot (Besaratnia et al. 2009; Calvisi et al. 2009). Histologically, cancer is characterized by several morphological alterations, including changes in tissue architecture, cytological abnormalities of both the nucleus and cytoplasm and the presence of abnormal mitoses. A stepwise several biochemical, genetic and biological alterations eventually result in a cancer.

Primary liver cancer or hepatocellular carcinoma (HCC) is a very common malignant hepatobiliary disease and it represents the fifth most frequent neoplastic disease which causes approximately 1 million deaths per year (Yang and Roberts, 2010, Cha et al. 2010). HCC is the third leading cause of cancer related death worldwide (Raphael 2012). Viruses and chemicals have been identified as the most important etiological factor associated with the development of human liver cancer (Carr et al. 2010). The most common cause of HCC is hepatitis B and C (Woo et al. 2008; Masuzaki et al. 2008, Gouas et al. 2010; Iavarone and Colombo 2011) and a

number of risk factors that have been identified (Shariff et al. 2009; Sherman 2010; Gomaa et al. 2008 and 2009). Most of HCC cases develop from a cirrhotic liver (Bartolomeo et al. 2011; Chagas et al. 2009; Orlando et al. 2009; Cammà et al. 2008) with an annual incidence of 2-6% for hepatitis B virus carriers (Kew 2010; Lim et al. 2009; Hadziyannis 2011) and 3-5% for hepatitis C virus-infected patients (Masuzaki et al. 2008; Rosen 2011). Males are more susceptible to HCC.

Despite the advances in cancer treatments there is no effective chemotherapeutic protocol to treat HCC (Andreana et al. 2009; Arii et al. 2010). Advanced HCC has a poor prognosis (Simile et al. 2011; Sonja et al. 2010). Historically, no effective systemic chemotherapy treatment options have been available for patients with advanced HCC (Bruix and Sherman 2011). Thus, proper understanding of the molecular basis of pathogenesis of HCC can lead us to plan for proper therapeutic strategies to combat the notorious disease.

Accumulating epidemiological evidence suggests that a pronounced predisposition to develop cancer as a consequence of a mutation in a single gene is rare (approximately 1-5%) (Frau et al. 2010). One possible explanation for this finding is that carcinogenesis is a multi-stage process involving a number of different genes and environmental factors (Chung et al. 2008; Forner et al. 2010; Frau et al. 2010). In connection with many distinct subtypes of cancer, some functional alterations are required for malignant transformation. They are, namely, sufficiency with respect to growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death (apoptosis), the potential for unlimited replication, sustained angiogenesis, tissue invasion and metastasis (Bergers and Hanahan 2008; Bartolomeo et al. 2011; Cao et al. 2010; Frau et al. 2010; Gouas et al. 2010). The exact number of distinct stages involved may vary from tumor to tumor, since some of these acquired characteristics probably interact with other processes (Roncalli 2010). Indeed, the heterogeneity of tumors, both with regards to morphology and pattern of gene expression, may even indicate the participation of many more sequential steps.

A highly regulatory network controls cellular proliferation in multicellular organisms. Normally cells in many tissues and organs remain in a non-proliferative state. In response to external stimuli such as growth factors, hormones or antigens, cells are stimulated to begin DNA synthesis and cellular proliferation according to the need of the living system. As soon as the need is fulfilled, the cell division stops. However, cancerous cells are characterized by the unrestrained cellular proliferation due to the alteration of normal cellular signalling process and they acquire complete or partial independence of mitogenic signals through production of growth factors (Garrett et al. 2008; Hironaka et al. 2009) and /or alteration in number or structure of cellular receptors (Lachenmayer et al. 2010) and/ or modulation in the activity of post receptor signalling pathway (Cavard et al. 2008; Chen et al. 2009). The communication of extracellular signals to the cells, then to the nucleus to modulate gene expression is governed by phosphorylation regulated signal transduction cascades which act to amplify the events generated at the cellular membrane by ligand-receptor interaction or cell stress. Therefore, identification of the extracellular factors that modulate cell proliferation and elucidation of the cellular molecular mechanism during the development of cancer can answer many fundamental questions in cancer cell biology. It is important to understand in details the

receptors and the signal transduction pathways involved in the pathogenesis of cancer to provide potential target for therapeutic intervention. Many studies have focused to identify molecular pathways to elicit cancer cell proliferation, including HCC. Here many of them have been highlighted to identify fundamental targets of hepatocellular oncogenesis. Thus, the present chapter has been projected to the molecular targets and approaches to intervene the targets for the management of HCC in humans in coming years.

2. Therapeutic targets for HCC

Three generally considered fundamental but interrelated targets of controlling oncogenesis are regulation of deregulated energy metabolism and ion homeostasis; signal transduction, oncogenes and growth factors; and immunomodulation. One of the most characteristic phenotypes of rapidly growing cancer cells is their propensity to catabolise glucose at high rates. Rapidly growing activity to cancer cells has a reduced number of mitochondria and increased glycolytic activity with a shift from respiratory to fermentative ATP supply to cover most of their energy requirement. The stimulation of the K^+ , H^+ and Na^+ fluxes is a general early response in most of the quiescent cells stimulated to proliferate by multiple combinations of growth promoting factors. Growth factors, cytokines exert their action on cell proliferation by modulation of cell signalling process. There is a strong relationship between the immune system and cell proliferation. Immune suppressive agents have a powerful effect on hepatocyte growth regulation in HCC.

Reviewing current literature, a selection of therapeutic targets of HCC has been described below.

Like most other cancers, growth factors, their receptors, and downstream signalling proteins play a pivotal role in the development and maintenance of HCC and are of significant interest for future therapeutic approaches. In foetal liver, a large number of growth factors such as epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), insulin-like growth factors (IGFs), platelet-derived growth factor (PDGF), transforming growth factors- α and - β (TGF- α , TGF- β), and vascular endothelial growth factor (VEGF) (Höpfner et al. 2008; Hoshida et al. 2008 and 2009) are produced. Their secretion either declines or shuts down in adult liver. However, during hepatic regeneration due to the cause of hepatic injury or damage many such growth factors (Böhm et al. 2010), namely, EGF, TGF- α , IGFs, and VEGF are upregulated in normal hepatocytes. The transient upregulation of those factors is dysregulated in the chronic injured liver leading to sustained mitogenic/ oncogenic signalling, during the development of HCC. FGF and PDGF released from non-hepatocyte sources such as activated hepatic stellate cells, myofibroblasts, endothelial cells, Kupffer cells, and bile duct epithelia have been shown to play important roles in promoting hepatic fibrosis and HCC growth (Friedman 2008). The ubiquitin-proteasome pathway has emerged as a key player in the regulation of several diverse cellular processes. Inhibition of poly-ubiquitination using proteasome inhibitors has shown some light in HCC treatment. Besides, immunomodulation has been found to be

effective in stabilizing HCC growth in patients. Number of immunomodulators has been investigated and few of them have been found to be effective. They have been discussed below under immunomodulation agents. Signal transduction, and growth factors; inhibitors of proteasome pathway, immunomodulation and antisense oligomer-mediated inhibition of targeted oncogenes have been projected as future targets and approaches of HCC (Table 1).

Molecular targets in HCC	Inhibitors / Modulators / Antisense oligonucleotides
Growth factors, e.g., EGFR, EGF, TGF- α , TGF- β , VEGF	Cetuximab, Gefitinib, Erlotinib, Vandetanib.
mTOR	Rapamycin, Temsirolimus, Salirasib, RAD001
Multikinase	Sorafenib, Everolimus, AP23573, RAD001.
Proteasome	Bortezomeb
Immunomodulators used in HCC	Thymostimulin, Retinoids, Everolimus, Azathioprine, 6-mercaptopurine.
Antisense oligonucleotides used in HCC	ISIS5132. ISIS2513

Table 1. Growth factors, proteasome-inhibitors, immunomodulators and antisense oligomers in HCC

3. Approaches

A selection of agents currently in the development and/or testing stages for the clinical application in targeted HCC treatment is summarized in the following section.

3.1. Therapies against EGFR

There are two classes of anti-EGFR agents found to have antitumor activity against HCC. One of them belongs to monoclonal antibodies (as an example cetuximab) which competitively inhibit extracellular endogenous ligand binding. The other class belongs to chemicals such as gefitinib, erlotinib which inhibit the intracellular tyrosine kinase domain. EGF, TGF- α , heparin binding-EGF and EGFR have been shown to involve in the pathogenesis of HCC. Thus, EGFR signalling pathways have become a potential investigating area of research to identify the target (s) to inhibit proliferation of HCC and metastasis. Gefitinib, erlotinib, cetuximab were tested in patients with advanced HCC (Thomas et al. 2007; Philip et al. 2005; Asnacios et al. 2008; Wu et al. 2011, Levêque 2011) and were reported to possess signals of activity in controlling the progress of HCC in a variable extent.

3.2. Targeting approaches towards VEGF and VEGFR

HCCs rely on the formation of new blood vessels for growth, and VEGF is critical in this process (Zhu et al. 2011). HCCs are with high vascular architecture and VEGF is a key factor in tumor angiogenesis (Bergers and Hanahan, 2008; Garrett et al. 2008; Hironaka et al. 2009). Therefore,

the inhibition of angiogenesis is a potential and promising therapeutic approach in HCC. Anti-VEGF therapy with sorafenib was the first systemic therapy against VEGF to demonstrate improved survival in patients with advanced-stage HCC (Cheng et al. 2009; Zhu et al. 2011, Miller et al. 2009; Zhu 2008, Llovet et al. 2008a). Sorafenib was also tested in advanced stage liver cirrhosis patients with unresectable HCC (Pinter et al. 2009). Bevacizumab alone or in combination with other agents showed promise in patients with advanced HCC (Siegel et al. 2008; Thomas et al. 2009; Thomas et al. 2008; Kaseb et al. 2012). However, the common bevacizumab-related side effects were hypertension, bleeding, and proteinuria (Thomas et al. 2009; Siegel et al. 2008a; Kopetz et al. 2009). Besides, inhibition of the tyrosine kinase activity of VEGFR has been tried as an effective measure to inhibit angiogenesis in HCC (Bhide et al. 2010). PTK787/ ZK222584 (vatalanib) is an oral angiogenesis inhibitor that targets tyrosine kinase activity of VEGFR (Gauler et al. 2012). Pan-VEGFR tyrosine kinase activity inhibitor with activity against PDGFRs also carries a new hope.

3.3. Multi-kinase inhibitor

Like all other cancers diverse signaling pathways in HCC are very complex. One of the key pathways regulating cellular proliferation is the mitogen activated protein Kinase (MAPK) pathway. Other pathways involved in the development of HCC include the PI3K/Akt/mTOR, hepatocyte growth factor (HGF)/c-MET, insulin-like growth factor (IGF) and its receptor (IGFR) pathways, and the Wnt- β catenin pathway (Cavard et al. 2008; Chen et al. 2009; Desbois-Mouthon et al. 2009; Takigawa and Nouse 2008; Zhang et al. 2008). The Raf family of kinases are central to this pathway where the transduction of extracellular growth signals from the cell surface to the nucleus occurs via the ras-raf-MEK-ERK signaling cascade. The several experiments have shown that Raf, MEK, MAP Kinase are downstream effector molecules of Ras and their sequential order in the pathway. The Raf serine/threonine kinases are the principal effectors of Ras in this mitogen activated protein Kinase (MAPK) signaling pathway. As serine/threonine kinases, Raf proteins phosphorylate and activate serine and threonine residues on subsequent downstream effector proteins of Ras. Therefore, molecularly targeted agents that interact with multiple signaling pathways/ effectors appear to be very promising in the treatment of patients with HCC (Cervello et al. 2012; Cheng et al. 2009). The novel bi-aryl urea sorafenib, an orally available multi-kinase inhibitor, targets kinases of wild-type B-Raf, mutant V559EB-Raf and cRaf, thereby blocking tumor growth (Spangenberg et al. 2008). There are three ras protooncogenes that encode 21 Kd proteins – H-Ras (Harvey murine sarcoma virus), N-Ras (neuroblastoma cell line) and two alternatively spliced K-Ras, K-Ras 4A, and K-Ras 4B; These isoforms are capable of differentially activating various critical effectors, thereby exerting distinct biologic effects. Sorafenib, an inhibitor of receptor tyrosine kinases was found to stabilize the advanced unresectable HCC patients by regulating angiogenesis, and was approved by regulatory agencies in 2007. It has a role on human VEGF receptors-2 and -3 (VEGFR-2/-3) and PDGF- β R. However, sorafenib has been also suggested to provide antitumor action in HCC by inhibition of the Raf/MEK/ERK pathway (Llovet and Bruix, 2008 and 2009). Multikinase inhibitor sunitinib is a small molecule that inhibits members of the split-kinase domain family of receptor tyrosine kinase including VEGFR types 1 and 2 (Llovet et al. 2008a). Antiangiogenic effects of sunitinib have been suggested through VEGFR and PDGFR.

However, a randomized phase 3 study in HCC failed to show a significant survival benefit as compared to sorafenib and study stopped in 2011.

3.4. mTOR inhibitors

mTOR inhibitors are potential anti-HCC agents for future (Zhou et al. 2009). Promising mTOR inhibitors are rapamycin and its analogues such as sirolimus, temsirolimus (CCI-779), everolimus (RAD001) and AP23573 (Nocera et al 2008; Rizell et al. 2008). Rapamycin and its analogues such as temsirolimus (the cell cycle inhibitor) and everolimus and AP23573 (an orally bioavailable derivative of rapamycin) modulate angiogenesis to improve survival of patients in advanced HCC (Heuer 2009, Huynh et al. 2008). RAD001, an orally-administered, novel mTOR inhibitor was evaluated in a phase I study (Huynh et al. 2008 and 2008a; Chen et al 2009). Treatment of patients with the combination of rapamycin/ rapamycin-analogue(s) with conventional anticancer drug(s) such as doxorubicin, vinblastine has been found to improve survival in advanced HCC patients (Spangenberg et al. 2008).

3.5. Proteasome inhibition

HCC is highly ubiquitinated. The ubiquitination is important to the development and progression of HCC. Proteasome inhibitor such as bortezomib blocks multi-ubiquitinated protein degradation by reversible and competitive inhibition of the active site threonine residue of the 26S proteasome (Cao and Mao, 2011; Boozari et al. 2009). Antineoplastic activity of bortezomib approved for the treatment of mantle cell lymphoma has already been shown to stabilize advanced HCC in patients (Höpfner et al 2008).

3.6. Immunomodulatory agents

An immunomodulator is a substance which has an effect on the immune system. An immunomodulator may be at the same time an immunosuppressant or an immunostimulant and can act on different targets within the immune system. Cell signalling process regulates immune system consisting of immunomodulatory endogenous chemicals and cells. Immunomodulators interfere with the signalling process by shifting the homeostasis of the immune system to reduce or eliminate disease symptoms. Thus these compounds are the obvious choice for therapeutic intervention of HCC. Thymostimulin (a standardized low molecular protein fraction containing thymosin alpha 1 and thymic humoral factor) has been shown to produce cytotoxic immune reaction against HCC. Phase II trials using thymostimulin in patients with advanced and metastasised HCC have shown to control metastatic HCC without predominant side-effects (Dollinger et al. 2010). However, thymostimulin administration in some patients was found to accumulate ascites and cause renal failure (Dollinger et al. 2010).

3.7. Antisense therapy

Antisense oligonucleotides offer one approach to target genes involved in cancer progression. They are typically less than 50 nucleotides long and are specifically designed to hybridize to corresponding gene/ mRNA by Watson-Crick binding. They inhibit mRNA function in several

ways, including modulation of splicing and inhibition of protein translation by disruption of ribosome assembly. Single stranded synthetic nucleic acid (oligonucleotide) when hybridize with DNA or RNA alters transcription or prevents translation thus, preventing or modifying protein production. Because of the volume of information nowadays available on gene sequencing, there has been burst of exploration of capacity for oligomers to inhibit gene/protein expression. Thus, antisense therapies focus on controlling the production of the proteins on a genetic level. A strand of mRNA is transcribed from DNA, and is a copy of the “coding” or “sense” strand of the gene. The main form of therapy uses the complementary or antisense strand to hybridize the sense strand or mRNA and thus it prevents production of the protein by blocking or altering transcription or translation (Figure 1). With the backbone chemical modifications (in phosphate linkage), antisense oligonucleotides increase resistance to nuclease digestion, prolong their biological half-lives and significantly suppress target-gene expression. Antisense oligonucleotides have been studied for several years as treatments for many diseases and genetic disorders. The therapy is based on the principles of genetic expression. The most widely used modified oligomers in antisense therapies is phosphorothioate oligonucleotides, which have much greater resistance to digestion by nucleases. Phosphorothioate oligonucleotides are rapidly and extensively absorbed and distributed from blood.

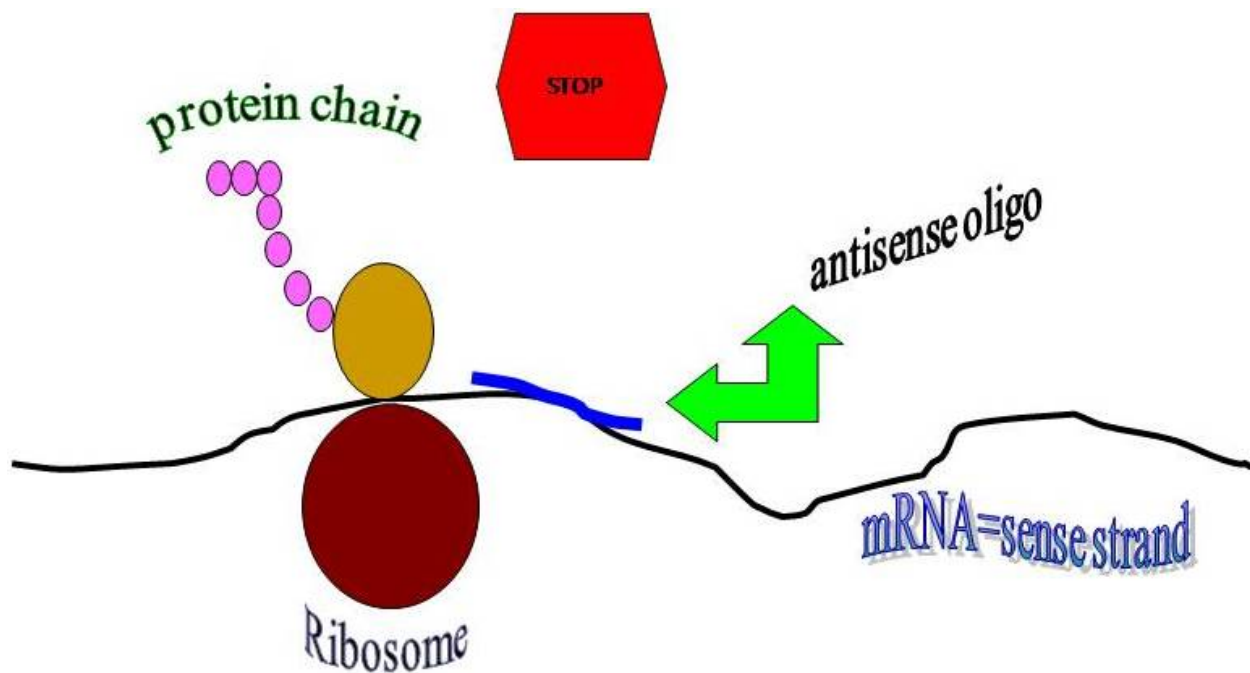


Figure 1. Antisense oligomer-mRNA duplex inhibiting to synthesize peptide chain

The first antisense treatment to get FDA approval to date has been Formivirsen (Vitravene), which is a treatment for cytomegalovirus (CMV) retinitis in people with acquired immunodeficiency disease (AIDS) (Rahman et al. 2008). Several antisense oligonucleotides were shown to target various oncogenes, to overcome tumour escape and to improve therapeutic activity.

Several studies have shown the anticancer potential of antisense oligonucleotides (Das et al. 2010; Rayburn and Zhang, 2008) and many of them are in clinical trial. They have less cytotoxic side-effects than conventional chemotherapy agents. Systemic treatment with fomivirsen is a milestone in the field of antisense treatment with antisense oligonucleotides. This has led the way for development of antisense oligonucleotides for various new potential targets for the treatment of cancer, including HCC.

4. Conclusion

Several experimental evidences have established that targeted inhibition of genes/ proteins involved in controlling HCC growth combined with cytostatic anticancer treatments is a promising approach for HCC therapy. Blocking of single gene/ protein has been found to control neoplastic cellular proliferation *in vitro* effectively. However, considering the multitude of molecular entities and signalling pathways that regulate the proliferation and the life/death decision in cancer cells, inhibition of a single target gene may not be sufficient to suppress tumor growth. The preclinical/ clinical trials of several potential compounds targeting liver cancer-relevant genes/ proteins may address more specific and adequate future therapies for HCC.

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