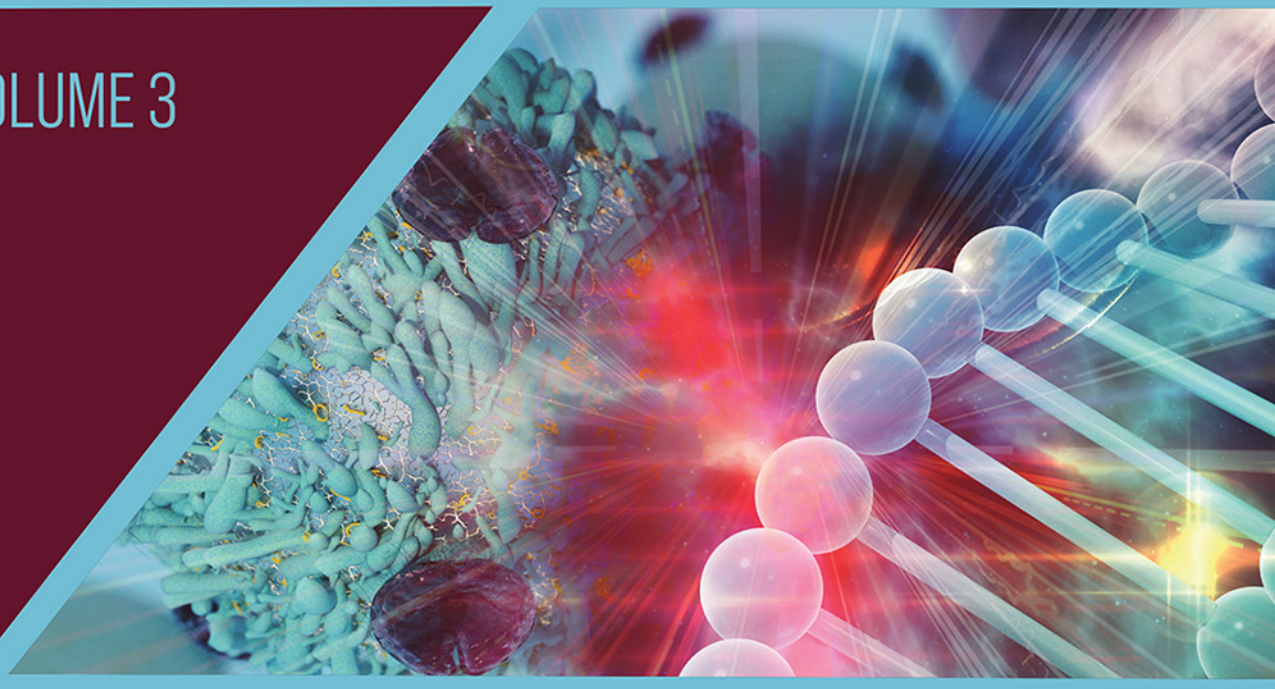
VOLUME 3



Theranostics and Precision Medicine for the Management of Hepatocellular Carcinoma

Translational and Clinical Outcomes

Editors
Ganji Purnachandra Nagaraju and Sarfraz Ahmad

THERANOSTICS AND PRECISION MEDICINE FOR THE MANAGEMENT OF HEPATOCELLULAR CARCINOMA VOLUME 3

Translational and Clinical Outcomes

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ACADEMIC PRESS
An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
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ISBN: 978-0-323-99283-1

Publisher: Stacy Masucci
Acquisitions Editor: Rafael Teixeira
Editorial Project Manager: Tracy Tufaga
Production Project Manager: Sreejith Viswanathan
Cover Designer: Mark Rogers

Typeset by MPS Limited, Chennai, India

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CHAPTER

25

Pharmacogenomics and outcomes for hepatocellular cancer treatment

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Abstract

Pharmacogenomics by name implies pharmacotherapeutics in relation to human genome. Currently pharmacogenomics is expanding its scope from single-gene screening to multiple genes, to enhance efficacy, safety and reduce the economic burden on healthcare system. Hepatocellular carcinoma (HCC) is a growing worldwide problem which is caused by several risk factors such as viral infections, food habits, and alcohol. The risk factors predominantly result in genetic mutations leading to HCC. These genetic abnormalities differ geographically which may decide the effectiveness of systemic treatments in HCC. In light of this, the current chapter discusses the geographical prevalence of genetic variants linked to HCC or HCC recurrence, as well as potential targets for systemic therapy efficacy.

Keywords: Liver cancer; systemic treatment; pharmacogenetics

Abbreviations

AKT	protein kinase B
APC	adenomatous polyposis coli
ARID2	AT-rich interactive domain 2
CDK4/6	cyclin-dependent kinase

Ganji Purnachandra Nagaraju, Sarfraz Ahmad (eds.)
Theranostics and Precision Medicine for the Management of Hepatocellular Carcinoma, Volume 3
DOI: https://doi.org/10.1016/B978-0-323-99283-1.00003-3

CK1α1	casein kinase1α1
DC	ductular cells
ECOG	Eastern Cooperative Oncology Group
EMT	epithelial-mesenchymal transition
ERK	extracellular-regulated kinase
GSK3-β	glycogen synthase kinase 3-β
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HH pathway	hedgehog pathway
Hhip	HH-interacting proteins
HPC	hepatic progenitor cells
LEF	lymphoid-enhancer-binding factor
MAPK	mitogen-activated protein kinase
OS	overall survival
PBAF	polybromo-associated factor complex
PI3K	phosphoinositide 3-kinase
PIK3CA	phosphoinositide-3-kinase-catalytic-alpha
PIP2	phosphatidylinositol 4,5-bisphosphate
PIP3	phosphoinositide 3-kinase
ptch1	protein-patched homolog
PTEN	phosphatase and tensin homolog
Raf	rapidly accelerated fibrosarcoma
Ras	protooncogene-derived protein
SHH	sonic HH
SMO	smoothened protein
Sufu	suppressor of fused homolog
TCF	T-cell-specific transcription factor
Wnt	wingless/int-1

Introduction

Hepatocellular carcinoma (HCC) is the most prevalent form of liver cancer. HCC is the fourth leading cause of cancer-related death globally. By 2030, the global burden of HCC mortality is expected to surpass 1 million deaths per year [1,2]. The HCC is more prevalent in developing countries such as Africa, Japan, and China. The principal etiology of HCC includes viral hepatitis, alcoholism, and aflatoxin exposure [2]. Other risk factors include smoking, obesity, and type 2 diabetes [3]. Viral hepatitis causing HCC includes hepatitis B virus (HBV) and hepatitis C virus (HCV) types. Latest WHO estimates revealed that 350 million population are affected with HBV and 177 million with HCV globally [4,5]. The regional prevalence of HBV and HCV is detailed in Table 25.1. The principal factors predisposing HCC vary by region. Aflatoxin and HBV are the major factors in Eastern Africa and China. In Japan and Egypt, HCV is the predominant factor. The HCC incidence in Mongolia is large and significantly related to HBV, HCV, or both diseases, as well as alcohol consumption [10]. Obesity is one of the risk factors of HCC and is associated with greater mortality in HCC patients [11].

TABLE 25.1 Regional incidence of hepatocellular carcinoma (HCC).

Region	HBV infection per total population	HCV infection per total population	HCC incidence	Reference
South-east Asia	100 million	10 million	27.6/lakh population	[6]
Africa	6.1%	18 million	>20/lakh population	[6]
Eastern Mediterranean Region	3.3%	0.8 million	>20	[7]
India	1.46%	0.5%–1.5%	0.9–9.7/lakh population	[8]
Egypt	14.5 million	7.8 million	33.5/lakh population	[9]
Europe	1.4 million	9 million	8.7–14/lakh population	[6]
Western Pacific Region	115 million	60 million	93.7/lakh population	[6]
America	0.7%	7–9 million	9.3–13.5/lakh population	[6]

HBV, hepatitis B virus; *HCV*, hepatitis B virus.

Pathophysiological aspects

Liver parenchymal cells constitute hepatocytes and ductular cells (DCs). These DCs represent hepatic progenitor cells (HPCs) [12]. Hepatocytes perform various physiological functions based upon their location such as high perfusion periportal region zone I to low perfusion centrilobular zone III. Cellular oxidative processes take place in hepatocytes of zone I and detoxification, biotransformation of drugs takes place in centrilobular zone hepatocytes [13]. The "space of Disse" located between the basolateral membrane of hepatocytes and sinusoidal lumen comprises Kupffer/macrophage cells and Ito/stellate cells. Stellate cells help in mechanisms of liver injury, fibrosis, and regeneration as well [14]. The HPCs stimulated by acute or chronic liver injury regenerate hepatocytes and cholangiocytes [15]. These HPC, upon persistent stimulation may cause early hepatic tumorigenesis and progress to HCC [16].

Chronic inflammation accompanied with fibrosis evidenced in liver cirrhosis principally ascends to HCC [17,18]. Cirrhotic events are inclined to dysplasia and liver malignancies. HCC pathogenesis includes genetic/epigenetic mutations of multiple signaling pathways leading to array of known clinical manifestations and biological events [19–21]. These pathways are discussed below and illustrated in Fig. 25.1.

p53 gene pathways

p53 gene central codons bind to deoxyribonucleic acid (100–293 amino acids) and initiate transcription of genes which are responsible for apoptosis and downregulation of angiogenesis. Nuclear import and export of *p53* was related to the antitumorigenesis action [22]. Derailment of these activities of *p53* in HCC and mutations at exon-7 was reported by many studies [23–28]. Mutation of *p53* also reduced sensitivity to chemotherapy and radiotherapy in recurrent HCC treatment [29,30].

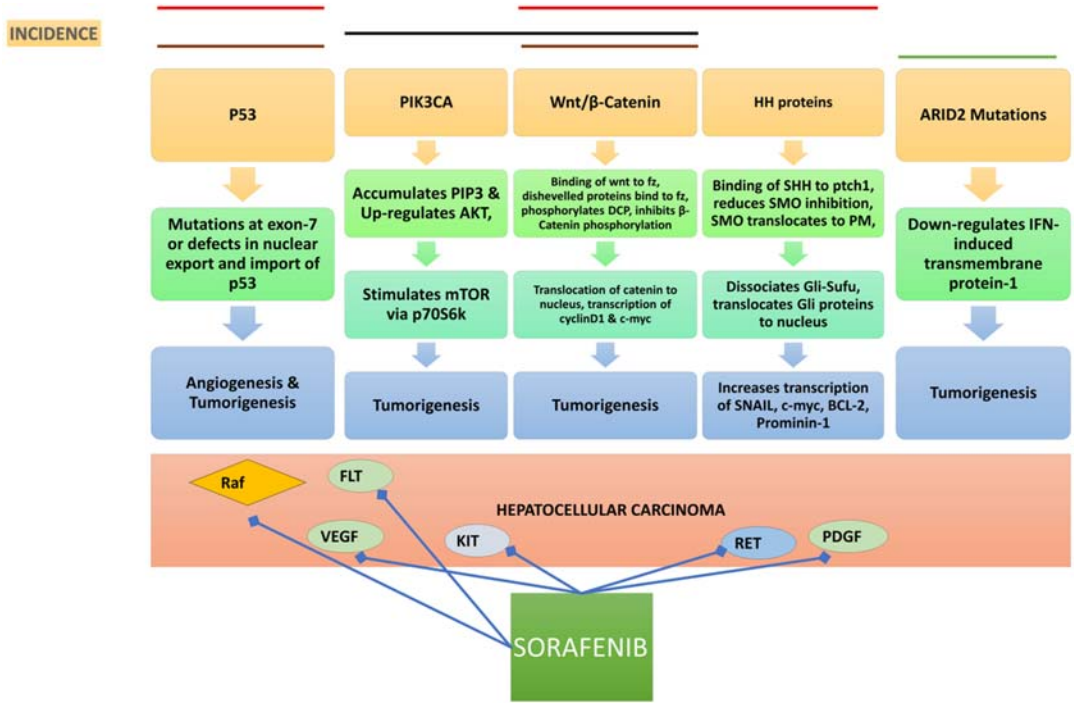

FIGURE 25.1 Illustration of pathways and their incidence in various geographical regions. *Red*, *black*, *brown*, and *green* lines represent China, Korea, Europe, and America, respectively.

Incidence of *p53* mutation in HCC patients was 48% in China [31], 41% in Egypt [32], 35.1% in Africa, 31.6% in Asia, 25.2% in Europe, 11.4% in America [33], 17.39% in Western Kenya [34], and 14.28% in India [35]. The incidence of p53 mutation in other type of cancer was 50%–70% in Western Europe, 50%–60% in Iran, 41% in Thailand and 34.8% in Brazil. Recurrence of HCC after resection treatment in patients with p53 mutation was in an average of 7.8 months. But in patients without p53 mutation showed recurrence of HCC in an average of 16.4 months [35–38].

Phosphoinositide-3-kinase-catalytic-alpha gene

Phosphoinositide-3-kinase-catalytic-alpha (PIK3CA) is an effector protein kinase of PTEN-AKT pathway. This protein is said to have inhibitory property of focal cell adhesion formation, cell motility, and initiation of MAPK signaling through growth factors. PI3K is involved in conversion of PIP2 to PIP3. The available PIP3 is utilized for activation of Akt. This promotes the activation of mTOR which may be tumorigenic acting through p70S6K or directly enhancing cell cycle progression by Akt through CyclinD1. Conversely, PTEN is involved in conversion of PIP3 to PIP2 and inactivates the Akt due to unavailability of PIP3.

PIK3CA gene encoded in PI3K catalytic site. Its mutations are responsible for upregulated activity of Akt [39,40]. Simultaneously, mutation identified at *intron4* gene of PTEN in HCC downregulated the dephosphorylation of PIP3 which may further increase the activity of Akt [41]. Many studies revealed beneficial effects of PTEN-targeted therapies in HCC.

Incidence of PIK3CA mutations in HCC patients was 35.6% in Korea, 3.5% in France, 4% in Switzerland, 1.11% in China [42]. A study has reported zero incidence of PIK3CA mutations in Japanese HCC patients during 2006 [43].

Wingless/int-1 (Wnt)/β-catenin pathway

Wnts are glycoproteins that bind to frizzled receptors (Fz) which are 7-transmembrane-span proteins homologous to G-coupled receptors [44,45]. Wnts regulate various cellular processes through canonical and noncanonical pathways. Canonical pathways are β-catenin dependent and, noncanonical pathways are β-catenin independent including Wnt/Ca + 2 pathway and Wnt/Planar Cell Polarity pathway [46]. The incidence of aberrant Wnt/β-catenin pathway is high in HCC and related to early carcinogenesis [47].

In absence of Wnts, the cytoplasmic destruction complex which includes axin, glycogen synthase kinase 3-β (GSK3-β), adenomatous polyposis coli (APC), and casein kinase1α1 (CK1α1) [48]. This destruction complex proteins phosphorylate β-catenin followed by ubiquitination which is catalyzed by E3-ubiquitin ligase [49,50]. As a result, the cytoplasmic β-catenin is degraded and kept at a minimal threshold level so that it is not translocated to nucleus [51]. In absence of β-catenin in nucleus, T-cell-specific transcription factor (TCF) and lymphoid-enhancer-binding factor (LEF) bind to Groucho proteins or transducin-like enhancer proteins and this complex targets histone deacetylases to silence the transcription [52,53].

Binding of Wnts to Fz receptor or low-density lipoprotein-receptor-related protein 5 and 6 activates the Wnt/β-catenin pathway [54–56], initiates binding of disheveled proteins to intracellular regions of Wnt-interacted receptors followed by phosphorylation of LRP6 and translocate destruction complex proteins [54,55,57–59]. This inhibits phosphorylation of β-catenin and increases cytoplasmic levels of β-catenin. This accumulation of unphosphorylated β-catenin is translocated to nucleus where it interacts with TCF and LEF resulting in initiation of transcription of cyclinD1, *c-myc*, etc. [60,61]. This action of β-catenin results in cell proliferations and tumorigenesis. Apart from Wnt overexpression, activating mutations of β-catenin and inactivating mutations of axin1, GSK3-β have been identified in HCC [62–65].

Incidence of β-catenin overexpression in HCC patients of China was 43.29% during 2008 [66], 39.53%–40.12% during 2009 [67,68], 43.5% during 2010 [69], 55.55% during 2011 [70], 68.04%–68.23% during 2012 [71,72]. 32.58%, 80.46% incidence was seen in the United States and Korea, respectively, during 2014 [73,74]. But the incidence was 32.6% during 2005 in Korea [75]. In Japan, the incidence was 78.5% (2000), 35.29% (2002), 46.87% (2005), and 12.8% (2008) [76–79]. In European countries, 34.04% (2013) incidence was seen in Netherland [80], 58.64% (2010) in Austria [81], 80% (2003) in Germany [82]. A study in African HCC patients revealed absolutely no incidence of β-catenin overexpression either in cytoplasm or nucleus [83]. In India, the incidence was 53% among

HCC patients [84]. Significant HCC recurrence was observed in patients with β-catenin pathway dysregulation [78,84].

Hedgehog pathway

In the adult liver, Hedgehog (HH) signaling has no function; in fact, normal hepatocytes have minimal concentrations of HH signaling proteins and no obvious HH pathway action. The hepatic endothelial and stellate cells produce HH-interacting proteins (Hhip) which antagonize HH-soluble ligands and inhibit the HH pathway. Sonic HH (SHH) ligand is the most commonly related to HCC. In absence of SHH, protein-patched homolog (ptch1) impede smoothened protein (SMO), but when SHH interacts with ptch1, SMO inhibition is reduced and subsequently activates Gli proteins (Gli 1,2,3) which regulates the transcription process. The SMO, upon activation translocate to plasma membrane from cytoplasm and also dissociates Gli-suppressor of fused homolog (Sufu) complex. This enables translocation of Gli proteins to nucleus where it interacts with Gli-binding consensus sequence and increases the transcription of *SNAIL*, *c-MYC*, *BCL-2*, and *Prominin-1*.

A study revealed 84% of incidence of HH pathway aberration in HCC patients in China [85]. A pilot study including 21 patients of HCC with liver transplantation in the United States, demonstrated HH pathway aberrations in all patients [86].

AT-rich interactive domain 2 (ARID2) pathway

Recently inactivating mutations of ARID2 gene is being investigated in HCC. The exact pathway mechanism is not completely elucidated. It is a component of polybromo-associated factor complex (PBAF) which is related SWI/SNF-chromatin-remodeling complex [87]. Inactivation of ARID2 causes downregulation of interferon-induced transmembrane protein 1 which are essential in IFN-induced antiproliferative activity [88].

Increasing ARID2 mutations was observed in US and European population (14% incidence), comparatively it was noticed in 2% Chinese HCC patients. These mutations had an association with viral infections [89].

Guidelines for treatment of hepatocellular carcinoma

Hepatocellular cancer treatment is based on the severity of disease categorized based on staging systems. Different countries follow different staging systems. EASL guidelines for HCC management recommend modified BCLC and AASLD guidelines endorse TNM (8th TNM edition) staging systems. The use of staging systems in management of HCC predicts the prognosis of the disease linked to treatment indication, and treatment outcomes. Both the guidelines suggest cirrhotic patients, noncirrhotic HBV/HCV patients and stage 3 fibrosis patients as target population for surveillance. These guidelines recommend systemic therapy for HCC patients who underwent resection or radiofrequency ablation, patients with cirrhosis plus advanced HCC. Sorafenib, regorafenib, lenvatinib, cabozantinib, and novolumab were the approved drugs for systemic therapy.

Challenges in treatment of hepatocellular carcinoma

The systemic treatments in advanced HCC included sorafenib as first-line drug. Other drugs are regorafenib, lenvatinib, cabozantinib, and novolumab. The main issues with systemic treatments are development of drug resistance and inability to completely cure or increase the HCC recurrence free survival.

Sorafenib acts through inhibition of multiple kinases such as raf kinase, and other kinases regulating various growth factors such as vascular endothelial growth factor, and platelet-derived growth factors [90]. These actions of sorafenib have shown proven benefits through attenuation of tumor angiogenesis, tumor cell proliferation, and accentuation of apoptosis [91,92].

The median overall survival (OS) has improved with sorafenib treatment in HCC patients. But this median OS differed in various studies. A study including 602 HCC patients from various sites of Europe, North America, South America, and Australia demonstrated a median OS of 10.7 months with sorafenib treatment [93]. A median OS of 6.5 months was seen with sorafenib treatment in 271 HCC patients of China, South Korea, and Taiwan [94]. Median OS of 12.3 months with sorafenib was reported by a study which recruited 1492 HCC patients from Asia, Europe, and North America [95]. 467 HCC patients treated with sorafenib in France had a median OS of 9.9 months [96]. A study including 360 HCC patients from Asia alone had a median OS of 10 months with sorafenib treatment [97]. HCC patients ($n = 206$) of Japan had a median OS of 11.5 months with sorafenib treatment [98]. One study has reported 53% disease progression and 15% toxicity in sorafenib treatment group resulting in discontinuation from the study, which included HCC patients ($n = 1155$) from Asia (65%), Europe (23%), and America (13%) [99].

Regorafenib is another second-line drug in treatment of HCC. It acts through inhibition of kinases as similar to sorafenib. But regorafenib profile differs with sorafenib in inhibition of KIT tyrosine-protein kinase and tyrosine-protein kinase receptor Tie-2 resulting in stronger inhibition of angiogenesis [100]. In the randomized phase III RESORCE trial, regorafenib, an oral multikinase antagonist of numerous carcinogenic pathways, increased OS in HCC patients who had tumor progression after developing resistance to sorafenib [101]. The median OS for HCC patients in the Child-Pugh A class and stage 0 of the Eastern Cooperative Oncology Group (ECOG) was 11.08 months when regorafenib was included as second-line therapy. This conclusion is reassuring in a situation where effective therapy alternatives are limited, and it is comparable to the median OS reported in the SHARP trial using a first-line drug, sorafenib [93].

5-Fluorouracil (5-FU), an anticancer drug, stops cells from progressing into the S-phase and increases p53 expression [102]. Drug resistance to 5-FU is a problem for many malignancies, including liver tumors. HCC cells induce defensive autophagy against the drug utilizing noncoding RNAs [103]. Using 5-FU with other chemotherapy drugs can improve its effectiveness. Compared to patients who receive 5-FU alone (median OS 5.2 months), hepatic-arterial infusion of 5-FU in combination with cisplatin-enhanced survival (median OS 14 months) in HCC patients [104]. Recently a trial (NTC02967887) has been initiated to evaluate the efficacy of 5-FU combined with cisplatin in HCC patients with sorafenib resistance.

Pharmacogenomic considerations for hepatocellular carcinoma treatments

Sorafenib inhibits the Raf/MAPK pathway but subsequently activates the PI3K/AKT signaling, implying a connection between the MAPK/ERK as well as the PI3K/AKT mechanisms. The PI3K/AKT pathway's putative compensation mechanism may result in sorafenib failure in HCC patients [105,106]. As a result, a combination therapy may yield a better survival outcome by inhibiting several therapeutic targets in HCC. In HCC cells and sorafenib-resistant HCC cells, copanlisib-arrested cell cycle by disrupting the cyclinD1/CDK4/6 mechanisms, which significantly reduced cell activity and impeded the colony-formation process. Copanlisib also upregulated the AKT phosphorylation in both sorafenib treated and sorafenib-resistant HCC cell cultures. This potential benefit for late-stage HCC may be due to combination of sorafenib with copanlisib [107].

Palbociclib and ribociclib, two recent CDK4/6 antagonists, exhibited anticancer activity in SR HCC Cell lines and were synergistic with sorafenib. Both drugs caused cell-cycle arrest in Rb-expressing HCC cells [108,109]. Combining sorafenib, which modulates PI3K/AKT/mTOR signaling, with PKI-587, which predominantly acts on Ras/Raf/MAPK pathway, was found to be more effective than single-agent therapy [110]. But combination of full-dose sorafenib with 5 mg everolimus increased adverse effects when compared to sorafenib alone [111].

Sorafenib resistance is induced in HepG2 cells after prolonged treatment, along with increased epithelial-mesenchymal transition and invasive potency [112]. The epithelial-mesenchymal transition (EMT) is a sign for invasion and metastasis, and it is triggered by a variety of effectors, of the Wnt/β-catenin, and HH pathways [113–118]. E-cadherin was found responsible for upregulation of proteins-related SNAIL/slug pathway and β-catenin which causes metastasis and tumor recurrence [119–121].

ERK and AKT activation may be considered as marker for poor prognosis in HCC as it augments disease progression [122]. Sorafenib acts on ERK pathway but not on AKT pathway, but regorafenib acts on both the pathways. However, on prolonged exposure of regorafenib to HuH7 cells exhibited resistance with increased CD24, CD133 expression, and TGF-β activity [123].

To summarize, this chapter discussed geographical incidences of genetic mutations. China has higher incidence of p53, β-catenin, HH pathway mutations. Korea has higher incidences of PIK3CA and β-catenin mutations. Some regions of Europe showed incidences of p53 and β-catenin mutations. ARID2 mutations were seen in American population. This information of incidences may guide to effective treatments such as, sorafenib which is the mainstay of systemic therapy in advanced HCC may develop resistance due to influence of p53 mutations in Chinese population and European population, similarly PI3K/AKT pathway aberrations may impact HCC treatments in Korean population, β-catenin mutations, HH pathway aberrations in Chinese HCC patients. With these genetic variations influencing HCC treatments, there is further need to consider for improvements in HCC treatments regimens with respect to population of different regions and to discover new therapeutic targets that overcome these challenges which may increase the OS of the HCC patients or completely cure HCC. Understanding the significance of pharmacogenomics in the treatment of hepatocellular malignancies aids in the development of new successful targeted treatments.

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VOLUME 3

Theranostics and Precision Medicine for the Management of Hepatocellular Carcinoma

Translational and Clinical Outcomes

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Theranostics and Precision Medicine for the Management of Hepatocellular Carcinoma provides comprehensive information about ongoing research as well as clinical outcomes data about liver cancer. It presents detailed descriptions about diagnostics and therapeutic options for easy understanding, with a focus on precision medicine approaches to improve treatment outcomes for hepatocellular carcinoma (HCC).

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- Provides best practices for potential management of HCC in the clinical setting
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ISBN 978-0-323-99283-1