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Chapter

Liver Cancer-Genesis, Progression and Metastasis

Aqsa Nazir, Muhammad Aqib and Muhammad Usman

Abstract

Liver cancer or hepatocellular carcinoma (HCC) is a malignant tumor in liver tissue and worldwide it is fourth leading death cause among all cancers. The most common causes of liver cancer are hepatitis B or C virus infections, alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH), smoking and obesity. The development and metastasis of liver cancer is a multistage and branched process of morphological and genetic traits. Various corresponding signaling pathways such as Yes-Associated Protein-Hippo Pathway (YAP-HIPPO), Wnt/β-catenin and inflammation by interleukin-6 (IL-6), tumor necrosis factor (TNF), nuclear factor-Kb (NF-κB), biological pathways including epithelial–mesenchymal transition (EMT), tumor microenvironment, tumor-stromal interactions and cancer stem cells and gut microbial dysbiosis are allied to both origination, progression and metastasis of liver cancer. Numerous therapeutic approaches are classified into different categories such as pharmacological therapy including sorafenib, lenvatinib and ramuciruma, surgery of HCC patients includes surgical resection, adjuvant therapy after surgical resection and liver transplantation. Loco-regional ablative therapy includes cryotherapy, ethanol injection and radiofrequency ablation, cytotoxic chemotherapy, natural compounds such as piperine, as curcumin and oleocanthal, oncolytic virus therapy, immunotherapies and nanotechnology.

Keywords: hepatocellular carcinoma (HCC), inflammation, disease progression, Dysbiosis, hepatitis B and C

1. Introduction

Liver cancer is a malignant tumor which is commonly occurs in cirrhosis and chronic liver disease patients. Liver cancer comprises of different types, the most common type is hepatocellular carcinoma (HCC) or primary liver cancer and other rarely occurring types includes hepatoblastoma and intrahepatic cholangiocarcinoma depend upon their origin such as liver stem cells, hepatocytes, cholangiocytes, and hepatoblasts [1]. Worldwide, the fourth leading cause of all cancers related deaths is primary liver cancer or HCC and its prevalence is 75% of all types of liver cancers. Out of all types of cancer related patients, every fifth male and seventh in female is diagnosed with liver cancer. Moreover, World Health Organization (WHO) declared that if it is not properly treated then ultimately in 2030 more than one million individuals will die from this ailment [2].

The liver cancer is most prevalent in Middle and Western Africa and East and Southeast Asia countries, whereas lowest ratio was found in Northern and Eastern Europe and South-Central and Western Asia. The variation in prevalence of liver cancer in different regions is due to diverse exposure to hepatitis viruses and other environmental pathogens. As in developing countries, 60% infection is caused by hepatitis B virus (HBV) and 33% infection is caused by hepatitis C virus (HCV) of total liver cancer. Currently, in United States and Central Europe, liver cancer prevalence and mortality is also increased to an alarming situation as more than 750,000 new cases annually, because of high HCV by regular drug use and nonalcoholic fatty liver disease by obesity epidemic, or might be due to alcohol-related cirrhosis. In spite of the advancement, liver cancer is still one of the most challenging cancer to treat. The clinical output remains low and about one-third patients eligible to curative approaches of HCC such as local destructive therapies, surgery and liver transplantation. The surgical removal is possible in 5–15% of patients in early stages, without cirrhosis and due to reduced hepatic restoration capacity in later stages. Therefore, the survival rate can be increased by early diagnosis and application of curative approaches. In early HCC treatment the five-year survival rate is 47–53%, which is still not satisfactory. However, the chances of recurrence of HCC remain high even after curative treatment [3].

2. Risk factors

The most common etiological risk factors of liver cancer are hepatitis B or C virus infections, alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH) and chronic alcohol consumption, although smoking, obesity, iron overload and diabetes are also associated with liver cancer [4]. Worldwide about 80% of HCC is allied to chronic infections of hepatitis B and C viruses, as hepatitis B virus is responsible more than the hepatitis C virus. About 10–25% HCC or cirrhosis deaths cause by hepatitis B viruses and it mainly affect in early age of life. The vaccine for hepatitis B marketed in 1982, have been targeted to newborns. In 2017, about 187 WHO member countries vaccinated the newborns and globally 84% population received three doses of hepatitis B vaccine. However, hepatitis C virus rarely affect children, and only 15–45% patients recovered from this and remaining people lead to chronic infection of liver. It is asymptomatic, and for many years, chronic infections not clinically evident [5].

Alcohol and smoking are major contributor to liver cancer. The USA studies showed that light-to-moderate alcohol consumption which is less than three drinks per day significantly reduced HCC risk [6]. The alcohol consumption is more in high societies as compared to low income regions, while smoking ratio is high in middle and low income regions as compared to high income countries. A report in 2014 found that cigarette smoking at that time was linked with a 70% high risk of liver cancer, while 40% in previous years [7]. Obesity cause low grade inflammation, leads to metabolic dysfunction, development of NAFLD to NASH, cirrhosis, fibrosis and in turn liver cancer. Research claimed that overweight and obesity cause 18% and 83% high risks of liver cancer and the HCC risk twice with the diabetes disease [5].

Some other risk factors of liver cancer are congenital abnormalities, toxic aflatoxin or arsenic contaminated food and autoimmune liver diseases. The congenital abnormalities include hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency and hereditary tyrosinemia. However, the aflatoxins are released by the fungi such as

Aspergillus parasiticus and *Aspergillus flavus* in contaminated food. The autoimmune hepatitis is also a cause of liver cirrhosis and HCC but the chances of occurrence is far less than the hepatitis B and C viruses [8–10]. All these risk factors are cumulative and influence each other such as if a person is suffering with hepatitits B or C and consume alcohol then he will be at severe risk of the pathogenesis of HCC by the interplay of environmental, viral, diet and host factors. These factors develop chronic liver disease which may lead to liver cirrhosis by numerous mutagens for example oxidative stress, chemical exposure and deviation in the DNA repair leads to genome alteration which ultimately results in cancerous genome in which chronic inflammation, reactive oxygen and nitrogen species, and mutation are the main aspects of hepatocytes necrosis.

3. Progression and metastasis of HCC

The main mechanism in the development of liver cancer is the inflammation in liver, except the cause of it. The inflammation is the automatic immune response to the targeted cells, which leads to hepatic necrosis. In early stages the inflammatory signaling pathway is activated by reactive oxygen species (ROS) and nitric oxide (NO), which produce chemokines, prostaglandins, cytokines, growth factors and proangiogenic factors, that transforms the hepatocytes and cause initiation of anti-apoptotic processing and restriction of immune surveillance and develop liver fibrosis and in later stages the liver tissue damaged permanently, called liver cirrhosis. More than 80% of primary liver cancer is caused by the chronic liver diseases commonly appear on a background of liver cirrhosis. If it persists and not treated it will metastasis to other liver tissues and diagnosed as liver cancer or HCC, causing morbidity and the mortality (**Figure 1**) [12, 13].

3.1 Signaling pathways

The development of liver cancer is a multistage and branched process of morphological and genetic traits. The tumor in liver is not only associated with cellular malignancy but also linked with genome abnormality, which ultimately cause neoplastic growth. In HCC, frequently mutation occurs in cell cycle genes i.e. CDKN2A (cyclin-dependent kinase inhibitor 2A) and CCND1 (encodes cyclin D1) and cancer gens such as WNT, TP53, and CTNNB1(encodes βcatenin). The hepatic-carcinogenesis emerged by two most important oncogenic events such as telomerase reverse transcriptase (TERT) activation and MYC activation. These genes activated in various forms of liver tumors. The TERT activation is required for
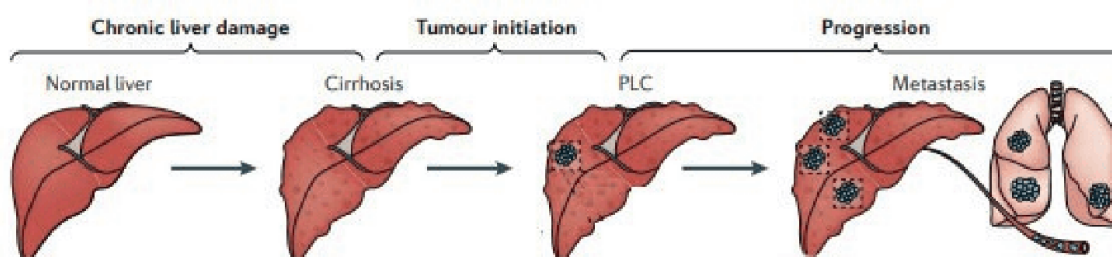

Figure 1.
Progression and metastasis of liver cancer [11].

unlimited proliferation and MYC activate for transformation of normal liver cells into HCC at later stage of cancer [11, 14]. Along with genetics, the epigenetics also play a vital role to the pathogenesis of cancer. The epigenetic alterations include DNA hypo-methylation or hyper-methylation, chromatin remodeling, dysregulation of histone adaptation patterns, aberrant expression of micro-RNAs (miRNAs) and long noncoding RNAs (lncRNAs) are allied with HCC. As in hepatitis B, the HBx protein constitutively activates the pathways in **Figure 2**. The epigenetic alteration patterns can affect the frequencies and types of genetic modifications at the adjacent chromatin regions and some of the genetic mutations in HCC regulate epigenetic changes in host gene expression. Therefore, both factors appear to be inseparable and promote tumorigenesis synergistically.

Researchers are trying from decades to reveal the molecular mechanisms of cancer origination and progression. Conversely, the heterogeneity and diverse characteristics of cancer commonly cause confusion. Nowadays, it is widely recognized that cancer develops from normal cells to malignant stages in many years because of its multi-step process. The cells become tumorigenic and show malignant phenotypes due to numerous hallmarks. Same as for other solid tumors, the HCC is also described with those cancer hallmarks for example evading growth suppressors, sustained cell proliferation, cell death resistance, metastasis, invasion, angiogenesis, and deregulated energy metabolism. These hallmarks and genetic or epigenetic alterations linkage helps to recognize the molecular mechanisms. However, various corresponding signaling pathways are allied to both origination and progression of liver cancer. These mechanisms include Yes-Associated Protein-Hippo Pathway (YAP-HIPPO), Wnt/β-catenin and inflammation by interleukin-6 (IL-6), tumor necrosis factor (TNF), nuclear factor-Kb (NF-κB). Moreover, PPARγ induced lipid metabolism, epigenetic alterations like acetylation of histones, DNA methylation, and noncoding RNAs also cause progression and metastasis of HCC [11, 15].

Hippo-YAP pathway control the size, multiplication, apoptosis, and invasion of hepatic cells by YAZ-HIPPO receptors, which regulate the YAZ/TAZ transcriptional genes. WNT/AXIN controls the β-catenin protein transfer to the nucleus, forming the YAZ/TAZ-β-catenin-TCF trimer, which stimulate TGF-β as a profibrotic agent and C-Myc as a proliferative agent, cause cancer initiation, proliferation, progression, resistance to anticancerous drugs [16, 17]. The NF − κB is inhibited by IκB protein, when IκB is phosphorylated by kinase complex (IKK) into in Ser32 and Ser36, IκB is degraded by proteasomal complex and translocate NF − κB P50/P65 which mainly involved in apoptosis inhibition, tumor cell proliferation, progression, cancer initiation and drug resistance. PPARγ at one side inhibit the β-catenin and NF-κB signaling pathways by bonding to its ligands, on the other side it is involved in apoptosis, inhibition of cell proliferation, and metastasis by binding to the peroxisome proliferating response elements (PPRE) which act as specific response elements in nucleus [18, 19]. These signaling pathways upregulate or downregulate according to etiological factors of HCC. For example, Hepatitis B is a DNA virus and it incorporate into host by various ways such as hijack its machinery, oxidative stress, and Hepatitis B protein x. Hepatitis B activate TERT, Cyclin A2, PDGFR, EGFR gene expressions. Hepatitis B protein x stimulates Wnt/β-catenin, NFB, TGF-β, P53 and ROS signaling pathways for the pathogenesis of HCC. While hepatitis C is a RNA virus and it induce inflammation by release of pro-inflammatory cytokines such as IL-6, TNF-α, IL-1 and IL-18, modify TGF-β signaling pathway and glucose and lipid metabolism for the HCC development. Similarly, chronic alcohol consumption activates cytochrome CYP2E1 and cause liver steatosis and inflammation which leads to HCC.
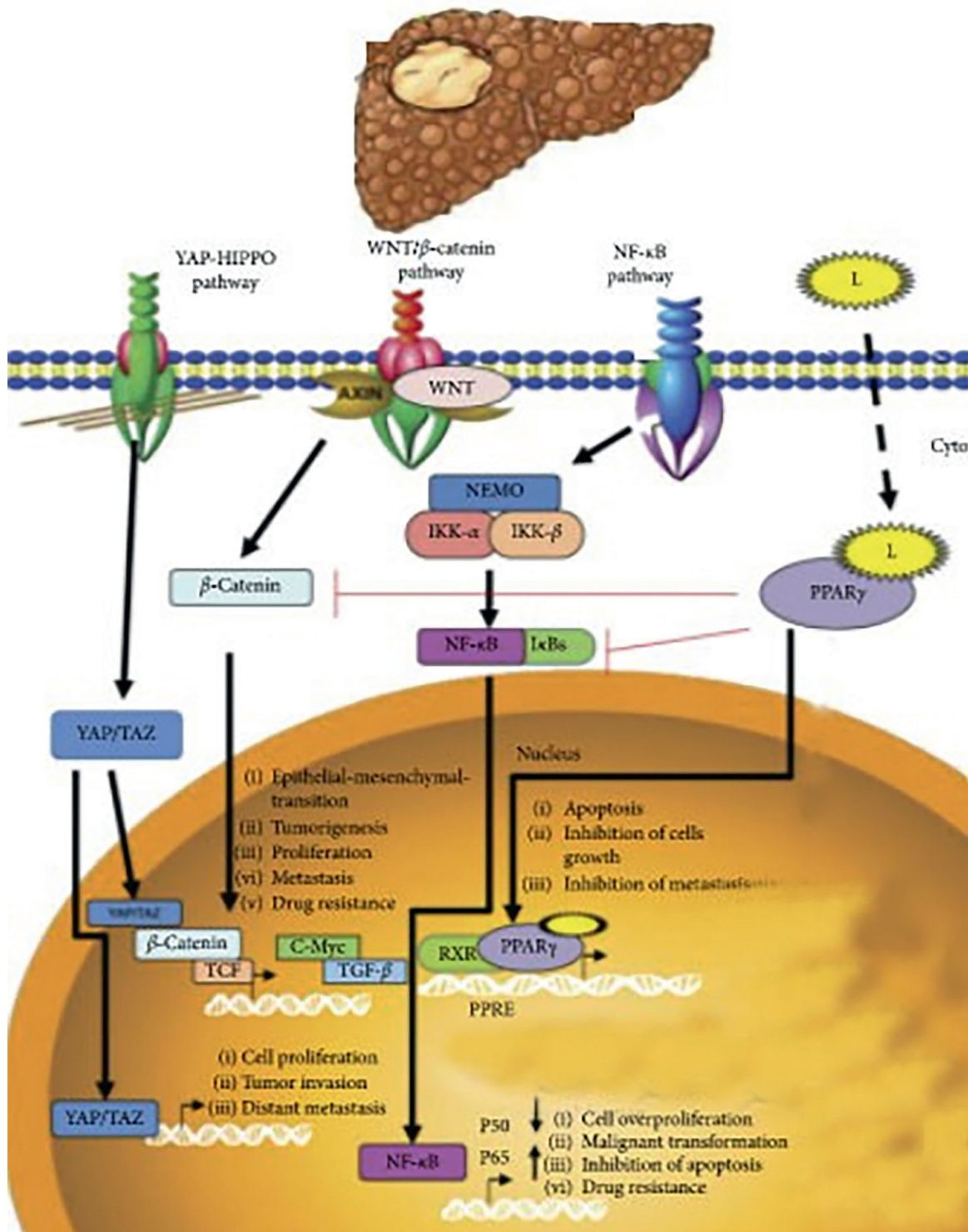
Figure 2.
Different signal pathway of HCC progression.

Histone modification is carried out by enzymes which add or remove acetyl groups with histones. The de-acetylation of histone proteins by histone acetyltransferase (HAT) enzyme leads to malignant proliferation, transformation, and invasion of tumor cells. The DNA methylation is common in liver cancer and 3000 hypo-methylated promoters were identified in HCC tumor, one of them is CpG methylation which is controlled by DNA methyltransferases (DNMTs) enzyme. The DNMTs also methylated the genes like p16, p15, E-cadherin, hyper-methylated in cancer 1

(HIC-1), and Ras association domain family 1 isoform A (RASSF1A), which involved in cell adhesion, mobility, proliferation and invasion. The microRNAs (miRNAs) dysregulation causes abnormal gene expressions, leads to development, invasion, and metastasis of tumor cells. The main two miRNAs which contribute to HCC development are miR-122 and miR-221. In miR-122 liver become inflamed, steatohepatitis, and fibrosis occurs, whereas in miR-221 cellular pathways modulated, specifically linked to cell proliferation, survival, and metastasis [20–22]. Hepatitis B protein x blocks expression of E-cadherin and activates histone deacetylases 1 and 2. Hepatitis B protein x also affects expression of several miRNAs, which are also important in maintaining hepatitis C virus replication, persistence and progression of chronic liver disease to HCC. Hepatitis B and alcohol both involved in DNA methylation proliferate hepatocytes and eventually cause HCC. Hepatitis C virus core protein and the E2 envelope protein stimulate cell growth in liver cancer by lipid peroxidation and a mitochondrial dysfunction with oxidative stress. The hepatitis C core protein also alter gene expression and intracellular regulation mechanisms. Moreover, the hepatitis C virus non-structural 5A protein interacts with beta-catenin and stimulates its transcriptional activity in a phosphoinositide-3 kinase-dependent fashion to promote HCC pathogenesis.

3.2 Biological pathways

There are some other biological mechanisms which also play a vital role in progression of HCC such as epithelial–mesenchymal transition (EMT), tumor microenvironment, tumor-stromal interactions and cancer stem cells. In EMT process, epithelial cells drop their adhesive properties, which allow the mesenchymal membrane to migrate the cells, that grabbed by cancer cells and increase their dissemination all over the body. In HCC the EMT effectors i.e. cadherins, vimentin, fibronectin and integrins transformed and allow mesenchymal phenotype easily. The transcriptional factors like Slug, Twist and Zeb upregulated in supporting EMT pathway during HCC progression. Moreover, tumor-stromal interactions also promote HCC development, as hepatic stellate cells (HSCs) accumulate by the stimulation of hypoxia-induced platelet-derived growth factor-BB (PDGF-BB) and multiply in the tumor stroma along with upsurge in vascular endothelial growth factor-A (VEGF-A) expression in HSCs result in HCC angiogenesis. Similarly, signal transducer and activator of transcription (STAT3) act as a mediator between liver cancer cells and stromal cells interactions and regulate micro-environment for tumor formation [9, 23]. Alcohol consumption, hepatitis B and C all promote EMT pathway, and tumor micro-environment is also affected by hypoxia and hypoxia might stimulate EMT and the liver fibrosis and cirrhosis is highly activated by HSCs, all these factors contribute to the progression of HCC.

The cancer stem cell (CSC) also involved in progression, aggressiveness and metastasis of HCC, by the action of several surface markers such as epithelial cell adhesion molecule (EpCAM), CD13, CD44, CD90 and CD133. The acquisition of liver CSC in tumor cells caused by dedifferentiation and reprogramming of non-CSCs such as hepatoblasts, biliary cells and mature hepatocytes. For example, Sal-like protein 4 (SALL4) is a proto-oncogene in liver and embryonic stem cells and cause HCCC progression. The investigation proved that CSCs are considered to be more tumorigenic than non-stem cancer cells and they are resistant to numerous anticancer treatments, including chemotherapy and radiotherapy [24, 25]. The metabolic stress such as obesity and diabetes promotes Various evident studies show the signaling pathways,

their functional process and tumor features as descried in **Table 1**. Hepatitis B protein x promotes the development of stemness characteristics in liver cells, which is part of the mechanism whereby hepatitis B protein x contributes to hepato-carcinogenesis. The long-term inflammation by hepatitis B or C virus, chronic alcohol consumption or and NASH, highly contribute to reprogramming of non-CSC into CSCs.

3.3 Gut microbial dysbiosis

The gut-liver axis is a dual anatomical and functional interaction between and gastrointestinal tract mainly by portal vein blood circulation. The synergetic relationship between liver and gut microbiota is regulated by a complex network of interactions, comprises of neuroendocrine, immune, and metabolic systems. There is a tight junction within the gut epithelium which act as a natural barrier to bacteria and their metabolic products. There is evidence that the gut microbiota moves beyond the gut by intestinal dysbiosis, which involved in hepatic carcinoma progression. Dysbiosis is a process in which tight junction of proteins disrupt and gut mucous layer become thinner, which leads to dysfunctional intestinal barrier. Particularly, dysbiosis stimulate the release of cancer-promoting metabolites, like secondary bile acids which consist of deoxycholic acid (DCA). Dysbiosis is also commonly associated with decreased levels of bacteria that produce the anti-inflammatory and anti-tumorigenic metabolites, short chain fatty acids. The dysfunctional gut barrier in dysbiosis increase intestinal permeability, bacterial overgrowth, bacterial translocation and immune system dysplasia, which results in leaky gut. The gut microbial dysbiosis deteriorates

Functional process	Signaling pathway	Phenotypic and tumor features	References
Cell cycle	p53 and RB–E2F	Aggressive phenotype and loss of DNA damage repair mechanisms	[26]
Development and differentiation	WNT–β-catenin	Activation in tumor-initiating cells (early and late stages)	
	SALL4	Poor prognosis and activation in tumor-initiating cells	[27]
	NF2	Stem cell features and tumor initiation	
Proliferation and survival	EGFR	Aggressive phenotype and reprogramming	[28]
	IGF	Pre-neoplastic lesions (early stage)	
Immune response	IL-6 signaling	Progenitor-derived response to adjuvant interferon therapy	[29]
	NF-κB	Chronic inflammation	
Angiogenesis	PDGF	Liver cirrhosis	[27]
	VEGF	Aggressive phenotype, poor prognosis and metastasis	
Stress response	ROS, NO	Oxidative phosphorylation (late stage)	[26]

EGFR, epidermal growth factor receptor; IGF, insulin-like growth factor; IL, interleukin; IL-6R, IL-6 receptor; NF2, neurofibromin 2; NF-κB, nuclear factor-κB; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; SALL4, Sal-like protein 4; VEGF, vascular endothelial growth factor.

Table 1.
Major functional processes and signaling pathways in HCC development.

the metabolism, nutrition, immunity and inflammatory status of the liver. Numerous bacteria's such as *Streptococcus*, *Lactobacillus*, *Escherichia Shigella* and *Bacteroides* move into the portal vein and liver, which stimulates hepatic kupffer cells and stellate cells. They release a series of inflammatory mediators, increase levels of endotoxin, blood ammonia, provoke intestinal mucosal damage, stimulate liver cell steatosis and chronic inflammation, which cause the development of hepatic encephalopathy, liver fibrosis, cirrhosis and eventually leads to development of HCC [30].

Moreover, on the other hand, these liver diseases worse the gut microbial dysbiosis, as liver cirrhosis decreases gastric acid and bile acid secretion, function of lipopolysaccharide, bacteria, metabolites, and bowel movement, both leads to the overgrowth of intestinal bacteria and gut microbial dysbiosis.by affecting the stability and function of the gut microbiota. The gut microbiota of hepatic disorders such as hepatitis B and C viruses, ALD, NAFLD, NASH and HCC is significantly different from healthy microbiota such as amount of microbiota, species present, and metabolites produced due to gut microbial dysbiosis. For instance, in hepatitis B cirrhosis Faecalibacterium prausnitzii, and Enterococcus faecalis significantly increased, whereas *Bifidobacteria* and *Lactobacillus* significantly reduced, and in HCC patients

Liver diseases	Alteration in gut microbiota	Clinical significance	References
Chronic hepatitis C	*Streptococcus↑* *Lactobacillus↑* *Lachnospiraceae↓* *Ruminococcaceae↓*	HCV infection cause gut microbial dysbiosis, even in mild liver patients	[31]
Chronic hepatitis B	*Actinomyces↑* *Enterococcus faecalis↑* *Alistipes↓* *Bifidobacteria↓*	Gut microbial dysbiosis may effect disease development	[32]
ALD	*Lachnospiraceae↑* *Erysipelotrichaceae↑* *Lactobacillus↓* *Pediococcus↓*	ALD induced by alcohol and stimulate bacterial disruption in microbial dysbiosis	[33]
NASH (fibrosis)	*Escherichia Shigella↑* *Bacteroides↑* *Clostridium↓* *Prevotella↓*	These pathogens are primary contributor to NAFLD development	[34]
NAFLD	*Escherichia_Shigella↑* *Blautia↑* *Prevotellaceae↓* *Ruminococcaceae↓*	The decreased pathogens are detrimental for adults with NAFLD	[34]
Liver cirrhosis	*Enterobacteriaceae ↑* *Streptococcaceae↑* *Lachnospiraceae ↓* *Bacteroidaceae ↓*	Liver cirrhosis development linked with gut microbial dysbiosis	[35]
HCC patients	Lipopolysaccharide producing bacteria↑ *Escherichia coli↑* Butyrate-producing bacteria↓	Cirrhotic patients with are more susceptible to the to HCC progression by stimulating tumor growth	[36]

Table 2.
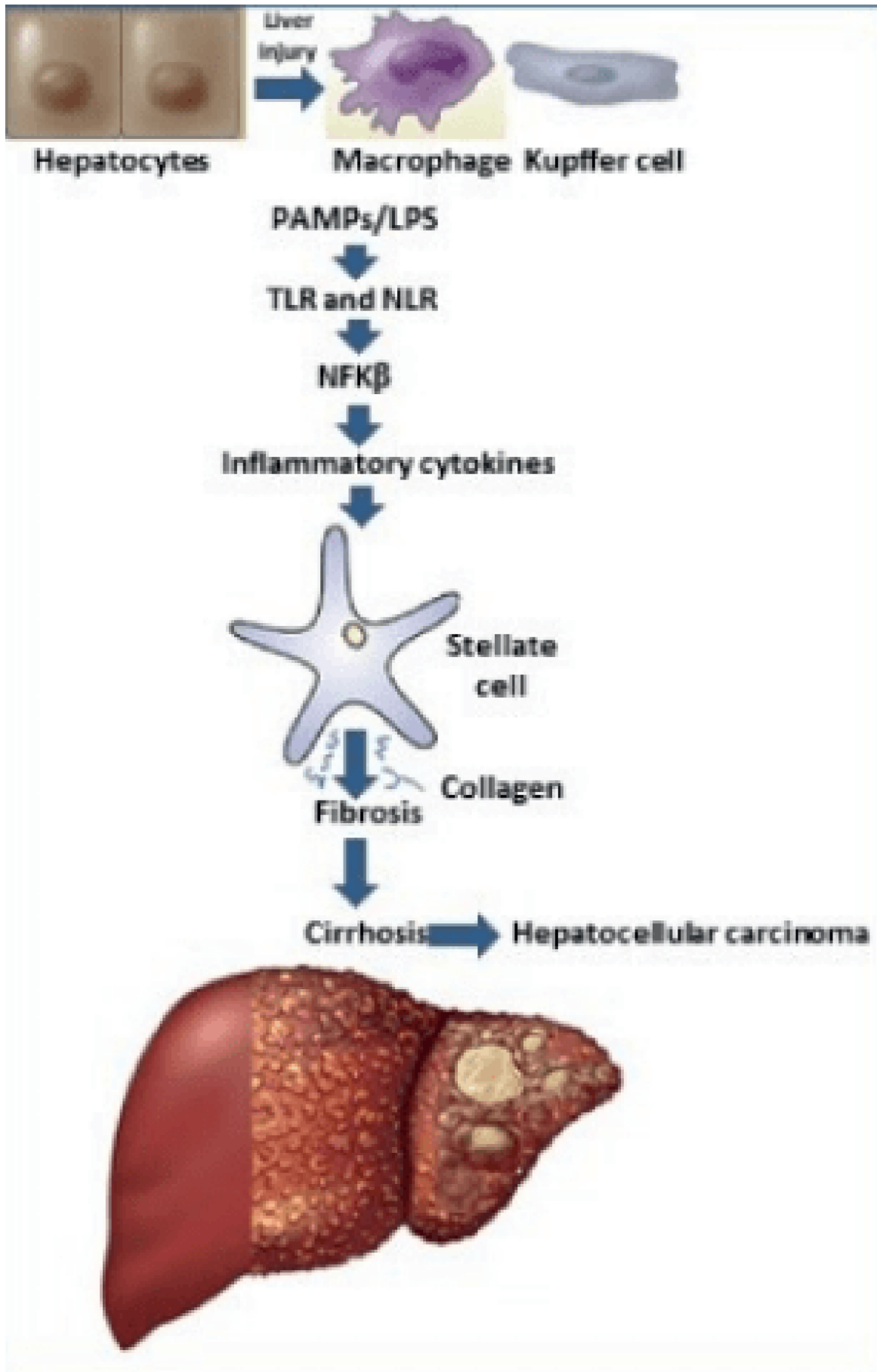*Alteration in gut microbiota in various liver diseases.*

Figure 3.
Activation of immune system in HCC [15].

the levels of Escherichia coli and other gram-negative bacteria upsurge in as described in **Table 2**. Moreover, along with microbial alteration energy-producing system, microbial metabolism and iron transport also differ in hepatic carcinoma patients and healthy people. The levels of and serum tumor necrosis factor (TNF-α), LSM levels, fecal secretory IgA and gene diversity index significantly increased, and these features of gut microbial dysbiosis affect disease progression [37, 38].

The relationship of gut microbial dysbiosis and HCC is complex. The pathogenic micro-organisms antigen pass through the gut epithelium and recognized by dendritic cells, which stimulate the adaptive immune system by altering the T cells response to influence the development of HCC. For instance, T helper 17 (Th17) cells are a unique subcategory of T helper cells, to produce inflammatory cytokines and angiogenic mediators such as IL-17A and IL-22. IL-17A, that eventually activate tumor angiogenesis. Moreover, pathogen-associated molecular patterns (PAMPs), including LPS, peptidoglycans, and flagelin stimulate NFKβ with the help of toll-like receptors (TLRs) and nod-like receptors (NLRs), which also leads to produce inflammatory chemokines and cytokines, which enter the liver by portal circulation. However, Kupffer cells are affect the LPS as compared to hepatocytes, while PAMPs activate stellate cells, which promote and progress fibrosis and HCC (**Figure 3**) [37].

4. Current therapies and their limitations

The several therapeutic approaches to treat HCC focus on the alteration of the processes such as cell cycle, apoptosis, and signal pathways. The treatments are classified into different categories which are described as follows.

4.1 Pharmacological therapy

Sorafenib is the manifold kinase inhibitor, which suppresses the activity of Raf-1 and some other tyrosine kinases, like vascular VEGFR-2, VEGFR-3, PDGFR, and FGFR-1 involved in cellular angiogenesis, proliferation, differentiation and survival. It is the front-line therapy and as first drug approved for systemic treatment of advanced HCC patients, who moderately conserved liver functions and not considered suitable for surgical resection or liver transplantation. The evidence showed that sorafenib response is mainly linked with correction of irregular glycosylation in erythroblastosis 26–1 (Ets-1) protein in HCC cells by promoting survival rate significantly, only in advanced HCC patients. A lot of patients quickly develop resistance against sorafenib. Therefore, Lenvatinib is an effective drug for the those HCC patients, in which surgery is not effective and they are resistant to sorafenib, but their survival rate can be increased by decreeing lymphangiogenesis and angiogenesis responses. Regorafenib is also a second-line oral drug which was developed by Bayer and it was FDA-approved in June 2017 for unresectable HCC. Ramuciruma is a drug which inhibit the binding of the VEGFR ligands as a human anti-VEGFR-2 monoclonal antibody. Drug resistant is always an issue for numerous drugs and their adverse side effects, such as sorafenib and lenvatinib cause hypertension, diarrhea and decreased appetite [15, 39].

4.2 Surgery

Surgery of HCC patients includes three main categories such as surgical resection, adjuvant therapy after surgical resection and liver transplantation. Surgical resection

is the HCC treatment for those patients who preserved liver function. The advancement of laparoscopic liver resection declines the operative blood loss, operation time, and length of hospital stay. If the surgical resection is done in early HCC (5 cm) patients with maximum preserved liver function, then the 5-yr survival rate can be 40–70%. The drawback of surgical resection is recurrence and its possible treatments include repeat hepatectomy, radiofrequency ablation, or salvage liver transplantation. After surgical resection, adjuvant therapy eliminates remaining cancer cells and inhibit secondary liver carcinogenesis. These therapies comprise of intra-arterial radiolabeled lip iodol, interferons, systemic and intra-arterial chemotherapy, acyclic retinoid, adoptive immunotherapy and sorafenib. The liver transplantation decreases postoperative liver failure risk, and best approach for moderate to severe cirrhosis or early-stage HCC patients. The liver transplant increase survival rate at 10 years which is more than liver resection, but the risks are there because of unacceptability of the donor liver by the body and cause high expense of short-term mortality [3, 40].

4.3 Loco-regional therapy

Loco-regional ablative therapy includes cryotherapy, ethanol injection and radio-frequency ablation. This therapy is the primary treatment for those HCC patients who are not capable of operation and it act as a bridge to liver transplantation or relaxing process to prolong the disease-free survival. For instance, radiofrequency ablation (RFA) is the process of coagulative necrosis for the thermal destruction of HCC cells and it is considered as far better than percutaneous ethanol injection (PEI), which is ablative therapy for early HCC patients. Moreover, RFA highly reduce the risk of morbidity in small HCC patients as compared to liver resection [41].

4.4 Cytotoxic chemotherapy

Chemotherapy is particularly workable for the patients with underlying non-cirrhotic liver. Chemotherapy cannot be used routinely for advanced HCC patients because HCC is chemotherapy-refractory tumor. Moreover, systemic chemotherapy is not tolerated by patients with underlying hepatic dysfunction. There are various chemotherapeutic agents, such as single-agent doxorubicin has an objective response rate of 20% or less with doses of 75 mg/m2 in advanced HCC patients. Systematic chemotherapy has limited efficacy on HCC because of low response rates and high toxicity, without increasing the significant survival rate such as gemcitabine- and doxorubicin-based chemotherapy treatment [3].

4.5 Natural compounds

Various natural compounds in fruits, vegetables, and spices function are helpful in suppressing mechanisms of cancer progression and in activating mechanisms of cancer prevention. These compounds promote anti-inflammatory, anti-oxidant, anti-tumor and anti-proliferative systems. Some compounds cause cytotoxicity to cancer cells and no effect on non-cancerous cells. For example, piperine is a natural compound, which inhibit enzymes of drug metabolism and it can be used in future as co-administrative with chemotherapeutic drugs to upsurge plasma concentrations. Some other natural compounds such as curcumin, oleocanthal, allium extracts and *Cnidium officinale* makino, also used to reduce HCC progression. The natural compounds may improve the effectiveness of current drug treatments without host

toxicity. For instance, polysaccharides from *Lentinus edodes* and *Tricholoma matsutake* improve the inhibitory effect of 5-fluorouracil in H22 cells of HCC patients [42].

4.6 Oncolytic virus therapy

Oncolytic virus therapy is a new anticancer approach which involve replication of oncolytic viruses in carcinogenic tissues to lyse tumor cells. They are specially designed agents such as antitumor, tumor-selective and multi-mechanistic such as extending from direct killing of virus-mediated cancer cells, pleiotropic cytotoxic immune effector process, by the exact transgene-encoded proteins activities. The viruses of different classes used in this process such as paramyxovirus, reovirus, herpes, simplex virus, parvovirus, poxvirus and adenovirus. Some of these viruses are genetically engineered to improve their therapeutic effects. The oncolytic viruses also activate immunogenic tumor cell death and regulate cellular tumor– resistance mechanisms which leads to identification of recently released tumor antigens by producing tumor cell lysates. Moreover, in HCC oncolytic viruses such as telomerase-specific replication, telomelysin (OBP-301) and competent oncolytic adenovirus established efficient replication in telomerase-positive tumor cells, by replacing the adenoviral E1A promoter with the tumor-specific telomerase reverse transcriptase (hTERT) promoter [43].

4.7 Immunotherapy

The immune therapeutic approaches in HCC, target tumor cells by activation and stimulation of the current tumor-specific immune response. In this therapy, the patients are treated with advanced melanoma by immune-checkpoint-mechanism inhibitors including anti –cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody. The programmed death 1 (PD-1), is a co-inhibitory receptor, which is dominated by activated T and B cells, and regulate peripheral immune tolerance. Furthermore, the in PD-1 and its ligands interactions such as programmed death ligand 1 (PD-L1) (B7-H1) and PD-L2 (B7-DC), is an immune suppressant mechanism and a vital immune barrier. Other immunotherapies include tumor-associated antigens (TAAs) recognition by cytotoxic T lymphocytes (CTLs) to improve host immunity. The HCC tumor has TAA, cyclophilin B, as a squamous cell cancerous antigen recognized by T cells (SART) 2, SART3, AFP, hTERT, glycopican-3 (GPC3), and melanoma antigen gene A (MAGE-A). The drug sorafenib inhibit immunosuppression, therefore can be considered as immunotherapy combination with this drug [41].

4.8 Nanotechnology

Nanotechnology is an emerging technique which modify the concept of current combination therapy methods and increase retention, permeability and pharmacokinetics. The nanoparticles approach is treatment programs which syndicate the separate agents to increase the effects of drug. For instance, in combination as chemo-sensitize cancer cells become resistant to drugs and to improve the drug's efficacy in treating tumors, nanoparticles improve the results by the addition of another molecule in the mechanism. In HepG2 cells, doxorubicin delivery and the lipid nanoparticle as chemo-sensitizer release over 48 h and led to possible synergy, to a decrease in cytotoxicity than free doxorubicin and doxorubicin-nanoparticles. In case of diethylnitrosamine-causing liver cancers, doxorubicin/curcumin approach than free doxorubicin/curcumin act as a synergistic inhibition of tumors growth [42, 44].

5. Conclusion

Liver cancer comprises of different types depend upon their origin such as liver stem cells, hepatocytes, cholangiocytes, and hepatoblasts, the most common type is hepatocellular carcinoma (HCC) or primary liver cancer Worldwide, its prevalence is 75% of all types of liver cancers and every fifth male and seventh in female is diagnosed with liver cancer. The etiology is linked with activation of multiple processes of apoptotic response, dysregulation of cell cycle and the stimulation of signaling pathways that cause fibrogenic and inflammatory response. Currently, numerous therapeutic options are working to treat patients with HCC, the aim of all of these approaches is to improve liver function, overall survival, and life quality of patients, but only a few of these bioactive techniques have shown successful responses without initiating side effects.

6. Future perspective

Although, various drugs have been tested and approved for advanced HCC, but one of the main reasons of low survival rate is drug resistance because of the intra-tumor heterogeneity during treatment. This is a huge hurdle for the long-term use of targeted therapies for primary liver cancer, that is why it is essential to explore the mechanism of drug resistance in future. Another challenge for targeted treatments is the deficiency of accurate targets and biomarkers such as breast cancer has the exact biomarker like HER2, but primary liver cancer has no accurate biomarkers and show heterogeneity and genomic diversity. While many mutant genes such as TERT and CTNNB1, have been found, but it is still not clear as they are driver gene or passenger gene in future, it is essential to understand the genomic architecture, mutation landscape, and driver genes to use new therapeutic interventions. Most of the patients are not adaptable to immune therapy, therefore future efforts in should be made in two directions for immunotherapy such as improving the existing immune response and stimulating a new immune response. Moreover, further study is undoubtedly compulsory to advance improvement in current diagnosis, to better comprehend the genomic profile and pathogenesis of HCC to develop novel therapeutics, containing multiple drugs or treatments, that capable of modifying various signaling and biological pathways associated with HCC pathogenesis.

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