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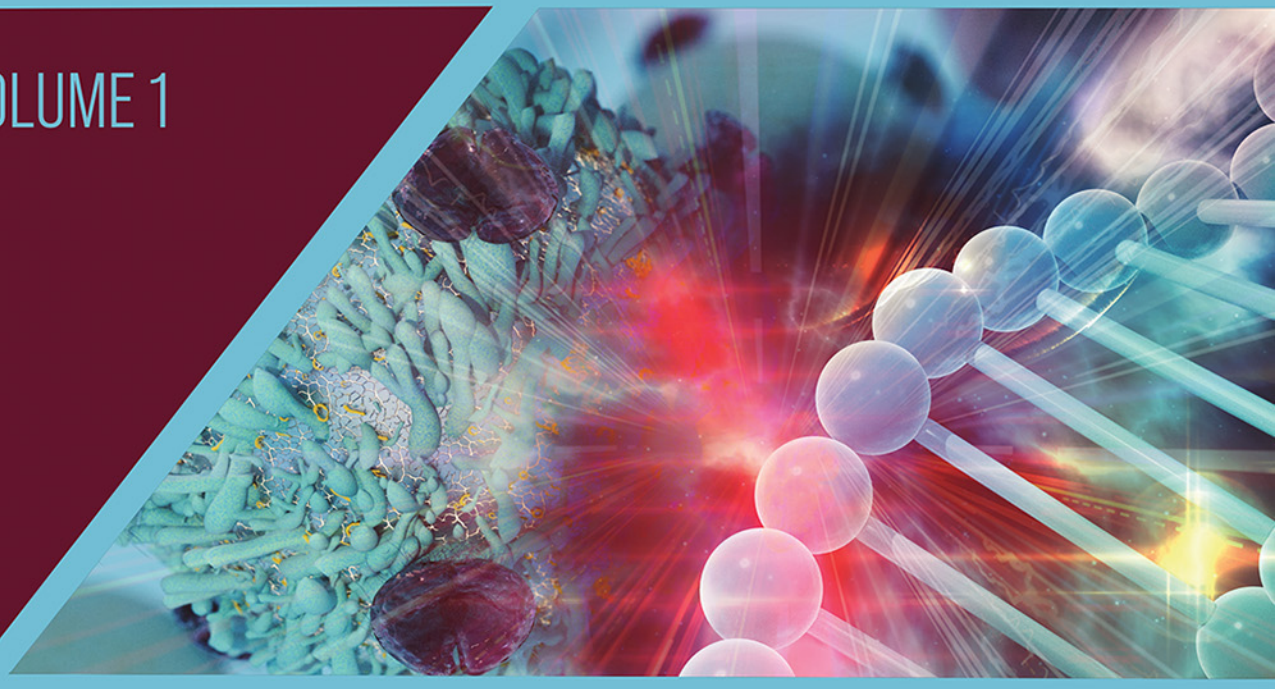

Theranostics and Precision Medicine for the Management of Hepatocellular Carcinoma

Biology and Pathophysiology

Editors
Ganji Purnachandra Nagaraju and Sujatha Peela

THERANOSTICS AND PRECISION MEDICINE FOR THE MANAGEMENT OF HEPATOCELLULAR CARCINOMA VOLUME 1

Biology and Pathophysiology

Edited by

GANJI PURNACHANDRA NAGARAJU, PhD, DSc, FAACC
School of Medicine, Division of Hematology and Oncology, University of Alabama, Birmingham, AL, United States

SUJATHA PEELA, PhD
Department of Biotechnology, Dr. BR Ambedkar University, Srikakulam, India

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Contents

List of contributors xv
About the editors xix
Preface xxi

1. Cell origin, biology, and pathophysiology of hepatocellular carcinoma 1

Begum Dariya, Sujatha Peela and Ganji Purnachandra Nagaraju

Abstract 1
Keywords 1
Abbreviations 1
Introduction 2
Cell of origin of HCC 2
Biology and pathophysiology 3
Molecular consensus of HCC 4
Signaling pathways 5
Chromatic remodeling 5
Conclusion 6
Conflict of interest 6
References 6

2. Hepatocellular carcinoma—An updated review 11

Varimadugu Aruna, A. Sneha and D. Sai Harshitha

Abstract 11
Keywords 11
Abbreviations 11
Introduction 12
Types of cancer 12
Hepatocellular carcinoma 13
Causes/risk factors 14
Symptoms 14
Genes involved 15
Progression 15
HCC caused by aflatoxins 17
HCC caused by the hepatitis virus 17
HCC caused by hepatitis B virus 17
HCC caused by hepatitis C virus 19
HCC caused by alcohol 19
HCC transcriptomic analysis 20
Screening and diagnosis 21
Tumor staging 21
Treatment 22
Liver transplantation 24
Conclusion and future perspectives 25
Conflict of interest 26
References 26

3. Risk factors and pathogenic mechanism—associated hepatocellular carcinoma 33

Nisha Sahu, Samrat Rakshit and L.V.K.S. Bhaskar

Abstract 33
Keywords 33
Abbreviation 33
Introduction 34
Risk factors 34
Viral hepatitis B and C 34
Alcohol 35
NAFLD-/NASH-induced HCC 35
Aflatoxins 36
Other chemical toxicants 36
Mechanisms of action 37
Hepatitis B virus infection 37
Hepatitis C virus infection 38
Alcohol 40
NAFLD-/NASH-induced HCC 41
Aflatoxins 43
Others 44
Conclusion 44
References 45

4. Effect of cirrhosis and hepatitis on the prognosis of liver cancer 51
Deepika Divya Kadiri, Sujatha Peela and Debayan Ganguli

Abstract 51
Keywords 51
Abbreviations 51
Introduction 52
Hepatocellular carcinoma 53
HBV and HCV assessment and the management of hepatitis 54
Hepatitis-associated symptoms and disorders at various stages 55
Cirrhosis 55
HBV and HCV infection 55
HIV-associated conditions 56
Autoimmune hepatitis 56
Fatty liver disorder 56
Alcohol 56
Immune factors 56
Liver cirrhosis—assessment and management of cirrhosis 56
Liver cirrhosis—associated symptoms and disorders at various stages 57
Disorders and symptoms 57
Stages 58
Assessment 59
Management 60
HCC-associated risk factors 60
Hepatitis C virus 60
Hepatitis B virus 60
Role of schistosomiasis 61
Role of aflatoxin B1 61
Pesticides 61
Diabetes mellitus 61
Diet 62
Relationship between hepatitis and cirrhosis 62
The role of HBV in stimulating hepatocarcinogenesis 62
The role of HCV in developing a prooncogenic microenvironment 63
Mechanism underlying the synergistic effect of cirrhosis and hepatitis on the prognosis of HCC 63
Viral hepatitis 64
Noninfectious/nonviral hepatitis 64
Conclusion 65
Conflict of interest 65
References 65

5. An overview on aflatoxin B1 induced initiation and progression of hepatocellular carcinoma 73
Chintapanti Swetha and Bala Prabhakar Girish

Abstract 73
Keywords 73
Abbreviations 73
Introduction 74
Aflatoxins 74
DNA methylation 75
Histone modifications 76
Noncoding RNAs 77
Conclusion 77
References 78

6. Modulatory effects of G protein—coupled receptor in hepatocellular carcinoma 81
Vidya Murugesan and Senthilkumar Rajagopal

Abstract 81
Keywords 81
Abbreviations 81
Introduction 82
GPCR receptors and signaling pathways implicated in cancer 83
GPR30 and GPR30-mediated signaling pathways—GMAPK (mitogen-activated protein kinases) 83
Mitogen-activated protein kinases 83
Lysophosphatidic acid receptor 84
LPAR-mediated signaling pathway 85
Receptor for angiotensin-II 85
Angiotensin receptor-mediated signaling pathways in cancer 85
Chemokine receptors 85
Chemokine receptor—mediated signaling pathways in cancer 86
Protease-activated receptors 86
Wnt signaling 86
The hedgehog pathway 87
Role of GPCRs in hepatocellular carcinoma 88
Role of chemokines in GPCR-mediated hepatocellular carcinoma 88
E-prostanoid receptors 90
Role of lysophosphatidic acid in GPCR-mediated hepatocellular carcinoma 90

Adrenergic receptors 90
Angiotensin II receptors 90
Smoothened receptors 90
Orphan GPCRs 91
Hepatocellular carcinoma: treatments based on GPCR signaling 91
Summary and future perspectives 91
Conflict of interest 91
References 92

7. Hepatocellular carcinoma stem cells, progression and therapy 97
Vijaya Nirmala Pangi

Abstract 97
Keywords 97
Abbreviations 97
Introduction 98
Tumor progression and proliferation 98
Role of MSC's in the initiation and progression of HCC 98
Role of Wnt/β-catenin pathway in CSCs initiation and progression 99
Role of miRNAs and lncRNAs in the development of cancer 99
MiRNAs associated with LCSCs 99
LncRNAs associated with LCSCs 100
Iron homeostasis in HCC 100
Therapy of liver cancer 100
Treatment for early liver cancer 101
Immunotherapy 101
MiRNAs as anticancer therapeutics 102
Therapeutic approaches to targeting lncRNA in cancer 103
Herbal medicine and HCC 103
Radiotherapy 104
References 105

8. Tumor microenvironment in heptocellular carcinoma 109
Gayatri Gouda, Manoj Kumar Gupta, Ravindra Donde, Lambodar Behera and Ramakrishna Vadde

Abstract 109
Keywords 109
Abbreviations 109
Introduction 110
Components of tumor microenvironment 111
Cancer-associated fibroblast 111
Extracellular matrix 112
Hepatic stellate cells 112
Endothelial cells 113
Tumor-associated macrophages 113
Tumor-infiltrating leukocytes 114
Cytokines 114
Growth factors 114
Matrix metalloproteinase 115
Hypoxia 115
Pathways involved in HCC development 116
Ras/Raf/MAPK/ERK pathway 116
NF-κB pathway 117
PI3K signaling pathway 117
Transforming growth factor β pathway 117
P53 signaling pathway 118
JAK/STAT pathway 118
Wnt/β-catenin pathway 118
Conclusion 119
Conflicts of interest 119
References 119

9. Polymorphisms in hepatocellular carcinoma 125
L.S.S. Srivani Nagam, Ramakrishna Vadde and Rajeswari Jinka

Abstract 125
Keywords 125
Abbreviations 125
Introduction 126
Diagnosis, staging, and grading 126
Risk factors 127
Treatment 129
Genes involved in the pathogenesis of hepatocellular carcinoma 129
Signaling pathways involved in pathobiology of hepatocellular carcinoma 130
Conclusion 131
Conflicts of interest 132
References 132

10. Environmental pollution and hepatocellular carcinoma 135
Srinivas Namuduri, Rama Rao Malla, Jagadeeswara Rao Kakarla and Gopamma Daka

Abstract 135
Keywords 135
Abbreviations 135
Introduction 136

Pollutants and hepatocellular carcinoma mechanism 137
Air pollutants 137
Particulate matter ($PM_{2.5}$) 138
Heavy metals 138
Organic pollutants 140
Industrial products 144
Radiation 145
Conclusion 146
Acknowledgment 146
Conflict of interest 146
Funding sources 146
References 146

11. Mitochondrial metabolism in progression of liver cancer 153
Richa Bajpai

Abstract 153
Keywords 153
Abbreviations 153
Introduction 154
Deregulated mitochondrial metabolism in HCC 155
ROS homeostasis in the progression of HCC 157
Mitochondrial dynamics in HCC 158
Mitochondrial signaling in HCC 159
Targeting mitochondrial metabolism: therapeutic opportunities for HCC 160
Conclusion 161
References 161

12. Role of succinate dehydrogenase in hepatocellular carcinoma 167
Gowru Srivani, Mohammad Imran, Neha Merchant, Jyothi Priya Mandala and Ganji Purnachandra Nagaraju

Abstract 167
Keywords 167
Abbreviations 167
Introduction 168
Structure of succinate dehydrogenase 168
Dysfunction of succinate dehydrogenase 169
Mutations in succinate dehydrogenase 170
Succinate dehydrogenase activity-regulation and expression of its gene 171
Transcription regulators 171
Posttranscriptional regulators 172
Posttranslational modifiers 172
Direct effectors 173
Role of SDHB in hepatocellular carcinoma 174
Clinical trials of succinic dehydrogenase and preclinical models 175
Conclusion 177
References 177

13. Telomerase in hepatocellular carcinoma 181
Radhika Tippani, Sirisha Kalam, Srinivas Podeti and Mahendar Porika

Abstract 181
Keywords 181
Abbreviations 181
Introduction 182
Telomerase and hepatocellular carcinoma 183
Several malignancies have telomerase reverse transcriptase promoter mutations 185
HCC TERT promoter point mutations 185
Telomerase reverse transcriptase promoter insertional mutations 188
Telomerase in malignant transformation 189
Diagnosis 190
Treatment perspectives 191
Conclusion 192
Conflict of interest 192
References 192

14. Glutamine metabolism in liver cancer: role in progression and potential therapeutic targeting 199
Yashwant Kumar Ratre, Arundhati Mehta, Rajesh Sharma, Vivek Kumar Soni, Dhananjay Shukla, Vibhay Nath Tripathi and Naveen Kumar Vishvakarma

Abstract 199
Keywords 199
Abbreviations 200
Introduction 200
Liver cancer metabolism 201
Amino acid metabolism in liver cancer 202
Glutamine metabolism and liver cancer 203
Role of glutamine addiction in liver cancer progression 205

Targeting glutamine metabolism in liver cancer 209
Conclusion and future prospective 210
References 212

15. Influence of endoplasmic reticulum stress and unfolded protein response in the onset and progression of hepatocellular carcinoma 219

Syamala Soumyakrishnan, Cheemachanahalli Muninanjappa Mohan Gowda, Shivanna Uma, Meghavarnam Anil Kumar, Sujatha Peela and Meenakshisundaram Sreepriya

Abstract 219
Keywords 220
Abbreviations 220
Introduction 220
ER stress and diseases of the liver 221
Unfolded protein response and its physiological significance 221
Unfolded protein response and malignant transformation—the dangerous duo 223
Autophagy and its relevance to ER stress and tumor progression in HCC 224
ER resident chaperones in quality control and altered expression in hepatocellular carcinoma 225
Signaling pathways controlling ER stress leading to UPR activation in hepatocellular carcinoma 226
Nrf2 signaling 226
Keap 1 229
Major molecular targets in UPR 230
Protein kinase R-like ER kinase 230
Inositol-requiring enzyme-1 231
Activating transcription factor 6 232
X-box-binding protein 1 232
Activating transcription factor 4 233
Indicators of ER stress and UPR response 233
C/EBP homologous protein 233
Binding immunoglobulin protein 234
UPR activation in cancer 234
Role of ER stress on immune evasion in hepatocellular carcinoma 235
Conclusion 235
Future perspectives 236
References 236

16. Role of exosomes in hepatocellular carcinoma progression and metastasis 243

Nirmala Gollarahalli Sannappa Gowda, Varsha Dilip Shiragannavar and Prasanna Kumar Santhekadur

Abstract 243
Keywords 243
Abbreviations 243
Introduction 244
Biogenesis of exosomes 246
Exosomes and their components 246
Exosome-associated proteins 247
Exosomes and cancer 247
AFLD, NAFLD, and exosomes 248
Exosomes and HCC 249
Exosomes as biomarkers 251
Exosomes as therapeutic molecule and personalized medicine for HCC patients 252
Conclusion and future perspectives 252
Some of the very important points to be considered in exosome research and therapeutic applications are as follows 253
Acknowledgments 253
Conflict of interest 253
References 253

17. Comparative genomics and molecular epidemiology on hepatitis virus–induced hepatocellular carcinoma 257

Dowluru S.V.G.K. Kaladhar and Tantravahi Srinivasan

Abstract 257
Keywords 257
Abbreviations 257
Introduction 258
Hepatitis virus 259
Hepatitis A virus 259
Hepatitis B virus 260
Hepatitis C virus 260
Hepatitis D virus 260
Hepatitis E virus 261
Structure and genome of HBV and HCV 261
Hepatitis B virus 261
HBV genome 262
Hepatitis C virus 263
HCV genome 264
Genotypes 264

HBV genotypes 265
HCV genotypes 265
Comparative genomics of HV 266
High- and low-risk types 268
Molecular epidemiology 268
Hepatitis E virus and hepatocellular cancer 268
Molecular mechanism of pathogenesis 269
HBV genome integration 269
Role of HBV proteins and microRNAs 270
Hepatitis B surface antigen 270
Hepatitis B X protein 270
Inflammation 271
HCV and cancer 272
Molecular mechanism of pathogenesis 272
Viral proteins 272
Core protein 273
NS3 273
NS5A and NS5B 273
Inflammation 274
Steatosis and insulin resistance 274
Conclusion 275
Conflict of interest 275
References 275

18. Noncoding RNAs in HBV-associated hepatocellular carcinoma 287
Seema Kumari

Abstract 287
Keywords 287
Abbreviations 287
Introduction 287
MicroRNA in hepatitis B—related hepatocellular carcinoma 288
LncRNA in HBV-related HCC 289
Circular RNA in HBV-related HCC 290
Conclusion 291
Conflict of interest 291
References 291

19. Role of genetic insights and tumor microenvironment in liver cancer: new opportunities for gene therapy 293
Urvashi Vijay, Pranathi Pappu, Dhatri Madduru, Ngalah Bidii Stephen, Prashanth Suravajhala and Obul Reddy Bandapalli

Abstract 293
Keywords 294
Abbreviations 294
Introduction 294
Hepatocellular carcinoma 294
Gene therapy 295
Gene regulation 296
pH—responsive gene carriers 296
Redox responsive gene carriers 297
ROS—responsive gene carriers 298
Responsive gene carriers with enzymes 298
Genetic insights in HCC gene therapy 299
Suppressor genes associated with tumor 299
Gene therapy 300
Immunotherapy 301
Proteins associated with tumor 301
Oncogenes 302
Chromosomal instability 302
MicroRNA 302
RNA editing 303
Long noncoding RNAs 303
Recent progress in therapeutics 303
Conclusion 305
References 305

20. Role of microRNAs in hepatocellular cancer pathogenesis and prognosis 311
Deepika Sarvepalli, Mamoon Ur. Rashid and Sarfraz Ahmad

Abstract 311
Keywords 311
Abbreviations 311
Introduction 312
Biogenesis of miRNA 312
miRNAs' role in pathogenesis of hepatocellular carcinomas 313
Conclusion 321
References 321

21. Long non-coding RNA: Emerging role in Hepatocellular Carcinoma 327
Kalyani Dasari

Abstract 327
Keywords 327
Abbreviations 327
Introduction 328
Hepatocellular carcinoma 328
Biology of lncRNA 329
Biogenesis of lncRNA 329

Conservation of lncRNA 330
Classification of lncRNA 330
Localization of lncRNA 330
Molecular mechanism of lncRNA 330
lncRNA and intercellular communication 331
Role of lncRNAs in cancer 331
LncRNA in HCC 332
lncRNA as diagnostic marker for HCC 332
Therapeutic approaches for HCC 332
HCC—treatment and drug resistance 333
lncRNA-clinical manifestation of HCC 333
Oncogenic lncRNA 333
Tumor suppressor lncRNA 335
lncRNA—potential therapeutics 336
lncRNAs—potential biomarkers of HCC 336
Conclusion 336
Acknowledgments 337
Conflict of interest 337
References 337

22. Risk factors and clinical aspects associated with hepatocellular carcinoma: role of long noncoding RNAs 341

Swarnalatha Kodidela, Abhayananda Behera and Aramati Bindu Madhava Reddy

Abstract 341
Keywords 341
Abbreviations 341
Introduction 342
Noncoding RNAs 344
Long noncoding RNAs 344
Molecular mechanisms and characterization of lncRNAs 344
Sponging microRNAs 345
Regulating functions of organelles 345
Biological functions and mode of action of lncRNAs in HCC development 345
LncRNAs in HCC 348
Risk factors for HCC 349
Diagnosis and treatment 350
LncRNAs are potential biomarkers and therapeutic targets for HCC 351
Conclusion 351
Acknowledgments 352
References 352

Index 357

CHAPTER

3

Risk factors and pathogenic mechanism–associated hepatocellular carcinoma

Nisha Sahu, Samrat Rakshit and L.V.K.S. Bhaskar

Department of Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur, India

Abstract

Hepatocellular carcinoma (HCC) is the most prevalent liver cancer, accounting for more than 80% of all liver cancers worldwide. HCC is the fourth leading cause of cancer-related death in 2018. Globally, nearly 800,000 new cases of HCC have been diagnosed each year. The development of HCC results from the dysfunction of a multistep biological mechanism in liver where healthy hepatocytes become malignant. Several factors like regulation of oxidative stress, genetic and epigenetic alterations, inflammation, and immunity are involved in the development of HCC. Hepatitis B and C, alcohol- and drug-induced steatohepatitis, aflatoxins, and carcinogens such as polyvinyl chloride, polychlorinated biphenyls, pyrethrins, chlordane, and dithiothreitol are all major risk factors for HCC. These risk factors often affect hepatocytes to cause hepatotoxicity by cholestasis, fatty liver, fibrosis, and cirrhosis leading to HCC. These risk factors modulate oxidative stress, proliferation, apoptosis, mitochondrial dysregulation, lipid metabolism, insulin resistance, and many more by regulating various signaling pathways such as P53, P73, Ras, Wnt/β-catenin, JAK/STAT3, Bcl-2, CDK-4, mitogen-activated protein kinase, tumor necrosis factor-α, and transforming growth factor-β are involved in the development of HCC. Understanding the potential mechanisms underlying these HCC-related risk factors will aid in the development of new therapeutic strategies to reduce HCC-related morbidity and mortality.

Keywords: Hepatocellular carcinoma; hepatitis B virus; hepatitis C virus; nonalcoholic fatty liver disease; nonalcoholic steatohepatitis

Abbreviation

EMT	epithelial-to-mesenchymal *trans*-differentiation
HBx	hepatitis B X protein
HBV	hepatitis B virus
HCV	hepatitis C virus

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HSCs hepatic stellate cells
MAPK1 mitogen-activated protein kinase 1
NAFLD nonalcoholic fatty liver disease
NASH nonalcoholic steatohepatitis
NF-κB nuclear factor-κB
PKR protein kinase R
TERT telomerase reverse transcriptase
TGF transforming growth factor
TNF-α tumor necrosis factor-α

Introduction

Hepatocellular carcinoma (HCC) is the most prevalent liver cancer, accounting for over 80% of all liver cancers worldwide. HCC was the fourth leading cause of cancer-related death in 2018 [1]. HCC incidence and mortality rates have been rising in recent decades, with about 800,000 new cases identified each year [2]. It has a wide geographic range, with many cases occurring in developing countries such as sub-Saharan Africa and Asia [3]. HCC is a complex disease that develops due to underlying liver dysfunction caused by a multistep biological mechanism in which healthy hepatocytes become malignant. The development of HCC is influenced by oxidative stress, genetic and epigenetic changes, inflammation, and immunity [4]. Further, HCC has been linked to a number of other environmental risk factors.

Viral infections such as hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most common causes of persistent liver inflammation [5]. This inflammation eventually weakens the liver immune system, contributing to the severity of the necrotic-inflammatory injury, the formation of liver fibrosis, and the progression of the disease to HCC [6]. Aflatoxin-contaminated food consumption, nonalcoholic steatohepatitis (NASH), environmental toxic intake, and exposure to additional chemical carcinogens (polyvinylchloride, trichloroethylene, and so on) are all significant risk factors (Fig. 3.1). Recent reports suggested that the metabolic syndrome, including diabetes as well obesity, raises the risk of HCC [7]. Chronic inflammation–induced hepatocyte necrosis, decreased regeneration potential, and fibrotic deposition are common early signs of HCC progression. Understanding the basic mechanisms underlying its emergence and progression may aid in its prevention. Disparities in HCC treatment can only be avoided if the disease is detected and treated early [8].

Risk factors

Viral hepatitis B and C

Chronic HBV and HCV infections are responsible for more than 80% of all HCC cases worldwide. Host factors, environmental factors, and hepatitis viruses all play a role in the development of HCC [9]. HCC cases are thought to be significantly higher in eastern Asia and sub-Saharan Africa, where HBV infection is thought to be widespread [10]. Increases in HCV infection, longer alcoholic intake, and nonalcoholic fatty liver disease (NAFLD) all

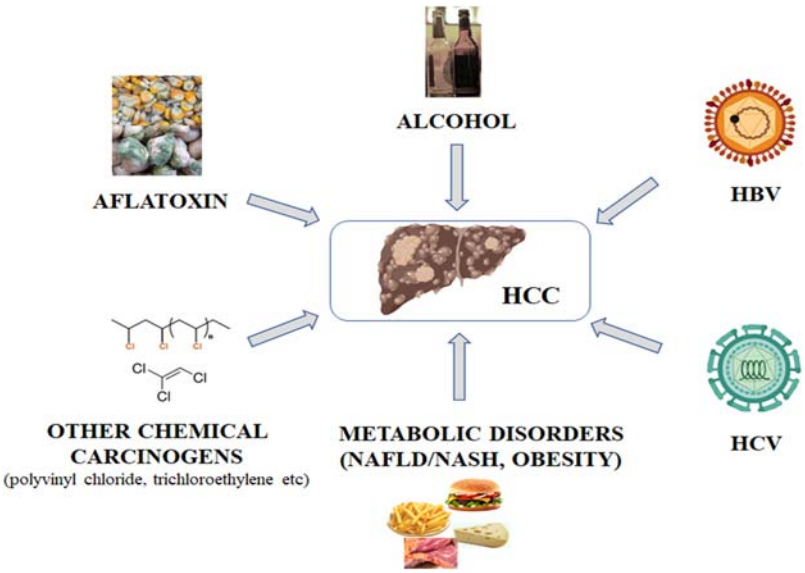

FIGURE 3.1 A number of risk factors contribute to the development of hepatocellular carcinoma.

contribute to a higher prevalence of HCC in Western countries. HCC develops in 2%–5% of cirrhotic patients with chronic HBV or HCV infection each year [1,11].

People who have been infected with HBV for a long time have a 5–100-fold increased risk of developing HCC [12]. Although HBV infection is asymptomatic in the early stages, 15%–40% of chronic HBV patients develop cirrhosis or cirrhosis-related complications over the course of their lives [13]. HBV DNA levels are higher in patients with chronic HBV infection, which is one of the major risk factors for the development of HCC. The most effective treatments focused on lowering HBV DNA levels rather than eradicating the infection completely [14].

Alcohol

Worldwide, alcohol consumption is the second leading cause of HCC [15]. In developed countries, particularly the United States and Europe, alcohol consumption is higher, and it is one of the leading causes of HCC in these regions [16]. Excessive alcohol consumption increased the risk of cirrhosis and HCC in a linear dose–response relationship [17]. When alcohol consumption exceeds 80 g a day for more than 10 years, the risk of HCC is expected to rise by five to seven folds [18]. Multiple studies have shown that alcohol use, either alone or in combination with HBV, HCV, and diabetes, causes HCC [19].

NAFLD-/NASH-induced HCC

NAFLD is the most common liver disease, accounting for nearly 25% of all liver diseases worldwide [1]. NAFLD is characterized by a number of liver diseases, including

triglyceride accumulation, apoptosis, inflammation, and fibrosis, collectively known as NASH [20]. NAFLD has emerged as a major risk factor for HCC in recent years, with studies indicating that it can increase the risk of HCC by up to 2.6 fold. Apart from NASH and NAFLD caused by cirrhosis, noncirrhotic NASH or benign steatosis has also been linked to HCC development [21].

Patients with NAFLD can develop a variety of liver diseases, ranging from simple steatosis to liver cell injury, as a result of triglycerides accumulation in their livers. NASH is the first stage of the inflammatory phase of NAFLD, which occurs in people who drink little or no alcohol [22]. The metabolic syndrome is key to the link between NASH and HCC. NASH causes inflammation, hepatocellular injury, and fibrosis, all of which raise the risk of HCC, which has a high mortality rate. NAFLD is the hepatic manifestation of metabolic syndrome and is associated with obesity and diabetes [23]. Metabolic syndrome is associated with the lipid accumulation in the liver. Excessive lipid accumulation leads to oxidative stress and mitochondrial dysfunction. Changes in lipid metabolism, changes in the immune system, and changes in growth and development pathways are all procarcinogenic processes caused by mitochondrial damage [24].

Aflatoxins

Aflatoxins are mycotoxins with a strong hepatocarcinogenic effect that can be found in a variety of cereals and oilseeds [25]. About 25% of the world's crops are thought to be contaminated with aflatoxins. In Western countries, exposure to aflatoxins is minimal, while in some West African countries, due to insufficient postharvest processing, more than 90% of the general population is exposed to aflatoxins [26]. Aflatoxin exposure is thought to be one of the causes of HCC, as evidenced by the presence of multiple aflatoxin contaminations in areas where HCC is prevalent [27]. The toxic metabolites of aflatoxin enter the human system through polluted animal and plant products eaten as food, particularly grains. There are nearly 18 aflatoxins identified, but 4 of them, AFB 1, AFB 2, AFG 1, and AFG 2, have been proven to carcinogenic in both animals and humans [28].

Other chemical toxicants

Exposure to hazardous chemicals at workplace is also a possible risk factor for HCC [29]. Workers are frequently exposed to a broad range of hazardous chemical agents as a result of a variety of workplace practices. The liver is the primary detoxifying organ, and it is responsible for all xenobiotics that enter the body. The liver is the main target organ because it is the primary site for a number of metabolic and excretory processes. Hepatotoxicity is caused by toxic chemicals carcinogens such as polyvinyl chloride, polychlorinated biphenyls, pyrethrins, chlordane, and dithiothreitol, which cause cholestatic injury, hepatocellular damage, fatty liver, fibrosis, and cirrhosis, as well as malignancies such as HCC [30]. Trichloroethylene, arsenic, cadmium, lead, thallium, and nickel, among other toxic metals found in contaminated ground water, have negative effects on the liver [31,32].

Mechanisms of action

Hepatitis B virus infection

HBV is a DNA-coated Hepadnaviridae virus. HBV is a reverse-transcribed, partially double-stranded DNA virus that is noncytopathic. The structural core protein (HBc), envelope proteins, reverse transcriptase, and an oncoprotein called the regulatory hepatitis B X protein (HBx) are all encoded by this viral genome [33,34]. These proteins play a crucial role in the progression of HCC. The size of the envelop protein is divided into three parts: small (S), medium (M), and large (L). To complete the replication process, the N-terminal extensions of the M and L types of envelop proteins interact with the endoplasmic reticulum (ER) membrane. Noncircularized HBV genomes have been confirmed to integrate into the hepatocellular genome after previously being thought to be unrelated to the virus's life cycle [35].

HBV can trigger HCC in a number of ways, including oxidative stress and viral proteins [36]. As a result of the incorporation of HBV DNA into the host genome, HBx mediates a specific mechanism that alters the expression of endogenic genes or promotes chromosomal instability [37]. Physical interactions between the virus and the ER trigger HBV-induced hepatocarcinogenesis by aggravating ER stress and ultimately triggering oxidative stress, which activates multiple signaling pathways, inducing mutations and triggering hepatic stellate cells (HSCs) [38]. Microdeletions of cancer-relevant genes such as telomerase reverse transcriptase (TERT) and mitogen-activated protein kinase 1 (MAPK1) from host DNA are frequently associated with HBV genome integration [39]. SRC (Proto-oncogene tyrosine-protein kinase Src) tyrosine kinases, Ras, Raf (rapidly accelerated fibrosarcoma), MAPK, extracellular signal–regulated protein kinase, JNK (Janus kinase), and other growth-control genes are all affected by HBx transcriptional activation activity [40]. Finally, HBx binds to and inactivates the tumor suppressor gene p53, resulting in uncontrolled cellular proliferation, compromised cell survival, and DNA-damage checkpoints (Fig. 3.2) [41].

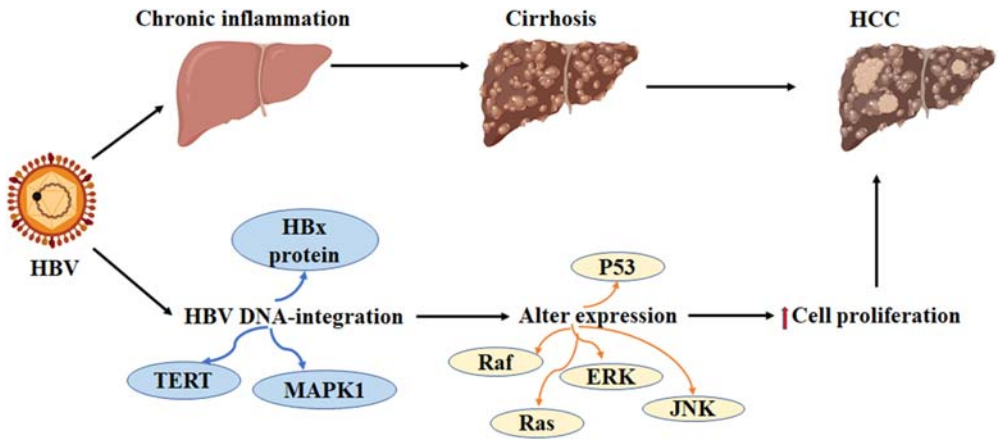

FIGURE 3.2 Mechanism of HBV involved in progression of HCC. *HBV*, Hepatitis B virus; *HCC*, hepatocellular carcinoma.

At the molecular and cellular levels, the HBx has a variety of functions, including disrupting apoptosis in hepatocytes and modulating DNA-binding specificity via transcriptional regulation of the p53 tumor suppressor gene, which is important in the progression of HCC [42,43]. The HBx is also involved in cell cycle progression and cellular signaling. The HBx interacts with a variety of host factors to activate the Ras–Raf–MAPK pathway, Src-dependent pathway, phosphatidylinositol 3-kinases (PI3K)–Akt pathway, nuclear factor-κB (NF-κB)/STAT-3 pathway, and wnt/-catenin pathway to maintain its genetic stability [44]. HBx alters the methylation profiles of oncogenes and tumor suppressor genes, as well as the acetylation of histone proteins in tumor-related genes and changes in many microRNAs, resulting in epigenetic changes [45].

Hepatitis C virus infection

HCV infection causes one-third of all HCC cases worldwide, making it a global health concern. The onset of cirrhosis increases the risk of HCC cases from 1% to 8% in patients with chronic HCV infection [46]. HCC caused by HCV infection is a common sign that a liver transplant is necessary [47].

HCV is a single-stranded RNA virus that belongs to the Hepacivirus family and is noncytopathic. After translation, this RNA encodes a 3000 amino acid polyprotein that is degraded into structural (S) and nonstructural (NS) proteins by proteolysis. The core protein, the envelope E1 and E2 glycoproteins, and the p7 protein are structural proteins that make up the viral particle and are involved in viral morphology and host cell entry [48]. Nonstructural proteins NS1, NS2, NS3, NS4A/B, and NS5A/B are involved in genome replication, particle assembly, and infection [49]. HBV infection, obesity, insulin resistance, and steatohepatitis all contribute to the development of HCV-related HCC [9]. Immune-mediated chronic inflammation is thought to aid in the development of HCC during HCV infection. Interfering with a variety of cell pathways that control energy metabolism, cell proliferation, and apoptosis can also cause HCC [50]. HCV can cause double-stranded DNA breaks, which can lead to mutations in genes such as BCL-6, TP53, immunoglobulin genes, and β-catenin [51].

HCV infection is a leading cause of HCC, and it is mediated by viral-induced factors as well as the host's immune response. Interactions of structural and nonstructural proteins with various host cellular proteins alter hepatocytes slightly (Fig. 3.3). HCV replicates in the cytoplasm of hepatocytes after integrating its genome into the host DNA. HCV-associated HCC is caused by virus-induced, often indirect, deregulation of host cellular processes such as liver cell proliferation and steatosis, oxidative stress and inflammation inducing mutations and genome instability, mitochondrial dysregulation, and generation of free radicals [52].

HCV may also cause HCC in the host cell by interfering with cellular regulatory pathways such as insulin resistance, proliferation, epithelial-to-mesenchymal *trans*-differentiation (EMT), apoptosis, DNA repair, and oxidative stress [49]. HCV core proteins, as well as various NS proteins, may all play a role in HCV-related HCC development and progression. HCV viral proteins can cause HCC by activating signaling pathways that promote cell division and growth, and also by inhibiting tumor suppressor genes [53].

The HCV core protein can cause lipogenesis and an increase in reactive oxygen species (ROS) production, which can lead to mitochondrial oxidation and oxidative stress metabolism

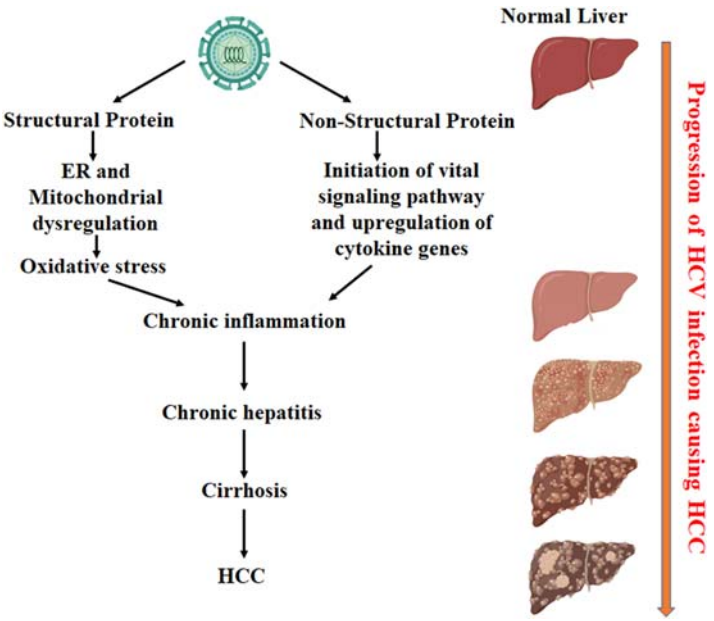

FIGURE 3.3 Mechanism of HCV involved in the progression of HCC. *HCC*, Hepatocellular carcinoma; *HCV*, hepatitis C virus.

problems [54]. HCV core protein inhibits tumor suppressor genes like p53 and retinoblastoma protein. The loss of p53 and retinoblastoma work together to cause a higher degree of HCC. P73 and P21, two tumor suppressor proteins, interact with core protein as well as tumor necrosis factor-α (TNF) signaling or a Bcl-2 family member that regulates apoptosis [55]. The HCV protein core also affects cell cycle signaling pathways by increasing cyclin E/Cdk2 levels, as well as RAF/MAPK, which promotes cell proliferation and development by inducing Wnt/-catenin and transforming growth factor (TGF)-β signaling pathways [56–58]. All of these pathways point to a role for this protein core in reducing apoptosis and promoting cell proliferation as HCC progresses. The E1/E2 structural proteins inhibit dsRNA protein kinase (PKR) and promote cell proliferation and survival by inhibiting NK (Natural Killer) or T-cell activation and the MAPK/extracellular signal regulation via the inclusion of transcription factor ATF-2 [59].

The nonstructural protein component of HCV aids in the growth of HCC through inducing TGF-β and activating HSCs. The TP53, TERT, and β-catenin genes are commonly mutated in HCC. Mutations of these genes impend telomere maintenance, which ultimately leads to increased oxidative stress. Nonstructural protein NS2 induces expression of cyclin E by triggering cyclin D/CDK4 and also play significant role in the process of apoptosis by intrusion with p53 pathway [60]. NS3, a nonstructural protein, regulates a number of signaling pathways that have the potential to transform cells. In addition, it interacts with protein kinase A and prevents it from translocating to the nucleus. It involves preventing immune surveillance by inhibiting type-1 interferon induction mediated by interferon response factor (IRF-3). Further, by targeting adaptor molecules in the TLR3 and RIG-1 signal pathways, NS3/4A inhibits IRF-3 transcription factor activation and promotes cell proliferation [61].

The other, nonstructural protein, NS5A is a transcription factor activator involved in cell proliferation and apoptosis inhibition via the cell cycle, Bcl-2, PI3K, Wnt/-catenin signaling, and mTOR (mammalian target of rapamycin) signaling [62]. It disrupts the PKR-p38 signaling pathway, resulting in abnormal mitosis, inhibits TGF signaling, preventing SMAD (Mothers against decapentaplegic (MAD) homolog) proteins nuclear translocation, and inhibits TNF-mediated apoptosis [63]. It affects the EMT pathway and aids in the conversion of epithelial cells to mesenchymal stem cells. TGF and NS5A work together to activate stellate cells, which leads to fibrosis. NS5B relocates Rb back into the cytoplasm after binding with it. E2F sensitive genes were activated to induce cell cycle progression due to the proteasomal degradation [64] (Fig. 3.4).

Alcohol

Excessive alcohol consumption activates Kupffer cells by stimulating monocytes. Activated Kupffer cells release chemokines and cytokines such as interleukin-6 (IL-6), TNF, and prostaglandin E2. Chronic hepatocyte regeneration–destruction, HSC activation, cirrhosis, caused by these cytotoxic effects, eventually lead to HCC [65]. Cirrhosis is one of the most important factors in the progression of HCC. Alcohol, on the other hand, can cause HCC through oxidative stress, inflammation, and endotoxemia. Acetaldehyde, which is produced from ethanol by the enzyme alcohol-dehydrogenase (ADH), disrupts the redox balance in mitochondria and inhibits hepatocyte-oxidation, leading to an increase in fatty acid oxidation and lipogenesis, which promotes steatosis and inflammation [66]. Acetaldehyde is a naturally occurring highly toxic and carcinogenic substance.

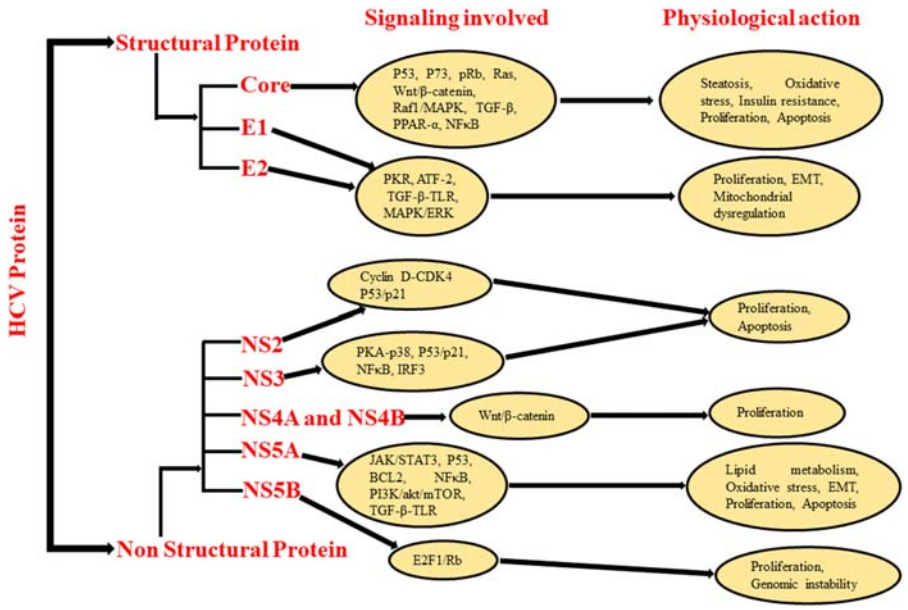

FIGURE 3.4 Role of different HCV proteins in the progression of HCC. *HCC*, Hepatocellular carcinoma; *HCV*, hepatitis C virus.

ADH-positive tumor cells have a high capacity for alcohol oxidation but a limited ability to remove acetaldehyde [67]. Excessive alcohol consumption activates cytochrome CYP2E1, which boosts acetaldehyde production in the liver. Accumulation of acetaldehyde causes mitochondrial dysregulation, which leads to an accumulation of ROS, which contributes to alcohol-induced oxidative stress in hepatocytes. Furthermore, the aggregation of intracytoplasmic lipid droplets in alcohol-induced steatosis may make hepatocytes more vulnerable to toxic effects [68]. Enzymatic inactivation, lipid peroxidation, and DNA mutations may all result in cellular damage and inhibit apoptosis when there is an excess of ROS produced in combination with the accumulation of injured proteins [18]. As levels of ROS increase, lipid peroxidation products such as malondialdehyde and 4-hydroxy-2-nonenal are produced, causing a mutation in the p53 gene at codon 249, which prevents cell apoptosis and promotes cell proliferation [69,70]. These lipid peroxidation products also result in the formation of HCC-causing mutagenic DNA adduct (Fig. 3.5).

DNA adducts such as *N*2-ethyl-20-deoxyguanosine and *N*2-propanol-20-deoxyguanosine can be formed by acetaldehyde, which is capable of initiating replication errors and alter the integrity of hepatocyte DNA [71,72]. The *O*6-methylguanosyl transferase, for example, forms adducts that weaken the process of DNA repair and can play a role in HCC [73]. Acetaldehyde may also form stable adducts with proteins, causing structural and functional changes. Furthermore, acetaldehyde destroys mitochondria, causing fatty acid oxidation to be inhibited. Acetaldehyde stimulates the synthesis of collagen in HSCs, which is a crucial step in the progression of cirrhosis and the growth of HCC. ROS are important mediators of tumor angiogenesis and metastasis, resulting in the activation of the NF-κB signal [74]. Iron overload and TNF-α from inflammatory cells also influence the production of ROS. Chronic alcohol intake also increases intestinal iron absorption and hepatic iron storage. Iron overload causes breakdown of DNA strands and mutation of p53 gene, which could cause HCC [75].

NAFLD-/NASH-induced HCC

The pathogenic pathways involved in HCC induced by NAFLD/NASH can be linked to metabolic syndrome and obesity-induced chronic inflammation [76]. Insulin resistance

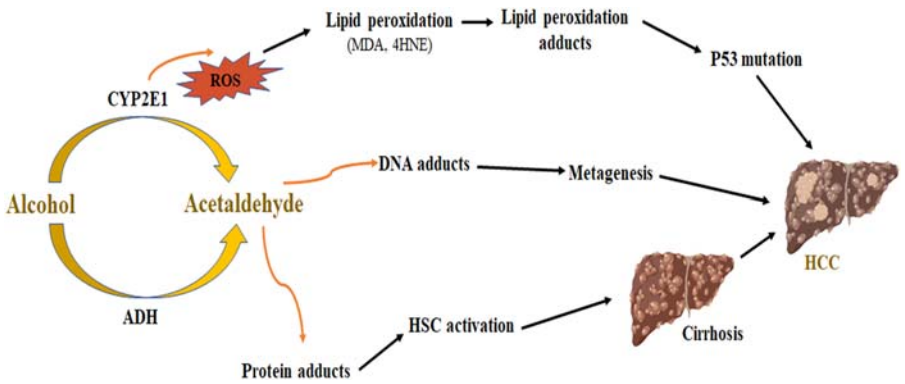

FIGURE 3.5 Alcohol-induced pathways involved in the progression of HCC. *HCC*, Hepatocellular carcinoma.

plays major role as one of the mediators, whether or not there is severe fibrosis or cirrhosis. Fig. 3.6 shows the interactions between NAFLD-/NASH-induced mechanisms leading to HCC. NAFLD is primarily caused due to the modulation of caloric excess by poor diet and a sedentary lifestyle [77]. Insulin resistance plays a critical role in this pathophysiological mechanism, as it leads to an increase in liver fat accumulation due to an increase in free fatty acid deposition (FFAs). The abundant amount of FFAs deposition cause lipotoxicity that promotes oxidative stress, protein misfolding and mitochondrial impairment within liver cells. ROS overproduction causes mitochondrial damage, lipid peroxidation, inflammation, and HSC activation, which leads to necrosis, cirrhosis, and HCC [78]. Insulin tolerance, lipid accumulation, apoptosis, and inflammation are all related to NAFLD pathogenesis by dysregulated ER stress in the liver (Fig. 3.6).

Metabolic stress increases ROS production and induces inflammatory cytokine release from liver cells, which triggering the JAK2/STAT (signal transducer and activator of transcription), MAPK, and PI3K signaling pathways in HCC cells by binding to their receptors [79]. TNF-α is promoting the progression of HCC activating hepatic progenitor cells, and IL-6 activates an oncogenic transcription factor that promotes cell proliferation and inhibits apoptosis, playing a role in the progression of NASH-related HCC [80].

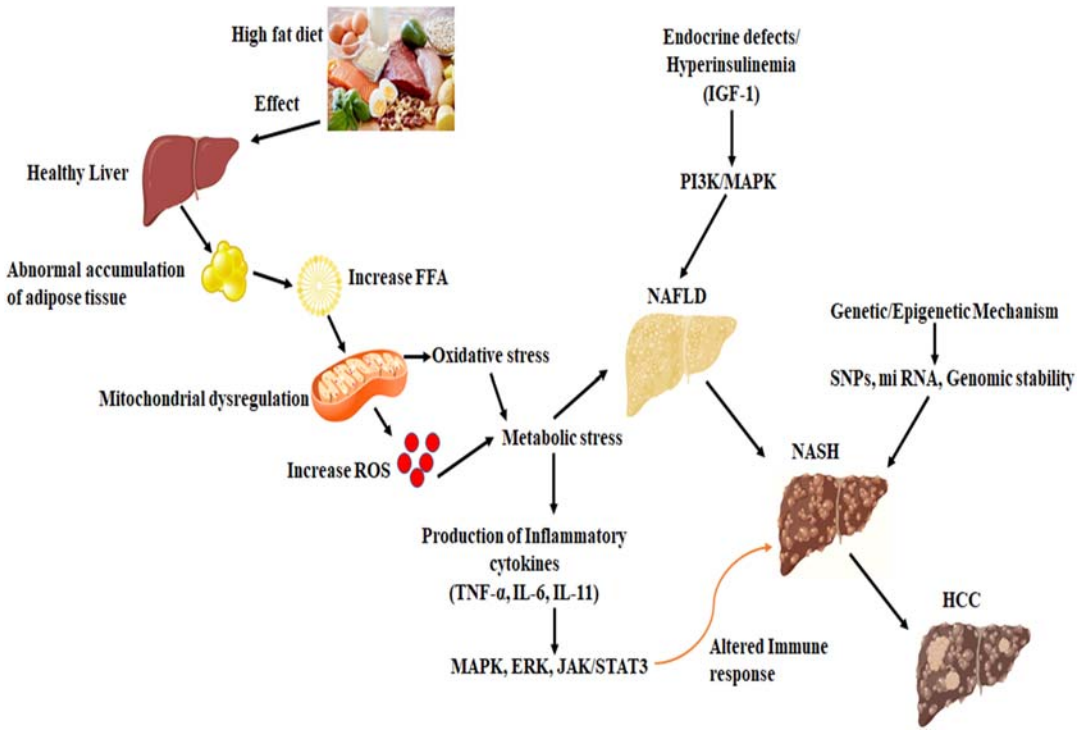

FIGURE 3.6 Interactions between NAFLD-/NASH-induced mechanisms leading to HCC. *HCC*, Hepatocellular carcinoma; *NAFLD*, nonalcoholic fatty liver disease; *NASH*, nonalcoholic steatohepatitis.

Several hormones, including insulin and insulin-like growth factor 1 (IGF-1), play important roles in developing NAFLD-related HCC [81]. Insulin resistance and hyperinsulinemia are often responsible for this to happen. Insulin and IGF-1 activate the PI3K and MAPK pathways through a cascade of signaling by binding to their respective receptors. Both the pathways are critical in the origination and progression of HCC since they regulate proliferation and apoptosis in the cell.

Several single nucleotide polymorphisms, several microRNAs (miRNAs), and genetic instability are also encouraging NASH to HCC progression [82]. Exome-sequencing study of HCC identified key mutations in some oncogenic genes, including TERT involved in p53 and Wnt/β-catenin signaling pathway. It also facilitates the binding of nucleotides to the ends of eukaryotic chromosomes [83]. Epigenetic changes, such as abnormal DNA methylation, silenced DNA repairing genes, metabolism of lipids and fibrosis progression, are also key factors in NASH progression [84]. Noncoding RNAs such as miRNAs interfere with transcription and translation by suppressing gene expression. These miRNAs involved in major cell signalings, pathways, including Wnt/β-catenin, MAPK, TGF-β, and PI3K/AKT/mTOR can be triggered in HCC [85].

Aflatoxins

Aflatoxin is mainly metabolized in the liver cells [86]. As a result of aflatoxin exposure, DNA adducts form in hepatocytes, activating the mutation site of the tumor suppressor gene p53, indicating aflatoxin's direct involvement in HCC [87]. The p53 gene induces apoptosis and cell cycle arrest, which contributes to the deactivation of mutations in the p53 gene or other pathway mechanisms, which can reduce hepatocyte susceptibility to other cancer-causing agents that trigger oncogenic pathways and influence the production of HCCs [88].

Aflatoxin carcinogenicity has been linked to hepatocytes, where they are first metabolized into reactive intermediate metabolites. AFB1-exo 8,9-epoxide, the first intermediate product of AFB1 metabolism by microsomal cytochrome enzyme, is one of the most well-studied aflatoxins (CYP450). This is thought to be the most serious cause of genotoxicity. The International Agency for Research on Cancer classified the most harmful hepatic carcinogen, AFB1, as a type I human carcinogen in 1993 [89]. CYP3A4, CYP3A5, CYP3A7, and CYP1A2 are cytochrome P 450 enzymes that transform aflatoxins to AFB1 in the liver. AFB1 is gradually converted into the AFB1 form amidopyrimidine adduct, a cancer-causing agent. AFB1 metabolites interact with DNA by alkylating bases, causing cell cycle disruption and mutations in the tumor suppressor gene p53 [90]. The most common mutations in the TP53 tumor suppressor gene (AGG to AGT), which result in the substitution of arginine for serine, are transversions [91]. When AFB1 binds to DNA, it forms a promutagenic adduct called 8,9 dihydro-8-(N7-guanyl)-9-hydroxy AFB1 (AFB1-N7-Gua), which can be transformed into secondary byproducts, including an apurinic site and AFB1-form amidopyrimidine (AFB1-FABY). This adduct causes a transverse mutation from guanine (G) into thymine (T) (Fig. 3.7).

There is a direct connection between HBV and aflatoxin exposure in HCC risk [92]. Chronic HBV infection activates the cytochrome P450s enzyme, which converts inactive AFB1 to the mutagenic AFB1−8,9-epoxide, which binds to the guanine base and causes

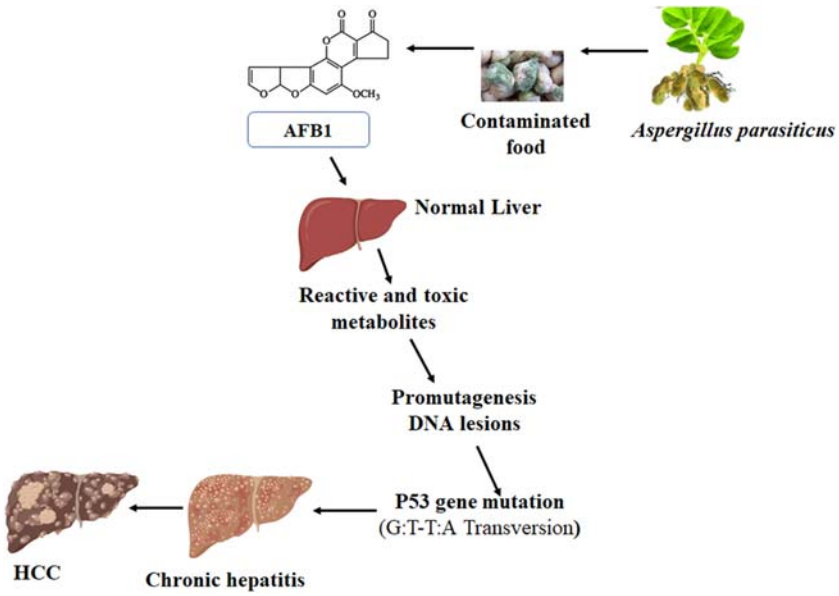

FIGURE 3.7 Interactions between aflatoxin-induced mechanisms leading to HCC. *HCC*, Hepatocellular carcinoma.

mutations [93]. Chronic HBV infection induces hepatic cell necrosis, which raises the risk of AFB1-induced TP53 mutations. In addition, the oncogenic HBV protein inhibits nuclear excision repair, which is responsible for removing AFB1–DNA adducts [94].

Others

Chemical solvents (aromatic, chlorinated, toluene, dioxin, xylene, and alicyclic hydrocarbons) and trichloroethylene and perchloroethylene have been linked to exacerbating liver damage, which may contribute to the production of HCC [95]. These chemical compounds (dichlorodiphenyltrichloroethane and nitrosamines) can interact with proteins and nucleic acids and induce a cancer-causing condition in the liver. Because of the toxicity of these metabolites, they can be oxidized to form an increase in ROS output. Overproduction of ROS activates signaling pathways that promote hepatic inflammation, apoptosis, necrosis, and HCC growth. They also shorten telomeres and regulate the CYP3A1 gene, all of which have oncogenic effects [96,97].

Conclusion

The pathogenesis of HCC is an elaborated and multitiered process that comprises diverse cellular and molecular signaling pathways. Chronic HBV and HCV infection, NAFLD/NASH, alcohol intake, aflatoxin, chemical contaminants, and genetic disorders

are all considered to raise the risk of HCC progression, making it a significant public health issue. The mechanisms underlying all of this toxicant-induced hepatic carcinogenesis are complex and vary depending on the etiologic factors. These toxic agents increase oxidative stress, inflammation, dysregulation of lipid metabolism, fibrosis, cirrhosis, and disruption of the host immune system resulted in chromosomal instability and gene expression changes. Other factors that have been related to the production of HCC include genomic methylation and miRNA expression. Furthermore, toxic metabolites formed by these toxicants are likely to function simultaneously and in concert to trigger cellular signaling, genetic, and epigenetic mechanisms that promote HCC progression. Understanding the potential mechanisms underlying these HCC-related risk factors will aid in the development of novel therapeutic strategies to reduce HCC-related morbidity and mortality. Further studies on the mechanisms and metabolism of carcinogenic agents that mediate the oncogenic process are needed.

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VOLUME 1

Theranostics and Precision Medicine for the Management of Hepatocellular Carcinoma

Biology and Pathophysiology

Edited by

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

Sujatha Peela, Department of Biotechnology, Dr. BR Ambedkar University, Srikakulam, AP, India

Theranostics and Precision Medicine for the Management of Hepatocellular Carcinoma provides comprehensive information about ongoing research as well as clinical 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.

The first volume, **Biology and Pathophysiology**, discusses topics, such as tumor microenvironment in hepatocellular carcinoma (HCC), endoplasmic reticulum stress and unfolded protein response, effects of cirrhosis and hepatitis on the prognosis of HCC, mitochondrial metabolism, next-generation sequencing, and telomerase. In addition, it discusses exosome's role in HCC progression and metastasis, and chemokines.

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

Key features

- Provides updated literature review and detailed understanding of liver cancer tumor biology
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