

Contents

<i>Contributors</i>	<i>ix</i>
<i>Preface</i>	<i>xi</i>
1. Hepatocellular carcinoma (HCC): Epidemiology, etiology and molecular classification	1
Saranya Chidambaranathan-Reghupaty, Paul B. Fisher, and Devanand Sarkar	
1. Introduction	6
2. Etiology and risk factors	6
3. Liver cancer staging	31
4. Molecular classification of HCC	34
5. Discussion	47
Acknowledgments	48
References	48
2. Signaling pathways in hepatocellular carcinoma	63
Teresa García-Lezana, Juan Luis Lopez-Canovas, and Augusto Villanueva	
1. Introduction	64
2. Pathways involving growth factors	65
3. Pathways involved in cell differentiation and development	72
4. Nuclear signaling pathways	79
5. Emerging pathways	82
6. Conclusions	87
Acknowledgment	87
Conflict of interest	87
References	87
3. Hepatitis C virus associated hepatocellular carcinoma	103
Mousumi Khatun, Ranjit Ray, and Ratna B. Ray	
1. Introduction	104
2. HCV infection and immune responses	106
3. Risk factors for development of HCC from chronic infection	108
4. HCV regulation on metabolic pathways	109
5. Mechanisms of HCV associated HCC	111

6. Biomarkers for detection of HCV associated HCC	122
7. Therapeutic strategies for HCV associated HCC	123
8. Perspectives	125
Acknowledgments	127
References	127
4. NAFLD-related HCC	143
Bubu A. Banini and Arun J. Sanyal	
1. The problem of NAFLD-related HCC	144
2. Metabolic syndrome and NAFLD in driving HCC	146
3. NAFLD-related HCC	149
4. Molecular mechanisms of NAFLD-related HCC	150
5. Prevention and surveillance of NAFLD-related HCC	156
6. Management of NAFLD-related HCC	157
7. Conclusions/future directions	158
Acknowledgment	159
Disclosures	159
References	160
5. Atypical immunometabolism and metabolic reprogramming in liver cancer: Deciphering the role of gut microbiome	171
Rachel M. Golonka and Matam Vijay-Kumar	
1. Hepatocellular carcinoma (HCC): A heterogenous and complex liver disease	174
2. Gut microbiota dysbiosis as an identifier of HCC	177
3. HCC microenvironment favors immunosuppression: Is gut microbiota a driver of this immunologic signature?	179
4. Hijacking energy sources: Does gut microbiota have an influence on metabolic reprogramming in HCC?	201
5. Immunological and gut microbiota therapeutics for HCC	209
6. Summary and future perspectives	217
Acknowledgment	218
References	218
6. Systemic therapy of liver cancer	257
Tarik Demir, Sunyoung S. Lee, and Ahmed O. Kaseb	
1. Introduction	258
2. Staging	259
3. Liver function	260
4. Current systemic treatment	262

Contents

5. Histological variants	283
6. Conclusion	285
Acknowledgment	286
References	286
7. Immunotherapy in hepatocellular cancer	295
Christos Fountzilas, Rachel Evans, Sabah Alaklabi, and Renuka Iyer	
1. Introduction	295
2. Immune checkpoint inhibitors in hepatocellular carcinoma	298
3. Future directions	307
4. Conclusion	312
References	312
8. Intrahepatic cholangiocarcinoma: Morpho-molecular pathology, tumor reactive microenvironment, and malignant progression	321
Alphonse E. Sirica, Mario Strazzabosco, and Massimiliano Cadamuro	
1. Introduction	322
2. iCCA classification, cell origins, and molecular subtypes	324
3. Fibroinflammatory cholangiopathies, mechanisms, and cholangiocarcinogenesis	339
4. The desmoplastic reaction and iCCA progression	344
5. Immune milieu in iCCA	355
6. Challenges and clinical implications	359
Grant Support	367
Conflict of interest statement	367
References	367