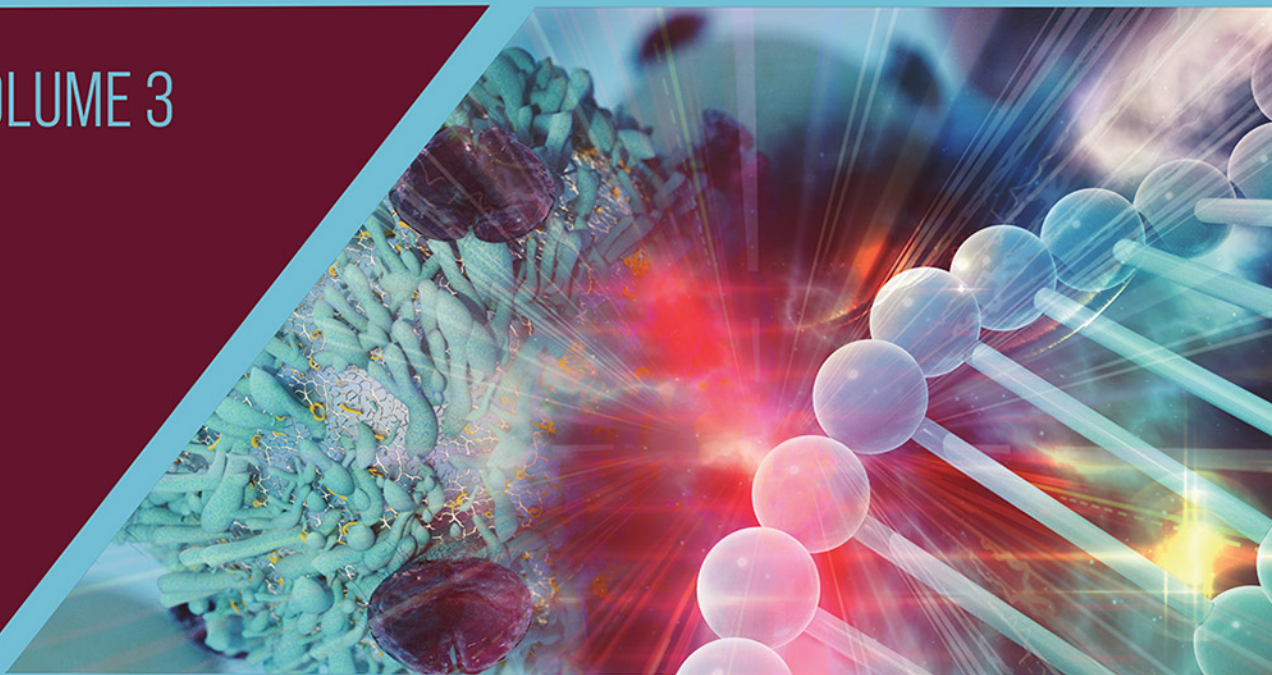


VOLUME 3



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

Edited by

GANJI PURNACHANDRA NAGARAJU, PhD, DSc, FAACC

*School of Medicine, Division of Hematology and Oncology, University of Alabama,
Birmingham, AL, United States*

SARFRAZ AHMAD, PhD, FAACC, FABAP

*AdventHealth Cancer Institute, Florida State University (FSU) and University of Central Florida (UCF),
Colleges of Medicine, Orlando, FL, United States*



ELSEVIER



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
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

Copyright © 2022 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-323-99283-1

For Information on all Academic Press publications
visit our website at <https://www.elsevier.com/books-and-journals>

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



Contents

List of contributors xv

About the editors xix

Preface xxi

1. Nanoparticles for diagnosis and treatment of hepatocellular carcinoma 1

Sheik Aliya and Yun Suk Huh

Abstract 1

Keywords 1

Abbreviations 1

Introduction 2

Chitosan nanoparticles 3

Mesoporous silica nanoparticles 4

Iron oxide nanoparticles 5

Liposomal nanoparticles 5

Solid lipid nanoparticles 6

Gold nanoparticles 7

Titanium oxide nanoparticles 7

Pectin-based nanoparticles 8

mPEG-PLGA-PLL copolymer-based nanoparticles 9

Nanoparticles in clinical trials to treat hepatocellular carcinoma 9

Toxicity 10

Conclusion 11

References 11

2. Theranostics application of nanocarriers in hepatocellular carcinoma 15

Patnala Kiranmayi, Vishwas Soumya and Rama Rao Malla

Abstract 15

Keywords 15

Abbreviations 15

Introduction 16

Therapeutic application of nanocarriers in hepatocellular carcinoma 16

Theranostic applications of nanocarriers in hepatocellular carcinoma 22

Conclusion 23

Acknowledgment 23

Conflict of interest 23

References 24

3. Nanoparticle-based theranostics and their role in hepatocellular carcinoma 29

Devanabanda Malliah, Produtur Chandramathi Shankar and Ramakrishna Vadde

Abstract 29

Keywords 29

Abbreviations 29

Introduction 30

Pathogenesis 30

Nanotheranostics in hepatocellular carcinoma 31

Conclusions and future perspectives 39

Conflicts of interest 39

References 39

4. Therapeutic options for the management of hepatocellular carcinoma 43

Vibha Sinha, Sapnita Shinde, Vinit Singh Baghel, Naveen Kumar Vishvakarma, Dhananjay Shukla, Atul Kumar Tiwari, Ashwini Kumar Dixit, Sanjay Kumar Pandey, Sudhakar Dwivedi, Mrinalini Singh and Vineeta Dixit

Abstract 43

Keywords 43

Abbreviations 44

Introduction 44

Chemotherapeutic drugs 46

Sorafenib 46

Brivanib 46

Sunitinib 47

Everolimus 47

Doxorubicin	47
Gemcitabine	47
Immunotherapy	47
Checkpoint inhibitors	48
CTLA-4 blockers	48
Vaccine therapy	50
Oncolytic virus therapy	52
Phytochemicals	53
Curcumin	53
Resveratrol	55
Quercetin	55
Triptolide	55
Betulinic acid	56
Phloretin	56
Capsaicin	56
Nanomedicines	56
Curcumin-conjugated nanoparticles	57
Beta-Sitosterol	57
Conclusion	57
References	58

5. Targeting hepatocellular carcinoma by small-molecule inhibitors 63

Rahul Kumar Vempati and Rama Rao Malla

Abstract	63
Keywords	63
Abbreviations	63
Introduction	64
Small-molecule inhibitors and their relevance in cancer	65
Current small-molecule inhibitors used in HCC	65
Viral proteins as therapeutic targets for small-molecule inhibitors in HCC	67
Signaling pathway components as small-molecule targets in HCC	67
Drug resistance in HCC: a major concern for the development of new SMIs	68
Conclusion	72
Acknowledgment	73
Conflict of interest	73
Funding	73
References	73

6. Curing of liver cancer: an update on the efficacy of bioactive compounds 81

Anil Kumar Moola, S. Geetha Renuka, Harish Kumar Seenivasan, Nivethitha Manickam, Sujatha Peela and B.D. Ranjitha Kumari

Abstract	81
Keywords	81
Abbreviations	82
Background study of liver cancer	82
Introduction	83
Role of bioactive compounds in liver cancer	83
Bioactive compounds from plants for curing liver cancer	85
Bioactive compounds from microalgae for curing liver cancer	87
Bioactive compounds from bacteria and another microbial source for curing liver cancer	87
Conclusion and future perspectives	88
Conflict of interest	88
References	88

7. Plant therapeutics for hepatocellular carcinoma 93

Chandrasekhar Thummala and Ramachandra Reddy Pamuru

Abstract	93
Keywords	93
Abbreviations	93
Introduction	94
Biology of liver	95
Histopathology of liver	95
Liver cancer risk factors and diagnosis	96
Natural compounds on liver cancer	98
Curcumin	98
Silibinin/silymarin	98
Resveratrol	99
Tanshinone IIA	101
Emodin	102
Polyphyllin D	102
Ardipusilloside I	104
Panaxydol and ginsenoside	104
Astragaloside	104
Piper betel leaves	104
Green tea	104
Conclusion and future outlook	105

Acknowledgments 105
 Conflict of interest 105
 References 105

8. Phytochemicals for hepatocellular carcinoma therapy: from in vitro to clinic 109

Ganganapalli Supraja, Kalisetty Chengaiahgari Maheswari,
 Deepika Pamarthy and Kallimakula Venkata Reddy Saritha

Abstract 109
 Keywords 109
 Abbreviations 109
 Introduction 110
 Genes associated with hepatocellular
 carcinoma 110
 Genes involved in WNT- and TGF- β -signaling
 cascade 111
 Herbs and their secondary metabolites 111
Baliospermum montanum 112
Azadirachta indica 117
Artemisia absinthium 117
Astragalus membranaceus 117
Solanum nigrum 117
Tripterygium wilfordii 118
Mangifera indica 119
Woodfordia fruticosa Kurz 119
Allium sativum 119
Zingiber officinale 120
Calotropis procera 120
Cassia fistula 120
Aloe barbadensis Miller 121
Apium graveolens 121
Amaranthus spinosus 121
Asparagus racemosus 122
Arachniodes exilis 122
Annona reticulata 122
Brassica nigra 123
Citrus limon 123
Vitis vinifera 123
Lawsonia inermis 124
Moringa oleifera 124
Sesamum indicum 125
Phoenix dactylifer 125
Carica papaya 125
 Conclusion 125
 Conflict of interest 126
 References 126

9. Resveratrol for hepatocellular carcinoma therapy 133

Kalisetty Chengaiahgari Maheswari, Ganganapalli Supraja and
 Kallimakula Venkata Reddy Saritha

Abstract 133
 Keywords 133
 Abbreviations 133
 Introduction 134
 Structure 134
 Source 134
 Chemical synthesis 134
 Functions of resveratrol 135
 Resveratrol as a phytoalexin 135
 Resveratrol as a natural phenol 135
 Resveratrol as a natural antioxidant 136
 Resveratrol as anticarcinogenic agent 136
 Reactive oxygen species 136
 Role of resveratrol on hepatocellular carcinoma
 (liver cancer) 137
 Conclusions and future perspectives 138
 Conflict of interest 138
 References 138

10. Curcumin: a spice pigment against hepatic cancer 141

Vivek Kumar Soni, Yashwant Kumar Ratre, Arundhati Mehta,
 Ashwini Kumar Dixit, Mrigendra Dwivedi, Dhananjay Shukla,
 Ajay Kumar and Naveen Kumar Vishvakarma

Abstract 141
 Keywords 142
 Abbreviations 142
 Introduction 143
 Curcumin: the golden spice component 144
 Biological activity of curcumin 144
 Antioxidant activity 145
 Antiinflammatory activity 145
 Cardioprotective activity 146
 Immune regulatory activity 146
 Antidiabetic activity 147
 Antineoplastic activity 147
 Curcumin and liver cancer 147
 Curcumin and prevention of hepatic
 cancer 148
 Curcumin analog against liver cancer 149
 Limitations and prospects 151
 Conclusion 153

Acknowledgments 154
Declarations of interest 154
Funding 154
References 154

11. Curcumin formulated nanoparticles for hepatocellular carcinoma 161

Neha Merchant, Sujatha Peela, Afroz Alam and Ganji Purnachandra Nagaraju

Abstract 161
Keywords 161
Abbreviations 161
Introduction 162
Chemicals involved in hepatocellular carcinoma 164
Curcumin nanoformulations in hepatocellular carcinoma 164
Nanoparticles 164
Liposomes 165
Conjugates and cyclodextrins 166
Micelles, nanospheres, and microcapsules 166
Miscellaneous nanoformulations 166
Synthesis of nanoformulations 166
Anticancer properties of curcumin facilitated nanoformulations 167
Conclusion 168
Funding 169
Conflict of interest 169
References 169

12. Role of phytoconstituents in the hepatocellular carcinoma management: current perspective, challenges, and future perspectives 175

Archana Ashok Sharbidre

Abstract 175
Keywords 175
Abbreviations 175
Introduction 177
Hepatocellular carcinoma management with dietary natural products and combination therapy 177

Potent phytoconstituents having hepatocellular carcinoma activity 178
Polyphenols in hepatocellular carcinoma treatment 181
Phytoconstituents evaluated in clinical trials of hepatocellular carcinoma 185
Conclusions and future perspectives 185
Conflict of interest 187
References 187

13. Phytonanoformulations for hepatocellular carcinoma therapy 197

Mohammad Imran, Gowru Srivani and Ganji Seeta Rama Raju

Abstract 197
Keywords 197
Abbreviations 197
Introduction 198
Nanomedicine 200
Properties of nanoparticles 200
Size 203
Shape and charge 203
Nanocarriers 204
Nanophytochemicals used in cancer treatment 204
Phytochemicals used in the treatment of hepatocellular carcinoma 207
Conclusion 209
References 209

14. Immune checkpoint inhibitors for hepatocellular carcinoma 215

Venkata Prasuja Nakka

Abstract 215
Keywords 215
Abbreviations 215
Introduction 216
The immunology of hepatocellular carcinoma 217
Immune responses of the liver that promotes tumor cell proliferation 218
Immune checkpoint inhibitors and hepatocellular carcinoma 219
Combination immunotherapy: potential treatment of the future? 219
Conclusion and future perspective 221
Acknowledgments 222
References 222

15. Recent advancements in immunotherapy interventions for the management of liver cancer 225

Dhatri Madduru, Ngalah Bidii Stephen, Urvashi Vijay, Pranathi Pappu, Prashanth Suravajhala and Obul Reddy Bandapalli

Abstract	225
Keywords	226
Abbreviations	226
Introduction	227
Types of immunotherapy	228
T-cell therapy	228
Vaccines	229
Monoclonal antibodies	237
Immune checkpoint inhibitors	237
Immunotherapy using induced pluripotent stem cells	240
Advantages and disadvantages	240
Future direction and conclusion	241
References	241

16. Immunotherapy for hepatocellular cancer: a review of current status 245

James Yu, Vadim Zaytsev, Aimen Farooq, Anum Jalil, James Wert, Zohaib Ahmed and Sarfraz Ahmad

Abstract	245
Keywords	245
Abbreviations	245
Introduction	246
Hepatocellular carcinoma immunology	246
Immune checkpoint inhibitors	247
Checkpoint inhibitors for hepatocellular carcinoma monotherapy	251
Nivolumab	251
Pembrolizumab	251
Tislelizumab	251
Camrelizumab	252
Durvalumab	252
Tremelimumab	252
Combination treatment	252
Combination between two different immune checkpoint inhibitors	253
Combination between immune checkpoint inhibitors with molecularly targeted agents	253

Combination between immune checkpoint inhibitors with local therapy	254
Conclusions and future perspective	255
References	255

17. Updates on clinical trials for the management of hepatocellular carcinoma 259

Aimen Farooq, Zohaib Ahmed, James Wert, Anum Jalil, James Yu, Vadim Zaytsev and Sarfraz Ahmad

Abstract	259
Keywords	259
Abbreviations	260
Introduction	260
Staging and prognosis in hepatocellular carcinoma	260
Management of hepatocellular carcinoma	261
Locoregional treatments	261
Systemic therapies	264
Second-line systemic therapies	267
Regorafenib	267
Cabozantinib	267
Ramucirumab	268
Conclusions and future perspectives	269
References	270

18. Theranostic and precision medicine for the diagnosis of hepatocellular carcinoma 275

Rafael Miret, Amir Riaz, Sikandar Khan and Asad Ur Rahman

Abstract	275
Keywords	275
Abbreviations	275
Epidemiology	276
Ultrasound	277
Computed tomography	278
Magnetic resonance imaging	279
Tumor markers	279
Guidelines for hepatocellular carcinoma surveillance	280
Cost-effectiveness of hepatocellular carcinoma diagnostic modalities	283
Conflict of interest	283
References	283

19. Precision medicine approaches for treating hepatocellular carcinoma 287

Nadia Ahmed, Kevin Benny, Sohail Siraj, Hufsa Ali and Riyaz Basha

- Abstract 287
- Keywords 287
- Abbreviations 287
- General information on hepatocellular carcinoma 288
- Ablation 289
- Embolization 290
- Precision medicine definition and use in cancers in general 290
- Significance for using precision medicine approaches for treating hepatocellular carcinoma 291
- Chemo-resistive mechanisms in hepatocellular carcinoma 293
- Liquid biopsy 294
- Summary and conclusions 295
- Future directions 295
- Acknowledgments 296
- References 296

20. Decoding the functional role of extracellular vesicles in hepatocellular carcinoma: implications in clinical theranostics 301

Kalyani Patil, Said Dermime and Shahab Uddin

- Abstract 301
- Keywords 301
- Abbreviations 302
- Functional role of EVs in hepatocellular carcinoma: from angiogenesis to metastatic organotropism 304
 - HCC-derived EVs regulate the behavior of endothelial cells to induce angiogenesis 307
 - HCC-derived EVs target normal surrounding cells to regulate tumor progression 309
 - HCC-derived EVs target immune cells to evade immunosurveillance and generate immunosuppressive microenvironment 310

- HCC-derived EVs participate in metabolic reprogramming 315
- Stromal cell-derived EVs alter the biologic behavior of HCC cells to aid hepatocarcinogenesis and progression 316
- HCC-derived EVs confer drug resistance 320
- HCC-derived EVs facilitate organotropic metastasis 321

- EVs in targeted therapeutic interventions in HCC 325
 - EVs as efficient drug delivery systems 325
 - EVs as candidate immunotherapeutic agents in HCC 326
- Conclusion and future prospects 327
- Conflict of interest 328
- Funding 328
- References 329

21. Cathepsin B: structure, function, tumorigenesis, and prognostic value in hepatocellular carcinoma 341

Baha Aldeen Bani Fawwaz, Aimen Farooq, Mengni Guo, Gurdeep Singh and Sarfraz Ahmad

- Abstract 341
- Keywords 341
- Abbreviations 341
- Introduction 342
- Structure-function properties of cathepsin B 342
 - Structure of cathepsin B 342
 - Normal function of cathepsin B 343
- Tumorigenesis and metastatic role of cathepsin B in cancers with emphasis on hepatocellular carcinoma 344
 - Cathepsin B role in cancer and regulation 344
 - Cathepsin B role in fibrogenesis and cirrhosis 345
 - Cathepsin B role in modulating growth, invasion, and metastasis of hepatocellular carcinoma 345
- Prognostic values of cathepsin B in hepatocellular carcinoma 346
- Conclusions and future perspective 347
- Conflict of interest 347
- References 347

22. Chemotherapy for hepatocellular carcinoma—an updated review 351

Sarojamma Vemula, Jeelan Basha Shaik, Amooru G. Damu and Ramakrishna Vadde

- Abstract 351
- Keywords 351
- Abbreviations 351
- Introduction 352
- Risk factors and pathogenesis of hepatocellular carcinoma 352
- Chemotherapy for hepatocellular carcinoma 354
- Sorafenib—a first-line chemotherapeutic agent 355
 - Sunitinib 356
 - Brivanib 356
 - Linifanib 356
 - Erlotinib 357
 - Vandetanib 357
 - Nintedanib 357
 - Dovitinib 357
 - Doxorubicin 357
 - Everolimus 358
 - Axitinib 358
 - Tigatuzumab 358
 - Lenvatinib 358
 - Resminostat 359
 - Regorafenib 359
 - Cabozantinib 359
 - Ramucirumab 359
 - Tivantinib 359
- Immunotherapeutic agents 360
 - Tremelimumab 360
 - Nivolumab 360
- Conclusion 360
- Conflict of interest 361
- References 361

23. Recent advances in medical treatment of hepatocellular cancer 365

Ahmet Sümbül Taner and Ali Ayberk Beşen

- Abstract 365
- Keywords 365
- Abbreviations 365

- Introduction 366
- Lenvatinib 367
- Regorafenib 367
- Cabozantinib 368
- Ramucirumab 369
- Bevacizumab plus atezolizumab 369
- Nivolumab and nivolumab plus ipilimumab 370
 - Nivolumab 370
- Nivolumab plus ipilimumab 371
- Pembrolizumab 372
- Sequencing systemic in advanced hepatocellular carcinoma 373
- Conclusions and future perspectives 373
- References 373

24. Recent perspectives on therapeutic significance of microRNAs in hepatocellular carcinoma 377

Madelyn Miller and Shadab A. Siddiqi

- Abstract 377
- Keywords 377
- Abbreviations 377
- Introduction 378
 - Biogenesis of microRNAs 381
 - MicroRNA as diagnostic biomarker in hepatocellular carcinoma 388
 - MicroRNA as therapeutic targets in hepatocellular carcinoma 389
 - Exosomal microRNA in hepatocellular carcinoma 390
- Conclusions 392
- Acknowledgment 393
- References 393

25. Pharmacogenomics and outcomes for hepatocellular cancer treatment 401

Mohan Krishna Ghanta, Mohammad Faiz Hussain, Asmita Karnalkar, Sirpu Natesh Nagabhishek, Poojith Nuthalapati and L.V.K.S. Bhaskar

- Abstract 401
- Keywords 401
- Abbreviations 401

Introduction	402
Pathophysiological aspects	403
p53 gene pathways	403
Phosphoinositide-3-kinase-catalytic-alpha gene	404
Wingless/int-1 (Wnt)/ β -catenin pathway	405
Hedgehog pathway	406
AT-rich interactive domain 2 (ARID2) pathway	406
Guidelines for treatment of hepatocellular carcinoma	406
Challenges in treatment of hepatocellular carcinoma	407
Pharmacogenomic considerations for hepatocellular carcinoma treatments	408
References	409

26. Epigenetic biomarkers in diagnosis, prognosis, and treatment of hepatocellular carcinoma 415

Eka Kvaratskhelia, Ketevani Kankava, Sandro Surmava and Elene Abzianidze

Abstract	415
Keywords	415
Abbreviations	415
Introduction	416
DNA methylation in hepatocellular carcinoma	417
Histone modifications in hepatocellular carcinoma	423
Conclusion	427
Conflict of interest	429
References	429

Index 435

Pharmacogenomics and outcomes for hepatocellular cancer treatment

Mohan Krishna Ghanta¹, Mohammad Faiz Hussain²,
Asmita Karnalkar³, Sirpu Natesh Nagabhishek⁴,
Poojith Nuthalapati⁵ and L.V.K.S. Bhaskar⁶

¹Department of Pharmacology, MVJ Medical College and Research Hospital, Bangalore, India

²Department of General Surgery, Apollo Institute of Medical Sciences and Research, General Hospital, Hyderabad, India

³Department of Anaesthesia, BKL Rural Medical College & Hospital, Ratnagiri, India

⁴Cancer Biology Lab, Molecular and Nanomedicine Research Unit, Sathyabama Institute of Science and Technology, Chennai, India

⁵PJ Biosys, Irving, TX, United States

⁶Department of Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur, India

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

CK1 α 1	casein kinase1 α 1
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 C 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].

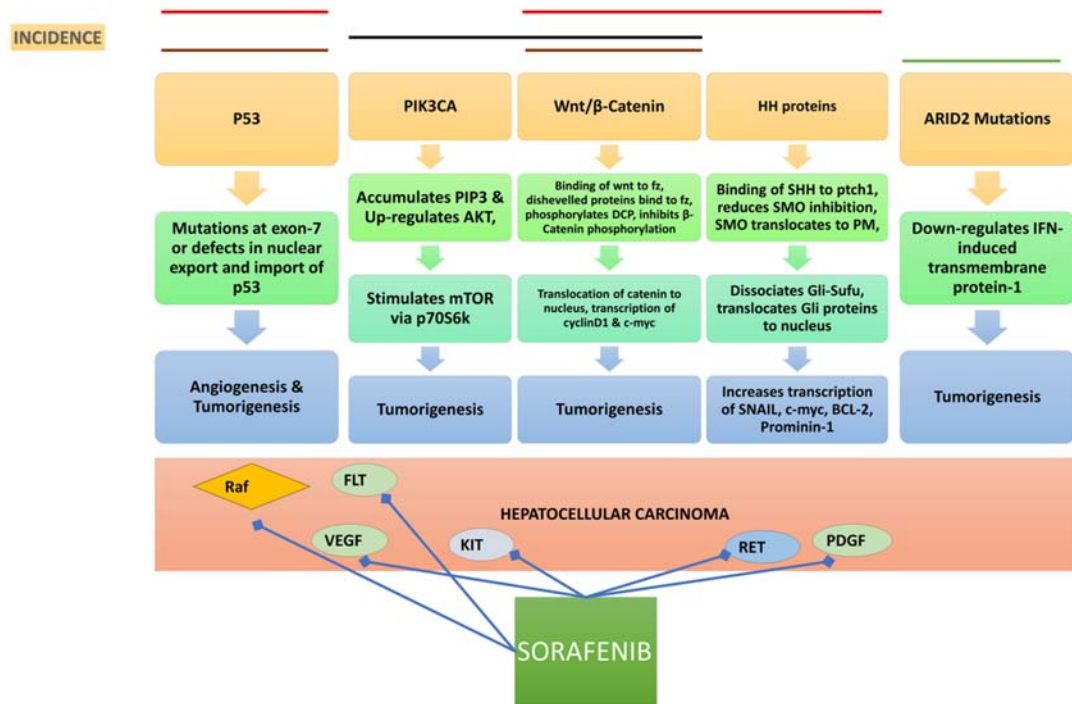


FIGURE 25.1 Illustration of pathways and their incidence in various geographical regions. Red, black, brown, and green lines represent China, Korea, Europe, and America, respectively.

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 kinase1 α 1 (CK1 α 1) [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 smoothed 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.

References

- [1] Anstee QM, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges *Nat Rev Gastroenterol Hepatol* 2019;16(7):411–28 Available from. Available from: <http://www.nature.com/articles/s41575-019-0145-7>.
- [2] Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level *JAMA Oncol* 2017;3(12):1683 Available from. Available from: <http://oncology.jamanetwork.com/article.aspx?doi=10.1001/jamaoncol.2017.3055>.
- [3] McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. *Hepatology* 2021;73(1):4–13.
- [4] Custer B, Sullivan SD, Hazlet TK, Iloeje U, Veenstra DL, Kowdley KV. Global epidemiology of hepatitis B virus *J Clin Gastroenterol* 2004;10(10):38 Available from. Available from: https://journals.lww.com/jcge/Fulltext/2004/11003/Global_Epidemiology_of_Hepatitis_B_Virus.8.aspx.
- [5] Petruzzello A, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: an up-date of the distribution and circulation of hepatitis C virus genotypes. *World J Gastroenterol* 2016;22(34):7824–40.
- [6] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries *CA Cancer J Clin* 2018;68(6):394–424 Available from. Available from: <https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.3322/caac.21492>.
- [7] Sabzalizadeh-Ardabili S, Alizadeh-Navaei R, Hedayatzadeh-Omran A, Janbabaei G. Cancer incidence and mortality pattern in Eastern Mediterranean Regional Office Countries and its association with the human development index *Clin Cancer Investig J* 2019;8(1):15. Available from. Available from: <http://www.cci-journal.org/text.asp?2019/8/1/15/255446>.
- [8] Chavda HJ. Hepatocellular carcinoma in India. *Indian J Surg* 2021. Available from: <https://doi.org/10.1007/s12262-021-02762-w>. Available from.
- [9] Ma W, Soliman AS, Anwar WA, Hablas A, El Din TB, Ramadan M, et al. Forecasted impacts of a sofosbuvir-based national hepatitis C treatment programme on Egypt's hepatocellular cancer epidemic: simulation of alternatives *BMJ Glob Heal* 2018;3(2):e000572 Available from. Available from: <http://gh.bmj.com/content/3/2/e000572.abstract>.
- [10] Chimed T, Sandagdorj T, Znaor A, Laversanne M, Tseveen B, Genden P, et al. Cancer incidence and cancer control in Mongolia: results from the National Cancer Registry 2008–12. *Int J cancer* 2017;140(2):302–9.
- [11] Gupta A, Das A, Majumder K, Arora N, Mayo HG, Singh PP. Obesity is Independently Associated With Increased Risk of Hepatocellular Cancer-related Mortality: A Systematic Review and Meta-Analysis. *Am J Clin Oncol* 2018;41(9):874–81.
- [12] He G, Dhar D, Nakagawa H, Font-Burgada J, Ogata H, Jiang Y, et al. Identification of liver cancer progenitors whose malignant progression depends on autocrine IL-6 signaling. *Cell*. 2013;155(2):384–96.
- [13] Saxena R, Theise ND, Crawford JM. Microanatomy of the human liver-exploring the hidden interfaces. *Hepatology*. 1999;30(6):1339–46.
- [14] Si-Tayeb K, Lemaigre FP, Duncan SA. Organogenesis and development of the liver. *Dev Cell* 2010;18(2):175–89.
- [15] Malato Y, Naqvi S, Schürmann N, Ng R, Wang B, Zape J, et al. Fate tracing of mature hepatocytes in mouse liver homeostasis and regeneration. *J Clin Invest* 2011;121(12):4850–60.
- [16] Tummala KS, Brandt M, Teijeiro A, Graña O, Schwabe RF, Perna C, et al. Hepatocellular carcinomas originate predominantly from hepatocytes and benign lesions from hepatic progenitor cells. *Cell Rep* 2017;19(3):584–600.
- [17] Block TM, Mehta AS, Fimmel CJ, Jordan R. Molecular viral oncology of hepatocellular carcinoma. *Oncogene*. 2003;22(33):5093–107.
- [18] Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. *Mol Cancer Res* 2006;4(4):221–33.
- [19] Bruix J. Usefulness of the molecular profile in the diagnosis, prognosis and treatment of hepatocellular carcinoma. *Gastroenterol Hepatol* 2014;37(2):81–9.
- [20] Luca A, Caruso S, Milazzo M, Mamone G, Marrone G, Miraglia R, et al. Multidetector-row computed tomography (MDCT) for the diagnosis of hepatocellular carcinoma in cirrhotic candidates for liver transplantation: prevalence of radiological vascular patterns and histological correlation with liver explants. *Eur Radiol* 2010;20(4):898–907.

- [21] McKillop IH, Moran DM, Jin X, Koniaris LG. Molecular pathogenesis of hepatocellular carcinoma. *J Surg Res* 2006;136(1):125–35.
- [22] Stewart ZA, Pietenpol JA. p53 signaling and cell cycle checkpoints. *Chem Res Toxicol* 2001;14(3):243–63.
- [23] Yu MW, Yang SY, Chiu YH, Chiang YC, Liaw YF, Chen CJ. A p53 genetic polymorphism as a modulator of hepatocellular carcinoma risk in relation to chronic liver disease, familial tendency, and cigarette smoking in hepatitis B carriers. *Hepatology*. 1999;29(3):697–702.
- [24] Lee YI, Lee S, Das GC, Park US, Park SM, Lee YI. Activation of the insulin-like growth factor II transcription by aflatoxin B1 induced p53 mutant 249 is caused by activation of transcription complexes; implications for a gain-of-function during the formation of hepatocellular carcinoma. *Oncogene*. 2000;19(33):3717–26.
- [25] Heinze T, Jonas S, Kärsten A, Neuhaus P. Determination of the oncogenes p53 and C-erb B2 in the tumour cytosols of advanced hepatocellular carcinoma (HCC) and correlation to survival time. *Anticancer Res* 1999;19(4A):2501–3.
- [26] Honda K, Sbisà E, Tullo A, Papeo PA, Saccone C, Poole S, et al. p53 mutation is a poor prognostic indicator for survival in patients with hepatocellular carcinoma undergoing surgical tumour ablation. *Br J Cancer* 1998;77(5):776–82.
- [27] Katiyar S, Dash BC, Thakur V, Guptan RC, Sarin SK, Das BC. P53 tumor suppressor gene mutations in hepatocellular carcinoma patients in India. *Cancer*. 2000;88(7):1565–73.
- [28] Jeng KS, Sheen IS, Chen BF, Wu JY. Is the p53 gene mutation of prognostic value in hepatocellular carcinoma after resection? *Arch Surg* 2000;135(11):1329–33.
- [29] Matsuzoe D, Hideshima T, Kimura A, Inada K, Watanabe K, Akita Y, et al. p53 mutations predict non-small cell lung carcinoma response to radiotherapy. *Cancer Lett* 1999;135(2):189–94.
- [30] Blandino G, Levine AJ, Oren M. Mutant p53 gain of function: differential effects of different p53 mutants on resistance of cultured cells to chemotherapy. *Oncogene*. 1999;18(2):477–85.
- [31] Chen GG, Merchant JL, Lai PBS, Ho RLK, Hu X, Okada M, et al. Mutation of p53 in recurrent hepatocellular carcinoma and its association with the expression of ZBP-89. *Am J Pathol* 2003;162(6):1823–9.
- [32] El-Kafrawy SA, Abdel-Hamid M, El-Daly M, Nada O, Ismail A, Ezzat S, et al. P53 mutations in hepatocellular carcinoma patients in Egypt. *Int J Hyg Env Health* 2005;208(4):263–70.
- [33] Tornesello ML, Buonaguro L, Tatangelo F, Botti G, Izzo F, Buonaguro FM. Mutations in TP53, CTNNB1 and PIK3CA genes in hepatocellular carcinoma associated with hepatitis B and hepatitis C virus infections *Genomics* 2013;102(2):74–83 Available from. Available from: <https://www.sciencedirect.com/science/article/pii/S0888754313000633>.
- [34] Odumo CO, Ondigo BN, Kimotho JH. Codon 249 P53 gene mutation among hepatocellular carcinoma patients in Western Kenya Open Access J Biomed Sci 2020;(4):1 Available from. Available from: <https://biomedscis.com/fulltext/codon-249-p53-gene-mutation-among-hepatocellular-carcinoma-patients-in-western-kenya.ID.000136.php>.
- [35] Lowe SW, Bodis S, McClatchey A, Remington L, Ruley HE, Fisher DE, et al. p53 status and the efficacy of cancer therapy in vivo. *Science*. 1994;266(5186):807–10.
- [36] Easson EC. General principles of radiotherapy The radiotherapy of malignant disease. London: Springer London; 1991. p. 111–29 Available from. Available from: http://link.springer.com/10.1007/978-1-4471-3168-7_5.
- [37] Chao C, Goldberg M, Hoffman JP. Surgical salvage therapy: abdominoperineal resection for recurrent anal carcinoma, metastasectomy of recurrent colorectal cancer, and esophagectomy after combined chemoradiation. *Curr Opin Oncol* 2000;12(4):353–6.
- [38] Law GL, Itoh H, Law DJ, Mize GJ, Merchant JL, Morris DR. Transcription factor ZBP-89 regulates the activity of the ornithine decarboxylase promoter. *J Biol Chem* 1998;273(32):19955–64.
- [39] Kang S, Bader AG, Vogt PK. Phosphatidylinositol 3-kinase mutations identified in human cancer are oncogenic. *Proc Natl Acad Sci U S A* 2005;102(3):802–7.
- [40] Link W, Rosado A, Fominaya J, Thomas JE, Carnero A. Membrane localization of all class I PI 3-kinase isoforms suppresses c-Myc-induced apoptosis in Rat1 fibroblasts via Akt. *J Cell Biochem* 2005;95(5):979–89.
- [41] Wang L, Wang W-L, Zhang Y, Guo S-P, Zhang J, Li Q-L. Epigenetic and genetic alterations of PTEN in hepatocellular carcinoma. *Hepatol Res* 2007;37(5):389–96.
- [42] Li X, Zhang Q, He W, Meng W, Yan J, Zhang L, et al. Low frequency of PIK3CA gene mutations in hepatocellular carcinoma in Chinese population. *Pathol Oncol Res* 2012;18(1):57–60.
- [43] Tanaka Y, Kanai F, Tada M, Asaoka Y, Guleng B, Jazag A, et al. Absence of PIK3CA hotspot mutations in hepatocellular carcinoma in Japanese patients. *Oncogene*. 2006;25(20):2950–2.

- [44] Schulte G, Bryja V. The Frizzled family of unconventional G-protein-coupled receptors. *Trends Pharmacol Sci* 2007;28(10):518–25.
- [45] He X, Semenov M, Tamai K, Zeng X. LDL receptor-related proteins 5 and 6 in Wnt/beta-catenin signaling: arrows point the way. *Development*. 2004;131(8):1663–77.
- [46] Habas R, Dawid IB. Dishevelled and Wnt signaling: is the nucleus the final frontier? *J Biol* 2005;4(1):2.
- [47] Whittaker S, Marais R, Zhu AX. The role of signaling pathways in the development and treatment of hepatocellular carcinoma. *Oncogene*. 2010;29(36):4989–5005.
- [48] Kimelman D, Xu W. beta-catenin destruction complex: insights and questions from a structural perspective. *Oncogene*. 2006;25(57):7482–91.
- [49] Behrens J, Jerchow BA, Würtele M, Grimm J, Asbrand C, Wirtz R, et al. Functional interaction of an axin homolog, conductin, with beta-catenin, APC, and GSK3beta. *Science*. 1998;280(5363):596–9.
- [50] Amit S, Hatzubai A, Birman Y, Andersen JS, Ben-Shushan E, Mann M, et al. Axin-mediated CKI phosphorylation of beta-catenin at Ser 45: a molecular switch for the Wnt pathway. *Genes Dev* 2002;16(9):1066–76.
- [51] Aberle H, Bauer A, Stappert J, Kispert A, Kemler R. Beta-catenin is a target for the ubiquitin-proteasome pathway. *EMBO J* 1997;16(13):3797–804.
- [52] Jennings BH, Ish-Horowicz D. The Groucho/TLE/Grg family of transcriptional co-repressors. *Genome Biol* 2008;9(1):205.
- [53] Chen G, Fernandez J, Mische S, Courey AJ. A functional interaction between the histone deacetylase Rpd3 and the corepressor groucho in *Drosophila* development. *Genes Dev* 1999;13(17):2218–30.
- [54] Kikuchi A, Yamamoto H, Kishida S. Multiplicity of the interactions of Wnt proteins and their receptors. *Cell Signal* 2007;19(4):659–71.
- [55] Gordon MD, Nusse R. Wnt signaling: multiple pathways, multiple receptors, and multiple transcription factors. *J Biol Chem* 2006;281(32):22429–33.
- [56] Wang H, Liu T, Malbon CC. Structure-function analysis of Frizzleds. *Cell Signal* 2006;18(7):934–41.
- [57] Kikuchi A, Yamamoto H, Sato A. Selective activation mechanisms of Wnt signaling pathways. *Trends Cell Biol* 2009;19(3):119–29.
- [58] Schwarz-Romond T, Fiedler M, Shibata N, Butler PJG, Kikuchi A, Higuchi Y, et al. The DIX domain of dishevelled confers Wnt signaling by dynamic polymerization. *Nat Struct Mol Biol* 2007;14(6):484–92.
- [59] Schwarz-Romond T, Metcalfe C, Bienz M. Dynamic recruitment of axin by dishevelled protein assemblies. *J Cell Sci* 2007;120(14):2402–12.
- [60] Schmitt-Graeff A, Ertelt-Heitzmann V, Allgaier H-P, Olschewski M, Nitschke R, Haxelmans S, et al. Coordinated expression of cyclin D1 and LEF-1/TCF transcription factor is restricted to a subset of hepatocellular carcinoma. *Liver Int*. 2005;25(4):839–47.
- [61] Kawate S, Fukusato T, Ohwada S, Watanuki A, Morishita Y. Amplification of c-myc in hepatocellular carcinoma: correlation with clinicopathologic features, proliferative activity and p53 overexpression. *Oncology*. 1999;57(2):157–63.
- [62] Merle P, de la Monte S, Kim M, Herrmann M, Tanaka S, Von Dem Bussche A, et al. Functional consequences of frizzled-7 receptor overexpression in human hepatocellular carcinoma. *Gastroenterology* 2004;127(4):1110–22.
- [63] de La Coste A, Romagnolo B, Billuart P, Renard CA, Buendia MA, Soubrane O, et al. Somatic mutations of the beta-catenin gene are frequent in mouse and human hepatocellular carcinomas. *Proc Natl Acad Sci U S A* 1998;95(15):8847–51.
- [64] Miyoshi Y, Iwao K, Nagasawa Y, Aihara T, Sasaki Y, Imaoka S, et al. Activation of the beta-catenin gene in primary hepatocellular carcinomas by somatic alterations involving exon 3. *Cancer Res* 1998;58(12):2524–7.
- [65] Audard V, Grimber G, Elie C, Radenen B, Audebourg A, Letourneur F, et al. Cholestasis is a marker for hepatocellular carcinomas displaying beta-catenin mutations. *J Pathol* 2007;212(3):345–52.
- [66] Zhai B, Yan H-X, Liu S-Q, Chen L, Wu M-C, Wang H-Y. Reduced expression of E-cadherin/catenin complex in hepatocellular carcinomas. *World J Gastroenterol* 2008;14(37):5665–73.
- [67] Du G-S, Wang J-M, Lu J-X, Li Q, Ma C-Q, Du J-T, et al. Expression of P-aPKC-iota, E-cadherin, and beta-catenin related to invasion and metastasis in hepatocellular carcinoma. *Ann Surg Oncol* 2009;16(6):1578–86.
- [68] Yu B, Yang X, Xu Y, Yao G, Shu H, Lin B, et al. Elevated expression of DKK1 is associated with cytoplasmic/nuclear beta-catenin accumulation and poor prognosis in hepatocellular carcinomas. *J Hepatol* 2009;50(5):948–57.
- [69] Liu L, Zhu X-D, Wang W-Q, Shen Y, Qin Y, Ren Z-G, et al. Activation of beta-catenin by hypoxia in hepatocellular carcinoma contributes to enhanced metastatic potential and poor prognosis. *Clin Cancer Res* 2010;16(10):2740–50.

- [70] Feng Z, Fan X, Jiao Y, Ban K. Mammalian target of rapamycin regulates expression of β -catenin in hepatocellular carcinoma. *Hum Pathol* 2011;42(5):659–68.
- [71] Zhao N, Sun B, Zhao X, Liu Z, Sun T, Qiu Z, et al. Coexpression of Bcl-2 with epithelial-mesenchymal transition regulators is a prognostic indicator in hepatocellular carcinoma. *Med Oncol* 2012;29(4):2780–92.
- [72] Geng M, Cao Y-C, Chen Y-J, Jiang H, Bi L-Q, Liu X-H. Loss of Wnt5a and Ror2 protein in hepatocellular carcinoma associated with poor prognosis. *World J Gastroenterol* 2012;18(12):1328–38.
- [73] Jin J, Jung HY, Wang Y, Xie J, Yeom YI, Jang J-J, et al. Nuclear expression of phosphorylated TRAF2- and NCK-interacting kinase in hepatocellular carcinoma is associated with poor prognosis. *Pathol Res Pract* 2014;210(10):621–7.
- [74] Lee JM, Yang J, Newell P, Singh S, Parwani A, Friedman SL, et al. β -Catenin signaling in hepatocellular cancer: implications in inflammation, fibrosis, and proliferation. *Cancer Lett* 2014;343(1):90–7.
- [75] Park JY, Park WS, Nam SW, Kim SY, Lee SH, Yoo NJ, et al. Mutations of beta-catenin and AXIN I genes are a late event in human hepatocellular carcinogenesis. *Liver Int* 2005;25(1):70–6.
- [76] Korita PV, Wakai Y, Shirai Y, Matsuda Y, Sakata J, Cui X, et al. Overexpression of osteopontin independently correlates with vascular invasion and poor prognosis in patients with hepatocellular carcinoma. *Hum Pathol* 2008;39(12):1777–83.
- [77] Tien LT, Ito M, Nakao M, Niino D, Serik M, Nakashima M, et al. Expression of beta-catenin in hepatocellular carcinoma. *World J Gastroenterol* 2005;11(16):2398–401.
- [78] Inagawa S, Itabashi M, Adachi S, Kawamoto T, Hori M, Shimazaki J, et al. Expression and prognostic roles of beta-catenin in hepatocellular carcinoma: correlation with tumor progression and postoperative survival. *Clin Cancer Res an J Am Assoc Cancer Res* 2002;8(2):450–6.
- [79] Endo K, Ueda T, Ueyama J, Ohta T, Terada T. Immunoreactive E-cadherin, alpha-catenin, beta-catenin, and gamma-catenin proteins in hepatocellular carcinoma: relationships with tumor grade, clinicopathologic parameters, and patients' survival. *Hum Pathol* 2000;31(5):558–65.
- [80] Witjes CDM, Ten Kate FJW, Verhoef C, De Man RA, IJzermans JNM. Immunohistochemical characteristics of hepatocellular carcinoma in non-cirrhotic livers. *J Clin Pathol* 2013;66(8):687–91.
- [81] Zulehner G, Mikula M, Schneller D, van Zijl F, Huber H, Sieghart W, et al. Nuclear beta-catenin induces an early liver progenitor phenotype in hepatocellular carcinoma and promotes tumor recurrence. *Am J Pathol* 2010;176(1):472–81.
- [82] Schmitt-Gräff A, Ertelt V, Allgaier H-P, Koelble K, Olschewski M, Nitschke R, et al. Cellular retinol-binding protein-1 in hepatocellular carcinoma correlates with beta-catenin, Ki-67 index, and patient survival. *Hepatology*. 2003;38(2):470–80.
- [83] Elmileik H, Paterson AC, Kew MC. Beta-catenin mutations and expression, 249serine p53 tumor suppressor gene mutation, and hepatitis B virus infection in southern African Blacks with hepatocellular carcinoma. *J Surg Oncol* 2005;91(4):258–63.
- [84] Verma A, Bal M, Ramadwar M, Deodhar K, Patil P, Goel M. Clinicopathologic characteristics of Wnt/ β -catenin-deregulated hepatocellular carcinoma. *Indian J Cancer* 2017;54(4):634–9.
- [85] Lin M, Guo LM, Liu H, Du J, Yang J, Zhang LJ, et al. Nuclear accumulation of glioma-associated oncogene 2 protein and enhanced expression of forkhead-box transcription factor M1 protein in human hepatocellular carcinoma. *Histol Histopathol* 2010;25(10):1269–75.
- [86] Dugum M, Hanouneh I, McIntyre T, Pai R, Aucejo F, Egtesad B, et al. Sonic Hedgehog signaling in hepatocellular carcinoma: a pilot study. *Mol Clin Oncol* 2016;4(3):369–74.
- [87] Yan Z, Cui K, Murray DM, Ling C, Xue Y, Gerstein A, et al. PBAF chromatin-remodeling complex requires a novel specificity subunit, BAF200, to regulate expression of selective interferon-responsive genes. *Genes Dev* 2005;19(14):1662–7.
- [88] Yang G, Xu Y, Chen X, Hu G. IFITM1 plays an essential role in the antiproliferative action of interferon-gamma. *Oncogene*. 2007;26(4):594–603.
- [89] Satoh S, Daigo Y, Furukawa Y, Kato T, Miwa N, Nishiwaki T, et al. AXIN1 mutations in hepatocellular carcinomas, and growth suppression in cancer cells by virus-mediated transfer of AXIN1. *Nat Genet* 2000;24(3):245–50.
- [90] Roberts PJ, Der CJ. Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. *Oncogene*. 2007;26(22):3291–310.

- [91] Liu Y, Poon RT, Li Q, Kok TW, Lau C, Fan ST. Both antiangiogenesis- and angiogenesis-independent effects are responsible for hepatocellular carcinoma growth arrest by tyrosine kinase inhibitor PTK787/ZK222584. *Cancer Res* 2005;65(9):3691–9.
- [92] Wiesnauer CA, Yip-Schneider MT, Wang Y, Schmidt CM. Multiple anticancer effects of blocking MEK-ERK signaling in hepatocellular carcinoma. *J Am Coll Surg* 2004;198(3):410–21.
- [93] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359(4):378–90.
- [94] Cheng A-L, Kang Y-K, Chen Z, Tsao C-J, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10(1):25–34.
- [95] Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib vs sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391(10126):1163–73.
- [96] Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux G-P, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2017;18(12):1624–36.
- [97] Chow PKH, Gandhi M, Tan S-B, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: selective internal radiation therapy vs sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018;36(19):1913–21.
- [98] Kudo M, Ueshima K, Yokosuka O, Ogasawara S, Obi S, Izumi N, et al. Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy vs sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial. *Lancet Gastroenterol Hepatol* 2018;3(6):424–32.
- [99] Cheng A-L, Kang Y-K, Lin D-Y, Park J-W, Kudo M, Qin S, et al. Sunitinib vs sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013;31(32):4067–75.
- [100] Frenette CT. The role of regorafenib in hepatocellular carcinoma. *Gastroenterol Hepatol* 2017;13(2):122–4.
- [101] Bruix J, Qin S, Merle P, Granito A, Huang Y-H, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;389(10064):56–66.
- [102] Luo L-J, Zhang L-P, Duan C-Y, Wang B, He N-N, Abulimiti P, et al. The inhibition role of miR-22 in hepatocellular carcinoma cell migration and invasion via targeting CD147. *Cancer Cell Int* 2017;17(1):17. Available from: <https://doi.org/10.1186/s12935-016-0380-8>. Available from.
- [103] Huo X, Han S, Wu G, Latchoumanin O, Zhou G, Hebbard L, et al. Dysregulated long noncoding RNAs (lncRNAs) in hepatocellular carcinoma: implications for tumorigenesis, disease progression, and liver cancer stem cells. *Mol Cancer* 2017;16(1):165.
- [104] Nouse K, Miyahara K, Uchida D, Kuwaki K, Izumi N, Omata M, et al. Effect of hepatic arterial infusion chemotherapy of 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan. *Br J Cancer* 2013;109(7):1904–7.
- [105] Zhang H, Wang Q, Liu J, Cao H. Inhibition of the PI3K/Akt signaling pathway reverses sorafenib-derived chemo-resistance in hepatocellular carcinoma. *Oncol Lett* 2018;15(6):9377–84.
- [106] Zhu Y, Zheng B, Wang H, Chen L. New knowledge of the mechanisms of sorafenib resistance in liver cancer. *Acta Pharmacol Sin* 2017;38(5):614–22. Available from: <https://doi.org/10.1038/aps.2017.5>. Available from.
- [107] Ye L, Mayerle J, Ziesch A, Reiter FP, Gerbes AL, De Toni EN. The PI3K inhibitor copanlisib synergizes with sorafenib to induce cell death in hepatocellular carcinoma. *Cell Death Discov* 2019;5(1):86. Available from: <https://doi.org/10.1038/s41420-019-0165-7>. Available from.
- [108] Reiter FP, Denk G, Ziesch A, Ofner A, Wimmer R, Hohenester S, et al. Predictors of ribociclib-mediated antitumour effects in native and sorafenib-resistant human hepatocellular carcinoma cells. *Cell Oncol* 2019;42(5):705–15.
- [109] Bollard J, Miguela V, Ruiz de Galarreta M, Venkatesh A, Bian CB, Roberto MP, et al. Palbociclib (PD-0332991), a selective CDK4/6 inhibitor, restricts tumour growth in preclinical models of hepatocellular carcinoma. *Gut*. 2017;66(7):1286–96.
- [110] Gedaly R, Angulo P, Hundley J, Daily MF, Chen C, Evers BM. PKI-587 and sorafenib targeting PI3K/AKT/mTOR and Ras/Raf/MAPK pathways synergistically inhibit HCC cell proliferation. *J Surg Res* 2012;176(2):542–8.

- [111] Koeberle D, Dufour J-F, Demeter G, Li Q, Ribi K, Samaras P, et al. Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29). *Ann Oncol* 2016;27(5):856–61.
- [112] van Malenstein H, Dekervel J, Verslype C, Van Cutsem E, Windmolders P, Nevens F, et al. Long-term exposure to sorafenib of liver cancer cells induces resistance with epithelial-to-mesenchymal transition, increased invasion and risk of rebound growth. *Cancer Lett* 2013;329(1):74–83.
- [113] Xu J, Lamouille S, Derynck R. TGF-beta-induced epithelial to mesenchymal transition. *Cell Res* 2009;19(2):156–72.
- [114] Ogunwobi OO, Liu C. Hepatocyte growth factor upregulation promotes carcinogenesis and epithelial-mesenchymal transition in hepatocellular carcinoma via Akt and COX-2 pathways. *Clin Exp Metastasis* 2011;28(8):721–31.
- [115] Lee JM, Dedhar S, Kalluri R, Thompson EW. The epithelial-mesenchymal transition: new insights in signaling, development, and disease. *J Cell Biol* 2006;172(7):973–81.
- [116] Wu Y, Zhou BP. New insights of epithelial-mesenchymal transition in cancer metastasis. *Acta Biochim Biophys Sin* 2008;40(7):643–50.
- [117] Singh A, Settleman J. EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer. *Oncogene*. 2010;29(34):4741–51.
- [118] Larue L, Bellacosa A. Epithelial–mesenchymal transition in development and cancer: role of phosphatidylinositol 3' kinase/AKT pathways. *Oncogene* 2005;24(50):7443–54. Available from: <https://doi.org/10.1038/sj.onc.1209091>. Available from.
- [119] Yao X, Wang X, Wang Z, Dai L, Zhang G, Yan Q, et al. Clinicopathological and prognostic significance of epithelial mesenchymal transition-related protein expression in intrahepatic cholangiocarcinoma. *Onco Targets Ther* 2012;5:255–61.
- [120] Masugi Y, Yamazaki K, Hibi T, Aiura K, Kitagawa Y, Sakamoto M. Solitary cell infiltration is a novel indicator of poor prognosis and epithelial-mesenchymal transition in pancreatic cancer. *Hum Pathol* 2010;41(8):1061–8.
- [121] Kim MA, Lee HS, Lee HE, Kim JH, Yang H-K, Kim WH. Prognostic importance of epithelial-mesenchymal transition-related protein expression in gastric carcinoma. *Histopathology*. 2009;54(4):442–51.
- [122] Schmitz KJ, Wohlschlaeger J, Lang H, Sotiropoulos GC, Malago M, Steveling K, et al. Activation of the ERK and AKT signalling pathway predicts poor prognosis in hepatocellular carcinoma and ERK activation in cancer tissue is associated with hepatitis C virus infection. *J Hepatol* 2008;48(1):83–90.
- [123] Karabici M, Azbazdar Y, Ozhan G, Senturk S, Firtina Karagonlar Z, Erdal E. Changes in Wnt and TGF- β signaling mediate the development of regorafenib resistance in hepatocellular carcinoma cell line HuH7 *Front Cell Dev Biol* 2021;2015 Available from. Available from: <https://www.frontiersin.org/article/10.3389/fcell.2021.639779>.

VOLUME 3

Theranostics and Precision Medicine for the Management of Hepatocellular Carcinoma

Translational and Clinical Outcomes

Edited by

Ganji Purnachandra Nagaraju, School of Medicine, Division of Hematology and Oncology, University of Alabama, Birmingham, AL, United States

Sarfraz Ahmad, AdventHealth Cancer Institute, Florida State University (FSU) and University of Central Florida (UCF), Colleges of Medicine, Orlando, FL, United States

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).

The third volume, **Translational and Clinical Outcomes**, discusses topics, such as clinical and safety assessment of HCC patients, liver transplantation as therapeutic option, immunotherapy interventions, and image-based surveillance. In addition, it discusses immunohistology of HCC-enabled precision medicine and artificial intelligence for HCC.

It is a valuable resource for cancer researchers, oncologists, graduate students, hepatologists, and members of global biomedical researchers who need to understand more about liver cancer to apply in their scholarly research works and/or clinical settings.

Key features

- Provides best practices for potential management of HCC in the clinical setting
- Discusses emerging treatment approaches based on artificial intelligence and precision medicine tools and techniques
- Brings updated research information on international clinical trials for potential treatment options of HCC



ACADEMIC PRESS

An imprint of Elsevier

elsevier.com/books-and-journals

ISBN 978-0-323-99283-1



9 780323 992831