Chapter 1

Introductory Chapter: Liver Cancer, Risk Factors and Current Therapies

Ahmed Lasfar

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.81720

1. Introduction

Liver cancer is one of the major cancers in the world [1]. Hundreds of thousand people are diagnosed each year with liver cancer. Unfortunately, liver cancer is the second most common cause of deaths associated with cancer complications, accounting for more than 70%. Hepatocellular carcinoma (HCC) is the most prevalent type of liver cancer [2]. More than two-third of patients newly diagnosed with HCC are aged >65 years, and this number is expected to increase as the world population ages [3]. Furthermore, there is heterogeneity in the aging process, which further contributes to the complexity of treatment decisions [4, 5].

HCC originates from normal hepatocytes. Hepatocytes are the cells forming the parenchymal tissue of the liver and make up the majority of liver's mass. Hepatocytes play a crucial role in liver functions [6]. They are involved in many biological processes including the metabolism of carbohydrates and lipids, protein synthesis, and notably body detoxification from harmful substances. Important proteins such as serum albumin, prothrombin, transferrin, fibrinogen, and complement are generated by hepatocytes. In addition to their main role in glycogenesis, hepatocytes make fatty acids from carbohydrates leading to triglyceride synthesis. Hepatocytes are highly involved in lipid metabolism and cholesterol synthesis. The detoxifying activity of hepatocytes includes drug metabolism, modification of endogenous compounds such as steroids and ammonia. However, hepatocytes might be overwhelmed with harmful agents and targeted with many hepatic viruses, leading to liver damage and ultimately to HCC [7]. The hepatocytes are commonly used for research in both academia and pharmaceutical industry in order to investigate the mechanisms of carcinogenesis, viral infections, and drug metabolism. Currently, highly innovative research in epigenetics and immunology is taken place in order to explore further liver diseases and develop novel therapies for HCC.

2. Epigenetic of HCC

Epigenetic modifications are crucial in HCC. They arise in the context of known risk factors leading to chronic liver disease and concern mostly chemical alterations of DNA and histones. DNA methylation is the commonly investigated, showing its relevance in the mechanisms of gene silencing. Currently, genome-wide methylation analysis indicates important changes in the methylation status of oncogenes, signaling molecules, and suppressor genes [8]. Therefore, targeting the epigenome could lead to novel therapies of HCC.

3. Immunogenicity of HCC

Tumor immunogenicity of HCC has been first demonstrated by using autologous tumor lysate and dendritic cells for the prevention of recurrence in HCC patients. Subsequently, several tumor-associated antigens (SART2, CypB, SART3, AFP p53, MRP3, and hTERT) have been identified and characterized in HCC, suggesting the development of highly effective immunotherapy [9, 10].

The modulation of immune costimulatory molecules has been also shown to play critical role in the pathogenicity of the liver. The costimulatory ligand member B7 is a crucial immune checkpoint in HCC [11]. B7-1, B7-2, B7-DC, and B7-H1 are expressed on professional antigen-presenting cells and regulate T cell activation after the binding with CD28, CTLA-4, or PD-1. B7-H3 is expressed in human HCC cells and is associated with tumor aggressiveness and post-operative recurrence [12]. Apparently, B7-H3 promotes aggression and invasion of HCC by targeting epithelial-to-mesenchymal transition via JAK2/STAT3/Slug signaling pathway [13].

4. Common risk factors for HCC

The major common risk factors for HCC are hepatic virus infection with HBV and HCV. Fatty liver disease, related or unrelated to alcohol abuse which frequently lead to liver cirrhosis, is the other major condition, increasing the risk for developing HCC (**Figure 1**).

4.1. Hepatitis B virus (HBV) infection

HBV is one of the most common etiologic factors leading to HCC worldwide. The risk of developing HCC is more than 15-fold in patients with HBV chronic infection [2, 14]. In most developed countries, around of 10% of HCC is associated with HBV infection which occurs through either parental contact with infected blood or sexual transmission. In contrast, other geographic regions in the world where HBV is endemic such as sub-Saharan Africa and Asia, HBV transmission occurs mainly via perinatal exposure [15, 16].

HBV patients are highly prone to secondary infection with hepatitis D virus (HDV). The HDV is dependent on HBV genome products to form its own. Infection with HDV is more frequent

http://dx.doi.org/10.5772/intechopen.81720

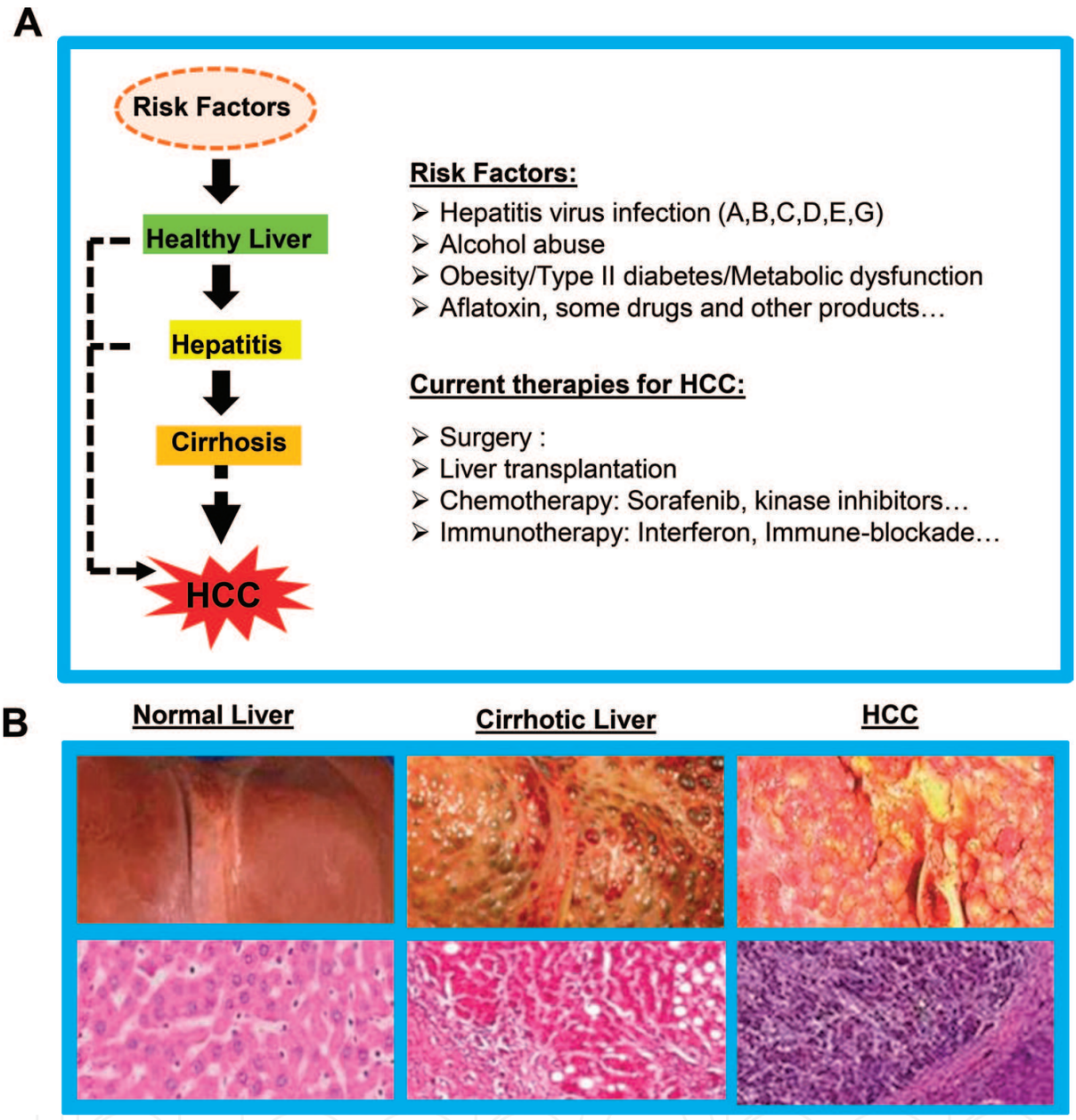

Figure 1. Risk factors and current therapies of liver cancer. Hepatocellular carcinoma (HCC) is the most prevalent type of liver cancer. A. Hepatocytes, the main liver cells are subjected to harmful conditions (hepatitis virus infections) causing hepatitis and frequently leading to cirrhosis and ultimately to HCC. Many treatment options are currently available for HCC. B. Gross anatomy and histology of healthy liver and liver diseases related to cirrhosis and HCC.

in sub-Saharan Africa, Mediterranean regions, and South America [17]. At least eight HDV genotypes, geographically distributed in different regions of the globe, have been reported. An estimated 20 millions of people are infected with one of HDV genotype. In combination with HBV infection, HDV precipitates liver failure and HCC [18]. The best treatment for HDV infection is the eradication of HBV through HBV vaccine.

Currently, 10 HBV genotypes have been described. Apparently, HBV-infected patients with C and D genotypes develop more frequently liver cirrhosis and HCC than HBV patients,

infected with the other genotype strains. Furthermore, those patients respond poorly to current therapies based on interferon or other antiviral agents [15, 16].

4.2. Hepatitis C virus (HCV) infection

HCV infection is also one of the frequent risk factors in developing HCC in the word. The risk of HCC is very high in patients chronically infected with HCV [19]. Coinfection with HIV or HBV increased this risk further. The high majority of coinfected patients with either HIV or HBV precipitate chronic hepatitis, leading to HCC. Suppression of HCV load by IFN therapy, apparently, participates in reducing the onset of HCC [20]. However, concerns regarding the impact of HCV direct-acting agents (DAAs) on the incidence of HCC continue to be raised in clinic [21]. The potential increased risk of HCC in HCV patients under DAAs therapy has been reported [22]. Therefore, interferon therapy should not be discontinued at least for HCV patients with high risk of HCC.

4.3. Alcohol abuse

Evidence shows that long-term alcohol use is responsible for alcoholic liver disease (ALD) and a high risk of developing HCC [23]. ALD is well characterized; however, little progress has been made for its treatment. It is well established that alcohol is highly toxic to hepatocytes. By causing continuous cell necrosis, it induces perpetual regeneration of hepatocytes and paves the way to carcinogenesis [24]. In addition, alcohol causes liver damage by promoting inflammation that precipitates cirrhosis and leads to HCC [23]. The effect of alcohol on liver disease is boosted in people with viral hepatitis [25].

4.4. Nonalcoholic steatohepatitis (NASH)

NASH is a condition of fatty liver disease in which liver has abnormal fat accumulation and increased inflammation. Although the exact etiology of NASH remains unknown, the risk factors include obesity, type II diabetes, and related metabolic dysfunctions. NASH patients with no cirrhosis have no increased risk of HCC, indicating that induction of liver cirrhosis is a leading cause of HCC. However, the outcome of NASH is much similar as other chronic hepatitis such as HCV infection [26]. Although the risk of developing HCC might be lower in NASH patients than HCV patients, the severity of HCC and patient survival in both cases remain similar.

5. Liver cirrhosis and other risk factors for HCC

The majority of HCCs arise from liver cirrhosis, a condition in which liver tissue is replaced by scar tissue [27]. The scar tissue jeopardizes the blood flow through the liver and retains it from functioning correctly. Cirrhosis results mainly from different chronic hepatitis mainly due to viral infections and fatty liver disease related or unrelated to alcohol abuse. Currently, besides HBV, HCV, and HDV, three hepatitis viruses are identified and have been demonstrated to

induce hepatitis: hepatitis A virus (HAV), hepatitis E virus (HEV), and hepatitis G virus (HGV). However, HBV and HCV are the most common inducers of hepatitis-related virus infections. People chronically infected with both hepatitis B and C present higher risk for developing HCC.

Besides hepatitis virus infection and fatty liver disease related or unrelated to alcohol consumption, aflatoxin has been shown to increase the risk of developing HCC [28]. Aflatoxin is a family of fungus toxins that could be present at high levels in frequently consumed food such as nuts, grains, and spices that are not adequately selected or properly stored. Aflatoxin enters the food supply and can be found in animal and human-processed foods. Animals can pass aflatoxin derivative products into milk, eggs, and meat. Overweight and obesity constitute other independent risk factors for HCC. Therefore, in order to efficiently prevent hepatitis and HCC, raising awareness through general public education should be highly supported [29].

6. Treatment options for HCC

Currently, many options are available for the treatment of HCC [30]. Potentially curative treatments like surgical resection or liver transplantation might be possible for less advanced HCC. Minimally invasive surgical technologies continue to improve increasing its safety and applicability for oncologic liver surgery. Different surgical procedures, including advanced surgical technologies, are currently performed.

Unfortunately, tumor recurrence and metastasis frequently occur after resection and limit the overall survival. In patients with unresectable HCC and preserved liver function, transarterial chemoembolization (TACE) can prolong survival. However, TACE is rarely curative. More than half of patients with HCC continue to die secondary to liver failure from progressing cirrhosis. Current chemotherapy, interferon treatment, or alternative medicine only partially benefits patients with advanced disease. Therefore, novel treatments for liver cancer, particularly advanced HCC, are in urgent need [31].

Since the introduction of sorafenib, a multikinase inhibitor that showed some benefits to HCC patients, other targeted and immune therapies emerged for the treatment of HCC. Currently, promising therapies for HCC are underway, including targeted therapy, immune checkpoint inhibitors, oncolytic viruses (OVs), and chimeric antigen receptor-redirected T cells (CAR-T cells). Combination strategies are also under investigation to promote further the treatment of advanced HCC [32].

7. Emergence of immune checkpoint inhibitors

HCC patients with advanced disease, not eligible for currently curative procedures, particularly surgery or local interventions, were selected to test the efficacy of immune checkpoint inhibitors in clinical trials [11]. CTLA-4 blockade with tremelimumab showed a high promise

for controlling the tumor in patients with advanced HCC and HCV infections. This new therapeutic strategy opened the way for testing other immune checkpoint inhibitors, controlling other pathways such as PD-L1/PD-1. Furthermore evidences showing high expression of PD-L1/PD-1 in HCC patients support the use of PD-L1/PD-1 inhibitors. Indeed the result of PD-1 blockade with anti-PD-1 antibody (nivolumab) in a large phase II trial, regrouping HCC patients resistant to sorafenib is very promising [33, 34].

Although immunotherapy for HCC seems promising, important concerns regarding the selection of patients that could mostly benefit from this therapy are now under intensive investigation. In this regard, the mechanisms of resistance to immune checkpoint inhibitors and the identification of markers, predicting the response to immunotherapy need to be considered in selecting patients for treatment [35, 36].

In conclusion, promising results with immune blockade inhibitors have been currently published in HCC clinical trials, using anti-CTLA-4 agent tremelimumab and anti-PD-1 agent nivolumab. We believe that in the near future, immune-based therapies and combination with chemotherapeutic agents will bring a paradigm shift for treatment of advanced HCC.

Author details

Ahmed Lasfar[1,2]*

*Address all correspondence to: ahmed.lasfar@pharmacy.rutgers.edu

1 Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ, USA

2 Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA

References

[1] Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends—An update. Cancer Epidemiology, Biomarkers & Prevention. 2016;**25**:16-27

[2] Mak LY, Cruz-Ramón V, Chinchilla-López P, Torres HA, LoConte NK, Rice JP, et al. Global epidemiology, prevention, and management of hepatocellular carcinoma. American Society of Clinical Oncology Educational Book. 2018;**38**:262-279

[3] Borzio M, Dionigi E, Parisi GC, Raguzzi I, Sacco R. Management of hepatocellular carcinoma in the elderly. World Journal of Hepatology. 2015;**7**:1521-1529

[4] Spolverato G, Vitale A, Ejaz A, et al. The relative net health benefit of liver resection, ablation, and transplantation for early hepatocellular carcinoma. World Journal of Surgery. 2015;**39**:1474-1484

[5] Zhao LY, Huo RR, Xiang X, Torzilli G, Zheng MH, Yang T, et al. Hepatic resection for elderly patients with hepatocellular carcinoma: A systematic review of more than 17,000 patients. Expert Review of Gastroenterology & Hepatology. 2018;**5**:1-10

[6] Rui L. Energy metabolism in the liver. Comprehensive Physiology. 2014;(1):177-197

[7] Wu MY, Yiang GT, Cheng PW, Chu PY, Li CJ. Molecular targets in hepatocarcinogenesis and implications for therapy. Journal of Clinical Medicine. 2018;**7**(8). pii: E213

[8] Bhat V, Srinathan S, Pasini E, Angeli M, Chen E, Baciu C, et al. Epigenetic basis of hepatocellular carcinoma: A network-based integrative meta-analysis. World Journal of Hepatology. 2018;**10**(1):155-165

[9] Mizukoshi E, Nakamoto Y, Arai K, Yamashita T, Sakai A, Sakai Y, et al. Comparative analysis of various tumor-associated antigen-specific t-cell responses in patients with hepatocellular carcinoma. Hepatology. 2011;**53**(4):1206-1216

[10] Mizukoshi E, Yamashita T, Arai K, Sunagozaka H, Ueda T, Arihara F, et al. Enhancement of tumor-associated antigen-specific T cell responses by radiofrequency ablation of hepatocellular carcinoma. Hepatology. 2013;**57**(4):1448-1457

[11] Kudo M. Immuno-oncology in hepatocellular carcinoma: 2017 update. Oncology. 2017;**93**(Suppl 1):147-159

[12] Kang F-b, Wang L, Jia H-c, Li D, Li H-j, Zhang Y-g, et al. B7-H3 promotes aggression and invasion of hepatocellular carcinoma by targeting epithelial-to-mesenchymal transition via JAK2/STAT3/Slug signaling pathway. Cancer Cell International. 2015;**15**:45

[13] Sun TW, Gao Q, Qiu SJ, Zhou J, Wang XY, Yi Y, et al. B7-H3 is expressed in human hepatocellular carcinoma and is associated with tumor aggressiveness and postoperative recurrence. Cancer Immunology, Immunotherapy. 2012;**61**(11):2171-2182

[14] Singh AK, Kumar R, Pandey AK. Hepatocellular carcinoma: Causes, mechanism of progression and biomarkers. Current Chemical Genomics and Translational Medicine. 2018;**12**:9-26

[15] Yuen M-F, Chen D-S, Dusheiko GM, Janssen HLA, Lau DTY, Locarnini SA, et al. Hepatitis B virus infection. Nature Reviews Disease Primers. 2018;**4**:18035

[16] Greten TF, Sangro B. Targets for immunotherapy of liver cancer. Journal of Hepatology. 2018;**68**:157-166

[17] Lempp FA, Yi Ni Y, Urban S. Hepatitis delta virus: Insights into a peculiar pathogen and novel treatment options. Nature Reviews Gastroenterology & Hepatology. 2016; **13**:580-589

[18] Botelho-Souza LF, Pinheiro Alves Vasconcelos M, de Oliveira dos Santos A, Villalobos Salcedo JM, Souza Vieira D. Hepatitis delta: Virological and clinical aspects. Virology Journal. 2017;**14**:177

[19] Page A, Zunirah A, Sujan R, Singal AK. Hepatitis C virus and hepatocellular carcinoma: A narrative review. Journal of Clinical and Translational Hepatology. 2018;**6**(1):79-84

[20] Ishikawa T. Secondary prevention of recurrence by interferon therapy after ablation therapy for hepatocellular carcinoma in chronic hepatitis C patients. World Journal of Gastroenterology. 2008;**14**(40):6140-6144

[21] Butt AS, Sharif F, Abid S. Impact of direct acting antivirals on occurrence and recurrence of hepatocellular carcinoma: Biologically plausible or an epiphenomenon? World Journal of Hepatology. 2018;**10**(2):267-276

[22] Lee M-H. Risk of hepatocellular carcinoma for patients treated with direct-acting antivirals: Steps after hepatitis C virus eradication to achieve elimination. Translational Gastroenterology and Hepatology. 2018;**3**:15

[23] Ramadori P, Cubero FJ, Liedtke C, Trautwein C, Nevzorova YA. Alcohol and hepatocellular carcinoma: Adding fuel to the flame. Cancers (Basel). 2017;**9**(10):130

[24] IH MK, Schrum LW. Role of alcohol in liver carcinogenesis. Seminars in Liver Disease. 2009;**29**(2):222-232

[25] Dolganiuc A. Alcohol and viral hepatitis: Role of lipid rafts. Alcohol Research: Current Reviews. 2015;**37**(2):299-309

[26] Said A, Ghufran A. Epidemic of non-alcoholic fatty liver disease and hepatocellular carcinoma. World Journal of Clinical Oncology. 2017;**8**(6):429-436

[27] Schuppan D, Afdhal NH. Liver cirrhosis. Lancet. 2008;**371**:838-851

[28] Liu Y, Wu F. Global burden of aflatoxin-induced hepatocellular carcinoma: A risk assessment. Environmental Health Perspectives. 2010;**118**(6):818-824

[29] Liu Y, Chang CC, Marsh GM, Wu F. Population attributable risk of aflatoxin-related liver cancer: Systematic review and meta-analysis. European Journal of Cancer. 2012; **48**(14):2125-2136

[30] Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;**68**(2):723-750

[31] Hernaez R, El-Serag HB. How we approach it: Treatment options for hepatocellular carcinoma. The American Journal of Gastroenterology. 2018;**113**:791-794

[32] Daher S, Massarwa M, Benson AA, Khoury T. Current and future treatment of hepatocellular carcinoma: An updated comprehensive review. Journal of Clinical and Translational Hepatology. 2018;**6**(1):69-78

[33] Kudo M. Immune checkpoint inhibition in hepatocellular carcinoma: Basics and ongoing clinical trials. Oncology. 2017;**92**(Suppl 1):50-62

[34] Waidmann O. Recent developments with immunotherapy for hepatocellular carcinoma. Expert Opinion on Biological Therapy. 2018;**18**(8):905-910

[35] Pitt JM, Vétizou M, Daillère R, Roberti MP, Yamazaki T, Routy B, et al. Resistance mechanisms to immune-checkpoint blockade in cancer: Tumor-intrinsic and -extrinsic factors. Immunity. 2016;**44**(6):1255-1269

[36] Varekia SM, Garrigósb C, Duranb I. Biomarkers of response to PD-1/PD-L1 inhibition. Critical Reviews in Oncology/Hematology. 2017;**116**:116-124