Chapter 16
The Role of Inflammation in Liver Cancer

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Abstract Persistent inflammation is known to promote and exacerbate malignancy. Primary liver cancer, mostly hepatocellular carcinoma (HCC), is a clear example of inflammation-related cancer as more than 90 % of HCCs arise in the context of hepatic injury and inflammation. HCC represents the fifth most common malignancy and the third leading cause of cancer-related death worldwide with about one million new cases diagnosed every year with almost an equal number of deaths. Chronic unresolved inflammation is associated with persistent hepatic injury and concurrent regeneration, leading to sequential development of fibrosis, cirrhosis, and eventually HCC. Irrespective of the intrinsic differences among various etiological factors, a common denominator at the origin of HCC is the perpetuation of a wound-healing response activated by parenchymal cell death and the resulting inflammatory cascade. Hence, the identification of fundamental inflammatory signaling pathways causing transition from chronic liver injury to dysplasia and HCC could depict new predictive biomarkers and targets to identify and treat patients with chronic liver inflammation. This chapter critically discusses the roles of several major cytokines, chemokines, growth factors, transcription factors, and enzymes as well as a distinct network of inflammatory signaling pathways in the development and progression of HCC. It also highlights and analyzes preclinical animal studies showing innovative approaches of targeting inflammatory mediators and signaling by a variety of natural compounds and synthetic agents to achieve effective therapy as well as prevention of hepatic malignancy. Additionally, current limitations and potential challenges associated with the inhibition of inflammatory signaling as well as future directions of research to accelerate clinical development of anti-inflammatory agents to prevent and treat liver cancer are presented.

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16.1 Introduction

Primary liver cancers can be categorized into angiosarcoma, cholangiocarcinoma, hepatoblastoma, and hepatocellular carcinoma (HCC). The latter is the most dominant form of primary liver cancer, accounting for more than 90 % of this cancer (El-Serag and Rudolph 2007). HCC represents the fifth most common malignancy and the third leading cause of cancer-related death worldwide (Nordenstedt et al. 2010). HCC has a dismal prognosis with a number of HCC-related deaths almost equal to the number of diagnosed cases (more than 600,000) each year (Sherman 2005). The median survival time of HCC patients is 7–8 months from the time of diagnosis (Wilson 2005), and a 5-year survival rate is below 9 % (Sherman 2005). The rate of HCC incidence continues to increase in several low-risk regions of the world, including developed countries in Western Europe, North America, and Oceania, while the rate is declining in several highest-risk countries of Asia (Center and Jemal 2011). The incidence of HCC has dramatically increased in the USA by more than 70 % during the last quarter century (El-Serag 2004), with approximately 31,000 new cases and about 22,000 deaths expected to occur in 2013 alone (Siegel et al. 2013). The annual health care cost associated with HCC in the USA has been estimated to be approximately 455 million dollars (Lang et al. 2009). The overall costs for HCC patients are two- to eightfold higher than those without HCC, and this underscores the huge burden of medical care expense of illness related to hepatic malignancy (White et al. 2012).

HCC is a complex and heterogeneous malignancy caused by a number of risk factors. The major origin of HCC development is viral hepatitis caused by hepatitis B virus (HBV) and HCV (Marrero and Marrero 2007; Schütte et al. 2009; Gao et al. 2012). Other non-viral risk factors include alcohol abuse, non-alcoholic steatohepatitis (NASH), type 2 diabetes mellitus, and hemochromatosis (El-Serag et al. 2006; Blonski et al. 2010). Accumulating evidence showed that obesity is related to both HCC incidence and mortality and represents an independent risk factor for HCC in patients with alcoholic and cryptogenic cirrhosis (Nair et al. 2002; Larsson and Wolk 2007; Gregor and Hotamisligil 2011). Environmental and dietary carcinogens, such as aflatoxin B_1 (AFB_1, a mycotoxin present in corn, soybean and peanuts) and nitrosamines (present in tobacco smoke, cosmetics, gasoline, and various processed foods, including cured meats, salami and fried fish) are known to cause HCC (Bartsch and Montesano 1984; El-Serag and Rudolph 2007). A cohort study conducted in Shanghai (China) showed that the risk of developing HCC in patients with HBV infection and AFB_1 exposure was more than 59-fold that of normal population (Qian et al. 1994). Similar results were reported by another study conducted in Qidong, a high AFB_1 contamination area in China (Ming et al. 2002). Epidemiologic studies have suggested that cigarette smoking is a risk factor for the development of HCC. Results based on a clinical study on Taiwanese patients indicate that 4-aminobiphenyl exposure, which is primarily a result of cigarette smoking, plays a role in the development of HCC in humans (Wang et al. 1998). Several studies have indicated a causal link between the use of oral contraceptives and HCC development (Kenya 1990; Korula et al. 1991). Finally, gender is another risk

factor for HCC as men are more susceptible than women with a male-to-female ratio of 2:1–4:1 (El-Serag and Rudolph 2007; Ruggieri et al. 2010).

Current treatment options for patients with HCC are limited. Surgical resection is the treatment of choice for patients with well-preserved hepatic functions. Unfortunately, it involves a high risk of postoperative complications and tumor recurrence. At the present time, liver transplantation is the most effective way to improve the survival of HCC patients (Dutkowski et al. 2010). However, this option has limitation due to inadequate number of qualified donors as well as occurrence of the disease in the transplanted liver. Although various strategies, such as cryoablation, microwave ablation, radio-frequency ablation, trans-catheter arterial chemoembolization, percutaneous ethanol injection, and yttrium-90 microspheres, are available for inoperable patients, difficulty in the management of patients and tumor recurrence remain two significant limitations for these treatments (Senthil et al. 2010). Currently, sorafenib [*N*-(3-trifluoromethyl-4-chlorophenyl)-*N*′-(4-(2-methylcarbamoyl pyridin-4-yl)oxyphenyl)urea, Nexavar®, Bayer] is the only drug approved by the United States Food and Drug Administration for the treatment of advanced HCC based on two large phase III clinical trials (Llovet et al. 2008; Cheng et al. 2009). Nevertheless, only moderate improvement of survival, a number of adverse side effects, and high costs underscore the need for other novel therapeutic as well as preventive approaches for HCC (Je et al. 2009; Lu 2010; Bishayee et al. 2010a; Bishayee 2012).

16.2 Cellular and Molecular Mechanisms of Liver Cancer

The molecular pathogenesis of hepatocellular cancer is very complex. The exact sequence of hepatocarcinogenesis, including the development of preneoplastic lesions and their growth and eventual progression to HCC, is not fully understood (Farazi and DePinho 2006). Several cellular phenomena, including alterations in tumor microenvironment, inflammation, oxidative stress, and hypoxia, act in concert with various molecular events to facilitate liver tumor initiation, progression, and metastasis (Aravalli et al. 2013). Mounting evidence indicates complex genetic and epigenetic alterations, chromosomal aberrations, mutations, abnormal expression of cellular proteins, overexpression of oncogenes, inhibition of tumor-suppressor genes, and altered molecular pathways lead to the development of HCC (Aravalli et al. 2008; Lachenmayer et al. 2010). Studies carried out during the last several decades have identified numerous signaling pathways activated in HCC, such as angiogenic signaling mediated through vascular endothelial growth factor and platelet-derived growth factor; Raf, mitogen-activated protein extracellular kinase (MEK), and extracellular signal-regulated kinase (ERK) (Ras/Raf/MEK/ERK); janus kinase (JAK)/signal transducers, and activators of transcription (STAT) (JAK/STAT); phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) (PI3K/Akt/mTOR); and Wnt/β-catenin and Hedgehog pathways (Huynh 2010; Hoshida et al. 2010; Whittaker et al. 2010; Nejak-Bowen and Monga 2011; Bishayee 2013).

16.3 Inflammation and Liver Cancer

Numerous epidemiological and clinical studies have provided convincing evidence that chronic inflammation leads to carcinogenesis (Demaria et al. 2010). Various types of cancer arise in the setting of chronic inflammation, indicating a strong link between inflammation and cancer (Mantovani et al. 2008; Grivennikov et al. 2010). It has been estimated that approximately 15 % of all human cancers are associated with inflammation and chronic infections (Coussens and Werb 2002). The development of HCC represents one of the most extensively investigated inflammation-related carcinogenesis events since more than 90 % of HCCs arise in the context of hepatic injury and inflammation (Nakagawa and Maeda 2012). HCC slowly unfolds on a background of chronic inflammation predominantly triggered by exposure to infectious agents, such as hepatotropic viruses, or to toxic compounds, for example, ethanol (Berasain et al. 2009a). Despite the intrinsic differences among various etiological factors for HCC, a common denominator at the origin this malignancy is the perpetuation of a wound-healing response activated by parenchymal cell death and the resulting inflammatory cascade. During chronic viral hepatitis, the host immune responses to HBV or HCV are often not strong enough to completely eradicate the infection, culminating in lingering stimulation of an antigen-specific immune response (Budhu and Wang 2006). The host immune cells are known to kill virus-infected liver cells, resulting in the production of various cytokines and growth factors and consequently inducing compensatory hepatocyte regeneration (Markiewski et al. 2006). The persistent cycle of "necro-inflammation" and hepatocyte regeneration is believed to enhance the risk of genetic mutation in hepatocytes, promoting survival and expansion of initiated cells (Nakagawa and Maeda 2012). All these events ultimately lead to deregulated hepatocytes proliferation which contributes to the development and progression of hepatic cancer. Moreover, oxidative stress through generation of reactive oxygen and nitrogen species in the initiated hepatocytes as well as inflammatory cells accelerate hepatocarcinogenesis through several mechanisms, including transcription and activation of cytokines and growth factors, oxidative DNA damage, DNA methylation, and hepatocyte injury (Tanaka et al. 2008; Chuma et al. 2008; Marra et al. 2011).

16.4 Inflammatory Mediators and Signaling Pathways Associated with Liver Cancer

Chronic inflammation is associated with persistent hepatic injury and concurrent regeneration, leading to sequential development of fibrosis, cirrhosis, and eventually HCC. Hence, the identification and analysis of fundamental inflammatory signaling pathways causing transition from chronic liver injury to dysplasia and HCC could depict new predictive biomarkers and targets to identify and treat patients with chronic liver inflammation (Weber et al. 2011). A growing number

of preclinical and clinical studies have identified a plethora of inflammatory mediators and signaling pathways implicated in hepatocellular cancer (Berasain et al. 2009a; Weber et al. 2011; Nakagawa and Maeda 2012; Wai and Kuo 2012; Szabo and Lippai 2012). It is interesting to note that these complex signaling molecules and pathways do not act independently, but are interconnected with extensive crosstalk. The following section highlights several major cytokines, chemokines, transcription factors, and proteins which belong to inflammatory signaling pathways implicated in hepatocarcinogenesis.

16.4.1 Cytokines

Cytokines are synthesized by various cell types in the liver. Hepatocytes also express cell surface receptors for cytokines. Various inflammatory cytokines, such as interleukin-1α (IL-1α), IL-1β, IL-6, IL-8 and tumor necrosis factor-α (TNF-α), participate in chronic hepatic inflammation, and IL-6 is probably the most important and studied one (Budhu and Wang 2006; Naugler and Karin 2008). During chronic hepatitis, activated Kupffer cells produce IL-6 which enhances local inflammatory responses and induce compensatory hepatocyte proliferation resulting in neoplastic transformation of hepatocytes (Naugler and Karin 2008). Elevated serum levels of IL-6 have been found in patients with chronic liver ailments, including alcoholic hepatitis, NASH, and hepatic infections with HBV and HCV (Deviere et al. 1989; Lee et al. 1998; Wieckowska et al. 2008). Moreover, higher serum levels of IL-6 have been found to be associated with increased risk of HCC development in patients with chronic hepatitis B and C infections (Nakagawa et al. 2009; Wong et al. 2009). All these reports underscore the pivotal role of IL-6 in chronic inflammation-mediated hepatocarcinogenesis in humans.

An elegant study conducted by Naugler et al. (2007) investigated the role of IL-6 in liver cancer using IL-6 knockout mouse model. IL-6 knockout mice exhibited a significant reduction of diethylnitrosamine (DENA)-initiated HCC development, suggesting direct involvement of IL-6 signaling in experimental hepatocarcinogenesis. The results from this study also showed the critical role played by the toll-like receptor (TLR) adapter protein MyD88 in the production of IL-6 by Kupffer cells during DENA-induced HCC development. The production of IL-6 by necrotic hepatocytes was reduced considerably in Kupffer cells deficient for MyD88. The ablation of MyD88 also suppressed DENA-induced hepatic tumorigenesis, indicating that IL-6 production by the TLR/MyD88/nuclear factor-kappaB (NF-κB) pathway is critical for HCC development. Another study from the same laboratory found that DENA-induced acute inflammatory response is triggered by IL-1α release from necrotic hepatocytes, and IL-1α stimulates IL-6 production by Kupffer cells (Sakurai et al. 2008). Moreover, the investigators have found that IL-1α released by damaged hepatocytes is essential for the compensatory proliferation which is essential for DENA-initiated hepatocellular carcinogenesis. Rogers et al. (2007) proposed a multistep model linking chronic hepatitis to

liver cancer through cytokine-mediated derangement of gender-specific cellular metabolism. This mouse model introduces a novel mechanism of inflammation-related carcinogenesis consistent with male-predominant HCC risk.

Several epidemiological studies reveal a strong link between obesity and development and progression of liver cancer (Nair et al. 2002; Larsson and Wolk, 2007; Gregor and Hotamisligil 2011). The connection between obesity and liver cancer is likely to be mediated, at least in part, by chronic inflammation (Sun and Karin 2012; Shimizu et al. 2013). Hypertropic adipocytes are known to accumulate excess lipids and release free fatty acids, and these cells together with various immune cells secrete a number of proinflammatory cytokines, including IL-6, IL-1β, IL-9, IL-10, IL-17, IL-18, and TNF-α (Sun and Karin 2012). It has been shown that macrophase infiltration into white adipose tissue, which is accompanied by IL-6 and TNF-α production, is an initial contributing event for the development of chronic low-grade systemic inflammation (Weisberg et al. 2003). Elevated concentrations of IL-6 have been found in type 2 diabetes, an inflammatory condition, inducing cellular insulin resistance (Senn et al. 2002; Donath and Shoelson 2011). Among obesity-related pathophysiological conditions that predispose HCC, insulin resistance and subsequent inflammatory cascades are considered to play a crucial role in the occurrence of HCC (Shimizu et al. 2013). Park et al. (2010) reported that dietary-induced or genetically induced obesity promotes DENA-initiated HCC with low-grade inflammation. Interestingly, ablation of IL-6 or TNF-α abolishes the tumor-promoting effects of these cytokines, indicating that IL-6 and TNF-α are required for the promotion of obesity-linked HCC.

IL-1β, another proinflammatory cytokine in hepatocarcinogenesis, is found to promote hepatic stellate cell proliferation, activation, and transdifferentiation into the myofibroblastic phenotype (Han et al. 2004). IL-1β can promote hepatic inflammation by inducing the production of C-reactive protein, a sensitive marker of infection and inflammation, independently of IL-6 (Weinhold and Rüther 1997). c-Jun N-terminal kinase (JNK) activation by IL-1β stimulated the pSmad3L/plasminogen activator inhibitor 1 pathway in facilitating hepatocytic invasion with simultaneous reduction of transforming growth factor-β (TGF-β)-dependent tumor-suppressive activity by the phosphorylated Smad3C/p21(WAF1) pathway (Matsuzaki et al. 2007). It has been reported that the C31T polymorphism in IL-1β could be a genetic marker for the development of hepatitis-associated HCC (Wang et al. 2003). According to a case-control study including 209 incident HCC cases, IL-1β-31T/C polymorphism may modify HCC risk in relation to alcohol intake or smoking (Sakamoto et al. 2008).

16.4.2 NF-κB Pathway

NF-κB, an important transcription factor that regulates innate immunity and inflammation, plays an essential function in the regulation of inflammatory signaling pathways in the liver (Xiao and Ghosh 2005; Muriel 2009). Accumulating

knowledge clearly indicate that NF-κB provides a critical link between inflammation and cancer (Karin 2009; DiDonato et al. 2012). Mammalian NF-κB consists of five members, namely RelA (p65), c-Rel, RelB, NF-κB1 (p50/p105), and NF-κB2 (p52/p100) (Ghosh and Karin 2002). Under normal physiologic conditions, p50 and p65 subunits of NF-κB dimerize are kept inactive in the cytoplasm through binding to the inhibitory protein known as inhibitor of NF-κB (IκB) (Hoffmann and Baltimore 2006). In response to various proinflammatory stimuli, including pathogen-derived lipopolysaccharide, viral and bacterial DNA and RNA, TLR-Myd88 signaling, and inflammatory cytokines (such as TNF-α and IL-1β), the IκB kinase (IKK) complex, which consists of two catalytic subunits, IKK-α and IKK-β, and a regulatory subunit, IKK-γ or NF-κB essential modulator (NEMO), phosphorylates IκB and subsequently induces its degradation by the 26S proteasome (Karin and Ben-Neriah 2000; West et al. 2006). Consequently, the activated NF-κB dimer is released and translocates into the nucleus, binds specific DNA sequences, and stimulates transcription of hundreds of target genes involved in inflammation, immune responses, cell proliferation, and cell survival (Pahl 1999; Ghosh and Karin 2002).

NF-κB has been found to be activated in virtually every chronic liver disease, including viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, and biliary liver disease (Luedde and Schwabe 2011). A wealth of information based on recently published studies illustrates a crucial role of NF-κB in connecting inflammation with hepatic oncogenesis (Arsura and Cavin 2005; Luedde and Schwabe 2011; He and Karin 2011). Several animal models have been developed to study the role of IKK/IκB/NF-κB signaling pathways in various cell populations during hepatocarcinogenesis. In Mdr2 knockout mouse model, which is an animal HCC model induced by chronic inflammation, inhibition of NF-κB with inducible IκB super-repressor resulted in decreased liver tumor progression (Mauad et al. 1994). Likewise, inhibition of NF-κB activation in liver parenchymal cells at later stages of hepatocarcinogenesis led to reduced inflammation-linked tumor progression in Mdr2 knockout mouse (Pikarsky et al. 2004). The liver tumor-promoting role of NF-κB has been confirmed by another study using hepatocyte-specific lymphotoxin αβ transgenic mouse model. In this inflammatory HCC model, inhibition of NF-κB via hepatocyte-specific deletion of IKK-β almost completely diminished HCC development (Haybaeck et al. 2009). In contrary, hepatocyte-specific deletion of IKK-β gene and therefore hepatocyte-specific inactivation of NF-κB signaling resulted in higher incidence of HCC in mice following exposure to hepatocarcinogen DENA (Maeda et al. 2005). Similarly, another laboratory found that inhibition of NF-κB through ablation of IKK-γ/NEMO, the regulatory subunit of IKK complex, in liver parenchymal cells led to spontaneous and sequential development of hepatosteatosis, hepatitis, fibrosis, and HCC (Luedde et al. 2007). Based on all these studies presented above, it can be concluded that NF-κB signaling possibly play dual roles in hepatocarcinogenesis depending on cancer model and stage of tumor development. Activation of NF-κB in non-parenchymal cells typically stimulates inflammation, fibrosis, and hepatocarcinogenesis. On the other hand, suppression of NF-κB activation in parenchymal cells accelerates hepatocarcinogenesis in several cancer models

and suppresses tumor formation in other models. During early stages of liver tumor development, the cytoprotective role of NF-κB prevails as it prevents hepatocyte death. In late stages, NF-κB promotes tumor cell survival and proliferation.

The influence of NF-κB signaling in myeloid cells has also been investigated utilizing DENA-induced HCC in mice. Ablation of IKK-β in both hepatocytes and myeloid cells (including Kupffer cells) has been found to inhibit DENA-induced HCC development (Maeda et al. 2005). This effect was accompanied by diminished production of proinflammatory cytokines, such as IL-6, TNF-α and hepatocyte growth factor, which are secreted by non-parenchymal cells in response to dying hepatocytes to stimulate compensatory proliferation of remaining hepatocytes (Maeda et al. 2005). Another study showed that IKK-β in myeloid cells, especially in Kupffer cells, has also been involved in the development of metastatic liver malignancy through IL-6 production (Maeda et al. 2009).

Several reports support the notion that NF-κB plays an indispensable role in the promotion of obesity-associated HCC. The effects of obesity-induced activation of NF-κB are believed to be mediated through the synthesis of NF-κB target genes, including IL-1β, IL-6, and TNF-α (Shoelson et al. 2006). Experimental results showed that high-fat diet increased NF-κB activation, resulting in sustained elevation of IKK-related kinase IKK-ε in the liver, adipocytes, and adipose tissue macrophages. Interestingly, IKK-ε ablation was found to reduce the expression of inflammatory cytokines and protected mice from high-fat diet-induced obesity, chronic hepatic inflammation, and hepatic steatosis (Chiang et al. 2009). Wang et al. (2009a) reported that administration of DENA enhanced the development of preneoplastic lesions in the livers of rats fed with a high-fat diet with simultaneous increase in TNF-α/NF-κB signaling and ERK-related hepatocyte proliferation. The role of hepatic NF-κB in obesity-associated liver tumorigenesis has been investigated in mice with liver-specific inactivation of the NF-κB essential modulator gene NEMO exposed to a high-fat diet. Hepatic NEMO deficiency has been found to synergize with high-fat diet in the development of liver steatosis, increased inflammation, and aggravated liver tumorigenesis (Wunderlich et al. 2008).

16.4.3 JAK-STAT Signaling

STAT proteins are known to play vital roles in cytokine signaling pathways involved in cell growth and differentiation in various species, including mammals (Darnell et al. 1994). The STAT family consists of seven members, such as STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. Among STAT family proteins, STAT3 has gained substantial attention as a convergent point for a number of oncogenic signaling pathways as well as regulator of signal transduction pathways of several proinflammatory cytokines and growth factors involved in hepatic damage and repair mechanisms (Taub 2003; Costa et al. 2003). Following phosphorylation and activation by JAKs, especially by JAK2, STAT3 undergoes dimerization before entry to nucleus for DNA binding (Yoshimura et al. 2007).

Subramaniam et al. (2013) have recently published an elegant review in which the authors presented an excellent overview of STAT3 signaling cascade and its interacting partners in the initiation of hepatocarcinogenesis and role of various STAT3-regulated genes in inflammation, survival, invasion, and angiogenesis during HCC progression. Based on an impressive number of studies, STAT3 has been recognized as a key player linking inflammation and liver cancer (Pfitzner et al. 2004; He and Karin 2011; Nakagawa and Maeda 2012; Subramaniam et al. 2013). He et al. (2010) have examined a large number of human HCC specimens and detected activated nuclear STAT3 in approximately 60 % of these samples with STAT3-positive tumors being more aggressive. These results are in agreement with a previous report in which STAT3 was found to be activated in the majority of HCC samples with poor prognosis, but not in surrounding non-malignant tissue or normal liver (Calvisi et al., 2006). Although the precise mechanisms of STAT3 activation in human HCC are not fully understood, the elevated expression of IL-6, IL-11, and IL-22 has been proposed to play an important role (He and Karin 2011).

Hepatocyte-specific STAT3-deficient mice have been used to investigate the role of STAT3 in experimental liver tumorigenesis induced by DENA. STAT3-deficient mice were found to exhibit more than sixfold reduction in liver tumor load compared to their normal counterparts (He et al. 2010). The suppressor of cytokine signaling 3 (SOCS3) is known to block STAT3 signaling, and hepatocyte-specific SOCS3 knockout mice have been found to be susceptible to HCC development, possibly due to activation of JAK/STAT and mitogen-activated protein kinase (MAPK) signaling (Ogata et al. 2006). Another study showed that hepatocyte-specific IL-6 and IL-6 receptor transgenic mice spontaneously developed hepatocellular hyperplasia and adenomas, which represent preneoplastic lesions in humans, with concomitant STAT3 activation (Maione et al. 1998). All these studies underscore the importance of IL-6/JAK/STAT3 pathway in the pathophysiology of liver cancer.

Several lines of evidence suggest possible interactions between STAT3 and NF-κB signaling pathways. It is well established that STAT3 and NF-κB coregulate various inflammatory and tumor-promoting genes (Yu et al. 2009). Moreover, STAT3 can directly interact with RelA (p65) subunit of NF-κB, confiding it in the nucleus, and thereby contributing to the constitutive activation of NF-κB in human neoplasm (Lee et al. 2009). In contrast, a separate study revealed that IKK-β/NF-κB signaling in hepatocyte negatively regulated STAT3 activation in DENA HCC animal model (He et al. 2010). Interestingly, similar inverse correlation between STAT3 and NF-κB signaling has also been observed in human HCC samples (He et al. 2010). SHP1 and SHP2, which dephosphorylate JAK2 and STAT3, function as negative regulator of JAK-STAT pathway. Hepatocyte-specific deletion of SHP2 promotes inflammatory signaling through the STAT3 pathway and hepatic inflammation/necrosis, resulting in spontaneous hyperplasia and development of hepatic tumors in aged mice. Additionally, SHP2 ablation dramatically enhanced DENA-induced HCC development, which was abolished by concurrent deletion of SHP2 and STAT3 in hepatocytes (Bard-Chapeau et al. 2011).

16.4.4 Epidermal Growth Factor Receptor Signaling

Epidermal growth factor receptor (EGFR), also known as ErbB1, is a transmembrane glycoprotein (170 kDa) consisting of an extracellular ligand-binding domain, a transmembrane domain, and a cytoplasmic domain that harbors a tyrosine kinase region. EGFR can be activated by a family of ligands, including epidermal growth factor (EGF), TGF-α, heparin-binding EGF (HB-EGF), betacellulin, epiregulin, and amphiregulin. Mounting evidence supports a role for the EGFR system in inflammation-related cell signaling with special emphasis in liver inflammation and HCC (Berasain et al. 2009b). Upregulation of EGFR has been found in human HCC samples, and several investigators have observed correlations between elevated levels of EGFR and poor patient survival (Berasain et al. 2007; Sibilia et al. 2007). Chronic activation of regenerative and wound-healing response mediated by EGFR signaling is thought to contribute tissue degeneration, resulting in chronic inflammation, fibrosis, and neoplastic transformation in the liver (Avila et al. 2006). Murillo et al. (2007) showed that TGF-β induced the expression of EGFR ligands, such as HB-EGF and TGF-α, in isolated fetal rat hepatocytes through the activation of NF-κB. The importance of EGFR in the activation of inflammation-associated NF-κB signaling has also been shown in the liver of transgenic mice overexpressing EGFR ligand TGF-α (Arsura and Cavin 2005).

16.4.5 Cyclooxygenase-Prostaglandin Pathway

One of the best characterized inflammatory pathways implicated in liver cancer is cyclooxygenase-2 (COX-2)-mediated prostaglandin pathway. COX-2, an inducible enzyme responsible for catalyzing the conversion of arachidonic acid to prostaglandins (PGs), plays a significant role in inflammation-associated hepatocarcinogenesis (Shiota et al. 1999). COX-2 has been found to be induced by proinflammatory mitogens, cytokines, and tumor promoters (Williams et al. 1999). Since chronic inflammation contributes to hepatocarcinogenesis and the expression of COX-2 has been known to be regulated by several transcription factors and cytokines implicated in inflammation, including NF-κB and IL-6, it is highly likely that inflammation-mediated induction of COX-2 may represent a pivotal step in hepatocellular carcinogenesis. As a matter of fact, it has been found that COX-2 is chronically overexpressed in chronic inflammation and cirrhosis as well experimental and human HCC (Wu 2006). Clinically, the expression of COX-2 in HCC has been found to be upregulated in well-differentiated HCC compared to less-differentiated tumor or histologically normal liver, indicating the involvement of COX-2 in early stages of hepatocarcinogenesis related to the inflammatory phenomena (Cervello and Montalto 2006; Giannitrapani et al. 2009). Additionally, evidence is available in the literature that COX-2 expressions are independent of tumor mass and tumor stage, and COX-2 signaling may play a key role both

in early as well as late states of hepatic cancer (Sung et al. 2004; Yildirim et al. 2008). COX-2-derived PG signaling has also been shown to be involved in cholangiocarcinoma, a highly malignant epithelial tumor arising within the biliary tract (Wu 2005).

Experimental evidence supports a close interaction between COX-2 and EGFR signaling pathways. The activation of EGFR in human HCC cells has been found to upregulate COX-2 expression and PGE2 synthesis (Dajani et al. 2008). Likewise, COX-2-derived PGE2 is known to transactivate the EGFR receptor (Wu 2005; Han et al. 2006). Moreover, COX-2-derived prostanoids may be one key signal in the activation of EGFR involved in the early stages of hepatic inflammation and neoplasia (Berasain et al. 2005; Castillo et al. 2006).

16.4.6 Inducible Nitric Oxide Synthase

Another important mediator linking chronic inflammation and liver cancer is nitric oxide (NO), produced by hepatic parenchymal and non-parenchymal cells from L-arginine through the catalytic function of inducible nitric oxide synthase (iNOS), also known as NOS2. NO reacts with superoxide ($O_2^{\bullet -}$) to form peroxynitrite ($ONOO^-$), a highly reactive nitrogen species that causes nitrative and oxidative DNA damage. Oxidative stress is known to elevate iNOS gene transcription and promoter activity in hepatocytes (Kuo et al. 1997). iNOS can bind and *S*-nitrosylate COX-2 protein to increase its activity (Kim et al. 2005). Mounting evidence underscores the vital role that iNOS plays in the development and progression of HCC as this enzyme has been found to be overexpressed in several rodent liver tumor models (Ahn et al. 1999; Denda et al. 2007; Calvisi et al. 2008). Interestingly, iNOS is a target gene for NF-κB and iNOS cross talk with NF-κB and Ha-RAS/ERK cascades influences HCC growth and prognosis (Calvisi et al. 2008). Additionally, iNOS expression has been found in hepatocytes and Kupffer cells in hepatitis, cirrhosis, and HCC (Rahman et al. 2001; McNaughton et al. 2002; Kawanishi et al. 2006).

16.4.7 Inhibitor of Apoptosis

The inhibitor of apoptosis (IAP) represents a family of proteins, including c-IAP1, c-IAP2, ML-IAP and XIAP, with significant roles in cancer-related inflammation and metastasis (Guicciardi et al. 2011; de Almagro and Vucic 2012). Alterations in IAPs have been observed in several types of human malignancies, including HCC, with chemoresistance, accelerated disease progression, and poor prognosis (Gyrd-Hansen and Meier 2010). IAPs are known to function by regulating caspases involved in apoptosis as well as modulate inflammatory signaling

through ubiquitin-mediated activation of NF-κB (Silke and Meier 2013). c-IAP1 and c-IAP2 function as key mediators of TNF-α-induced activation of NF-κB (Gyrd-Hansen and Meier 2010). A survivin-XIAP complex has been shown to activate NF-κB and accelerate metastasis in a splenic model of hepatic metastasis (Mehrotra et al. 2010).

16.4.8 Chemokines

Human chemokines are a family of small proteins (45–50 kb) containing a structural homologous conservative family of cysteine residues. Chemokines are classified into four groups, namely CXC, CC, CX3C, and C according to the presence of four cysteine residues in conserved locations. It is known that tumor cells can regulate chemokine expression to recruit inflammatory cells and also use these agents to facilitate tumor growth (Coussens and Werb 2002). Based on current knowledge, chemokines and their receptors, such as CXCL12-CXCR4 axis, CX3CL1-CX3CR1 axis, and CCL20-CCR6 axis, are believed to play intricate roles in HCC progression, growth, and metastasis, and immune response to HCC (Huang and Geng 2010). Activation of innate immune response in hepatocytes following chronic HCV infection leads to infiltration of proinflammatory and antiviral immune effector cells into the liver (Heydtmann and Adams 2009). This response is recruited to the liver, in part, by the chemokine CXCL10, which exerts its effects on resident and infiltrating cells. The deregulation of these cell populations within the liver may lead to chronic hepatic inflammation in HCV-linked HCC (Brownell and Polyak 2013).

16.4.9 MicroRNAs

MicroRNAs (miRNAs) are endogenous, small (20–25 nucleotides) noncoding RNA molecules that posttranscriptionally inhibit the expression of their target genes through mRNA degradation and/or translational inhibition (Bartel 2004). Several miRNAs function as oncogenes by inhibiting tumor suppressors and are overexpressed in cancers, whereas others function as tumor suppressors by inhibiting oncogenes and are downregulated or lost in cancers (Sengupta and Bishayee 2010). Aberrant expression of several miRNAs has been found to be involved in human liver cancer (Gramantieri et al. 2008; Braconi et al. 2011; Wong et al. 2013). Emerging experimental evidence supports the involvement of miRNAs in hepatocarcinogenesis via modulation of inflammatory signaling pathways. Ji et al. (2009) studied miRNAs expression profiles in human HCC samples and observed reduced levels of miR-26 expression as compared with paired non-cancerous

tissues. In addition, tumors with reduced miR-26 expression had activation of NF-κB and IL-6 signaling pathways. Another study demonstrated that low miR-26 played an important role in an experimental mouse model of HCC, and administration of this miRNA using adeno-associated virus resulted in inhibition of cancer cell proliferation, induction of tumor-specific apoptosis, and dramatic suppression of HCC development (Kota et al. 2009).

Wang et al. (2009b) showed upregulation of oncogenic miR-155 with concomitant suppression of its tumor-suppressor target CCAAT/enhancer-binding protein β (C/EBPβ) in choline-deficient and amino acid-defined diet (CDAA)-induced NASH that led to hepatocarcinogenesis in mice. The DNA-binding activity of NF-κB (indication of NF-κB activation) that transactivates *miR-155* gene was significantly elevated in the liver of mice fed with CDAA diet. Interestingly, the expression of miR-155 correlated with CDAA-induced hepatic inflammation as evidenced by histopathological changes. Ectopic expression of miR-155 promoted the growth of HCC cells, and its depletion resulted in an inhibition of tumor cell growth. This study also documented upregulation of miR-155 with a concurrent decrease in C/EBPβ level in primary human HCC samples compared with matching liver tissues.

Hepatocyte nuclear factor 4α (HNF4α) is a transcription factor essential for liver development and hepatocyte function. Recently, transient inhibition of HNF4α has been found to initiate hepatocellular transformation through a microRNA-inflammatory feedback loop circuit consisting of miR-124, IL6R, STAT3, miR-24, and miR-629. Moreover, it has been shown that once this circuit is activated, it maintains suppression of HNF4α and sustains hepatic oncogenesis. Finally, systemic administration of miR-124, which modulates inflammatory signaling, was effective in preventing and suppressing hepatocellular carcinogenesis (Hatziapostolou et al. 2011).

16.5 Inhibitors of Inflammation for the Prevention and Treatment of Liver Cancer

Numerous in vitro, in vivo, and clinical studies as described above have validated the critical role of chronic inflammation in the development and progression of liver cancer. Identification of cellular pathways necessary for the initiation and propagation of inflammatory cascade in HCC not only aids in understanding the pathophysiology, progression, and diagnosis but also provides a valuable tool in designing effective prevention and treatment of this disease. Hence, interfering with various inflammatory signaling molecules and pathways may offer potential opportunities for the development of novel drugs for the prevention as well as therapy of HCC. The following section highlights preclinical animal studies showing innovative approaches of targeting inflammatory mediators and signaling by a variety of natural compounds as well as synthetic agents.

16.5.1 Natural Compounds

A wide spectrum of phytochemicals present in fruits, vegetables, nuts, legumes, beverages, spices, and traditional medicinal herbs are endowed with potent anti-inflammatory properties implicated in cancer prevention and treatment (Murakami 2009; Kim et al. 2009; Aravindaram and Yang 2010; Gupta et al. 2010). Studies carried out in our laboratory and elsewhere strongly suggest that a number of bioactive components from dietary and non-dietary sources are capable of exerting liver cancer preventive and therapeutic efficacies through multiple mechanisms (Bishayee et al. 2010a, 2012; Darvesh and Bishayee 2010, 2013); Darvesh et al. 2012. As presented below and highlighted in Table 16.1, several phytoconstituents have been found to modulate various proinflammatory signaling during experimental hepatocarcinogenesis, resulting in liver cancer preventive or therapeutic effect.

N-acetylcysteine (NAC), a water soluble organosulfur compound present in garlic, exhibited chemopreventive potential against 2-amino-3,8-dimethylimidazo[4,5-*f*] quinoxaline (MeIQx)-initiated hepatocarcinogenesis in rats. NAC treatment during the post-initiation stage exhibited decreased number and area of glutathione *S*-transferase-placental form (GST-P)-positive foci by reducing cell proliferation which may involve downregulation of insulin-like growth factor I (IGF-I) and iNOS (Nishikawa-Ogawa et al. 2006).

Berberine, a bioactive alkaloid, is present in the root and bark of *Berberis aristata* or *Coptis chinensis*. Berberine showed antiproliferative effect during the early phase of hepatocarcinogenesis initiated by DENA and promoted with phenobarbital (PB) in rats, and this response was accompanied by inhibition of hepatic iNOS expression (Zhao et al. 2008).

Anthocyanins (glycosides) and anthocyanidins (aglycones) represent the most ample flavonoid pigments of various fruits and vegetables, including berries, grapes, apples, corn, and purple cabbage. Recently, our laboratory has shown that an anthocyanin-rich fraction from black currant (*Ribes nigrum* L.) fruit, containing cyanidin-3-*O*-rutinoside as the principle anthocyanin, significantly reduced the incidence and multiplicity of hepatic nodules during DENA-initiated and PB-promoted hepatocarcinogenesis in rats (Fig. 16.1) (Bishayee et al. 2011a). Subsequent study from our laboratory demonstrated that black currant anthocyanins afforded a striking inhibition of gamma-glutamyl transpeptidase (GGT)-positive preneoplastic foci during DENA/PB-mediated hepatocarcinogenic events by reversal of hepatic overexpression of COX-2 and iNOS and blockade of the nuclear translocation of NF-κB (Fig. 16.1) (Thoppil et al. 2012; Bishayee et al. 2013a).

Murugan et al. (2010) showed that black tea polyphenols (Polyphenon-B) reduced the multiplicity and volume of hepatic tumors in rats induced by *p*-dimethylaminoazobenzene (DAB) in rats with concomitant inhibition of hepatic NF-κB and elevation of IκB.

Chrysin (5,7-dihydoxy-flavone), a flavonoid present in honey, propolis, and several plant extracts, is available as a dietary supplement. This phytochemical has

Table 16.1 Modulation of inflammatory signaling in liver cancer by agents from dietary and non-dietary sources

Agents	Experimental models	Anti-hepatocarcinogenic effects	Anti-inflammatory mechanisms	References
Dietary compounds				
N-acetylcysteine	MeIQx-induced hepatocarcinogenesis in male F344 rats	↓GST-P-positive foci	↓IGF-I; ↓iNOS	Nishikawa-Ogawa et al. (2006)
Berberine	DENA-initiated and PB-promoted hepatocarcinogenesis in male Sprague-Dawley rats	↓hepatic proliferation	↓iNOS	Zhao et al. (2008)
Black currant anthrocyanins	DENA-induced hepatocarcinogenesis in male Sprague-Dawley rats	↓hepatic nodules; ↓GGT-positive foci	↓iNOS; ↓COX-2; ↓NF-κB	Bishayee et al. (2011a, 2013a), Thoppil et al. (2012)
Black tea polyphenols	DAB-induced hepatocarcinogenesis in male Sprague-Dawley rats	↓liver tumors	↓NF-κB; ↑IκB	Murugan et al. (2010)
Chrysin	DENA-induced hepatocarcinogenesis in male Wistar rats	↓hepatic nodules	↓COX-2; ↓NF-κB	Khan et al. (2011)
Curcumin	DENA-induced hepatocarcinogenesis in male Wistar rats	↓liver hyperplasia	↓NF-κB	Chuang et al. (2000)
	HepG2 xenograft in nude BALB/c mice	↓tumor angiogenesis	↓COX-2	Yoysungnoen et al. (2006)
EGCG	DENA-induced hepatocarcinogenesis in male C57BL/KsJ-db/db obese mice	↓foci, adenoma and HCC	↓p-IGF-IR; ↓p-ERK; ↓p-Akt; ↓p-STAT3; ↓p-JNK; ↓TNF-α; ↓IL-6; ↓IL-1β; ↓IL-18	Shimizu et al. (2011a)
Genistein	HepG2 xenograft in male nude BALB/c mice	↓tumor growth	↓COX-2; ↓NF-κB; ↓Akt	Ma et al. (2011)

(continued)

Table 16.1 (continued)

Agents	Experimental models	Anti-hepatocarcinogenic effects	Anti-inflammatory mechanisms	References
Geranylgeraniol	DENA/2-AAF-induced hepatocarcinogenesis in male Wistar rats	↓GST-P-positive foci; ↓hepatic nodules	↓NF-κB	Espindola et al. (2005)
Lycopene	DENA-initiated and NASH-promoted hepatocarcinogenesis in male Sprague-Dawley rats	↓GST-P-positive foci	↓pERK; ↓NF-κB; ↓TNF-α; ↓IL-1β; ↓IL-12	Wang et al. (2010)
Morin	DENA-induced hepatocarcinogenesis in male Wistar rats	↓hepatic ultra-structural changes	↓COX-2; ↓NF-κB; ↓p-Akt; ↓Akt	Sivaramakrishnan and Devaraj (2009, 2010)
Perillyl alcohol	DENA-induced hepatocarcinogenesis in male F344 rats	↓tumor	↑M6P/IGF-IIR; ↑TGF-β; ↑TGF-βB I, II, IIIR	Mills et al. (1995)
Pomegranate phytochemicals	DENA-initiated and PB-promoted hepatocarcinogenesis in male Sprague-Dawley rats	↓GST-P-positive foci; ↓hepatic nodules	↓iNOS; ↓COX-2; ↓NF-κB	Bishayee et al. (2011b, 2013b)
Resveratrol	DENA-initiated and PB-promoted hepatocarcinogenesis in male Sprague-Dawley rats	↓hepatic nodules	↓iNOS; ↓COX-2; ↓NF-κB; ↑TNF-α; ↑IL-1β; ↑IL-6	Bishayee and Dhir (2009), Bishayee et al. (2010b, c), Mbimba et al. (2012)
Saikosaponin-d	DENA-initiated hepatocarcinogenesis in Sprague-Dawley rats	↓hepatic nodules	↓COX-2; ↓C/EBPβ	Lu et al. (2012)
Silibin	HuH7 xenograft in nude mice	↓tumor growth	↓PTEN/p-Akt; ↓ERK; ↓NF-κB	Cui et al. (2009)

(continued)

Table 16.1 (continued)

Agents	Experimental models	Anti-hepatocarcinogenic effects	Anti-inflammatory mechanisms	References
Silymarin	DENA-initiated hepatocarcinogenesis in Wistar male albino rats	↓hepatic nodules	↓COX-2	Ramakrishnan et al. (2006, 2008)
Synthetic agents				
Acyclic retinoid	DENA-induced hepatocarcinogenesis in male *db/db* mice	↓hepatic adenoma	↓TNF-α; ↓IL-1β; ↓IL-6; ↓pERK	Shimizu et al. (2011b)
Aspirin	DENA- and NMOR-induced metastatic HCC in male F344 rats	↓metastasis	↓COX-2	Futakuchi et al. (2002)
Celecoxib	DENA-initiated and 2-AAF-promoted hepatocarcinogenesis in male Sprague-Dawley rats	↓GGT-positive foci	↓Translocation of NF-κB; ↑IκB-α	Márquez-Rosado et al. (2005)
Etodolac	Spontaneously developed HCC in male fatty liver Shionogi mice	↓HCC nodules	↓PGE2	Liu et al. (2006)
Fenretinide	DENA-initiated and 2-AAF-promoted hepatocarcinogenesis in male F344 rats	↓GST-P-positive foci; ↓hepatic nodules and HCCs	↓iNOS; ↑IκB; ↓NF-κB	Simile et al. (2005)
JTE-522	CDAA-induced hepatocarcinogenesis in male Wistar rats	↓GST-P-positive foci; ↓HCC	↓COX-2; ↓PGE2	Yamamoto et al. (2003)
Nimesulide	CDAA-induced hepatocarcinogenesis in male F344 rats	↓GST-P-positive foci; ↓hepatic nodules; ↓HCC	↓COX-2	Denda et al. 2002

(continued)

Table 16.1 (continued)

Agents	Experimental models	Anti-hepatocarcinogenic effects	Anti-inflammatory mechanisms	References
Pitavastatin	DENA-induced hepatocarcinogenesis in male *db/db* mice	↓preneoplastic foci	↓TNF-α; ↓IL-6	Shimizu et al. (2011c)
Roxithromycin	DENA-induced hepatocarcinogenesis in male Wistar rats	↓tumor volume	↓iNOS; ↓NF-κB	Ueno et al. (2005)
SC-236	CDE-induced hepatocarcinogenesis in C57Bl/6 J mice	↓dysplastic lesions; ↓foci; ↓nodular lesions	↓COX-2	Davies et al. (2006)
Sodium selenite	DENA-initiated and 2-AAF-promoted hepatocarcinogenesis in male Sprague-Dawley rats	Reversed histopathological alterations	↓NF-κB	Alwahaibi et al. (2010)
S-trans-trans-farnesylthiosalicylic acid	DENA-induced hepatocarcinogenesis in male Wistar rats	↓hepatic nodules; ↓GST-P-expressing hepatocytes	↓Ras membrane activity; ↓NF-κB; ↓STAT3	Schneider-Merck et al. (2009), Stärkel et al. (2012)
TNP-470	DENA-initiated and 2-AAF-promoted hepatocarcinogenesis in male Wistar rats	↓GST-P; ↓dysplastic nodules	↓iNOS; ↑IκB; ↓NF-κB	Mauriz et al. (2003)

↓, decrease or downregulation; ↑, increase or upregulation

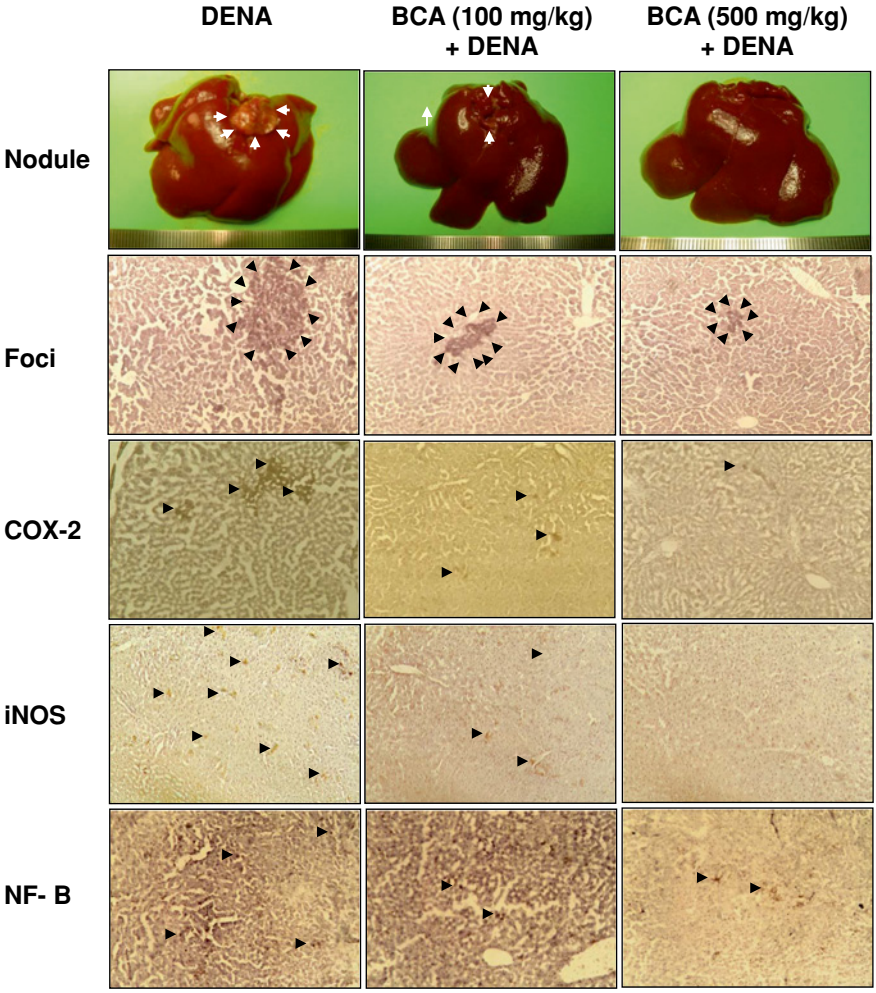

Fig. 16.1 Anti-inflammatory mechanisms implicated in the chemoprevention of rat liver carcinogenesis by black currant anthrocyanins (BCA). Male Sprague-Dawley rats were subjected to diethylnitrosamine (DENA) hepatocarcinogenesis. Rats were treated with BCA in diet (equivalent to 100 or 500 mg/kg body weight), starting the treatment 4 weeks before DENA administration and continued for 18 consecutive weeks following the carcinogenic exposure. Rats were sacrificed 22 weeks following the commencement of the study, and livers were subjected to morphological, histochemical, and immunohistochemical analysis. Chemoprevention of hepatocarcinogenesis by BCA was evidenced by reduced size of macroscopic hepatic nodules (indicated by *white arrows*) and microscopic gamma-glutamyl transpeptidase-positive preneoplastic hepatic foci (indicated by *black arrows*) in various rat groups (magnification: 100x). BCA downregulated hepatic expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in cytoplasm and reduced the nuclear expression of nuclear factor-kappaB (NF-κB) in a dose-responsive manner, indicating suppression of inflammatory cascade. Reproduced from Bishayee et al. (2011a, 2013a), and Thoppil et al. (2012) with permission

been studied for its chemopreventive activity during DENA-initiated early hepatocarcinogenesis in rats. Chrysin administration significantly reduced the number and size of hepatic nodules with an inhibition of hepatic expression of COX-2 and NF-κB (Khan et al. 2011).

Curcumin (diferuloylmethane) is the predominant active component present in the roots of perennial plant turmeric (*Curcuma longa*). Curcumin has been shown to prevent DENA-induced hepatic hyperplasia in rats with reduced hepatic NF-κB expression (Chuang et al. 2000). Yoysungnoen et al. (2006) reported antiangiogenic potential of curcumin in nude mice xenografted with HepG2 cells. Additional studies showed suppression of intratumor COX-2 expression.

Epigallocatechin-3-gallate (EGCG) is the primary catechin present in green tea. Shimizu et al. (2011a) have investigated the effects of EGCG on the development of DENA-induced liver tumorigenesis in obese and diabetic mice. EGCG in drinking water has been found to inhibit the phosphorylation of the IGF-IR, ERK, Akt, STAT3, and JNK proteins in the livers of experimental mice. The serum levels of insulin, IGF-I, IGF-II, free fatty acid, and TNF-α were all decreased by drinking EGCG, which also lowered the expression of TNF-α, IL-6, IL-1β, and IL-18 mRNAs in the livers.

Genistein, a phytoestrogen, can be found in soybeans and other legumes, such as chickpeas. Genistein retarded the growth of established tumors generated by injecting HepG2 cells in nude mice. Mechanistic results showed suppression of Akt activation, NF-κB activity, and downregulation of NF-κB regulated gene COX-2 (Ma et al. 2011).

Geranylgeraniol, a dietary diterpene, showed reduction in the number and size of GST-P hepatic foci and nodules during the pre- and post-initiation stages of DENA-induced hepatocarcinogenesis in rats. This study also revealed decreased cell proliferation, DNA damage, and NF-κB p65 expression following the treatment with geranylgeraniol (Espindola et al. 2005).

Lycopene, a bright red carotenoid pigment, is mostly found in tomatoes along with other red fruits and vegetables, including red bell peppers, red carrots, watermelons, and papayas. Lycopene as well as tomato extract curtailed the development of GST-P foci in DENA-initiated NASH-promoted hepatocarcinogenesis in rats. Additional results showed reduced activation of ERK and NF-κB and decrease in mRNA expression of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-12 (Wang et al. 2010).

Morin (3,5,7,2′,4′-pentahydroxyflavone), a bioflavonoid, is found in red wine, almonds, figs, and Osage orange. Sivaramakrishnan and Devaraj (2009, 2010) provided evidence for morin-mediated reversal of hepatic ultra-structural changes in DENA-exposed animals via apoptosis induction through modulation of the PI3K/Akt and NF-κB signaling pathways.

Perillyl alcohol, a monoterpene, is found in lavender oil, sage, cherries, orange peel, and peppermint. Mills et al. (1995) showed that dietary perillyl alcohol treatment in rats exposed to DENA inhibited hepatic tumor growth. The mRNA levels of mannose 6-phosphate/insulin-like growth factor-II receptor (M6P/IGF-IIR),

and TGF β type I, II, and III receptors (TGF-β I, II, III R) were also significantly increased in the liver tumors of perillyl alcohol-treated rats.

Our laboratory has demonstrated that a pomegranate-based formulation containing various phytochemicals, including caffeic acid, gallic acid, and ellagic acid, exerts a striking chemopreventive activity in rats subjected to DENA-PB hepatocarcinogenesis as evidenced by reduced incidence, number, multiplicity, size, and volume of hepatocyte nodules as well as GGT-positive focal number and area (Bishayee et al. 2011b). We have also reported that pomegranate bioactive phytoconstituents are capable of suppressing DENA-induced inflammatory cascade by reversing the elevated expression of iNOS, COX-2, and NF-κB during experimental hepatocellular carcinogenesis in rats (Bishayee et al. 2013b).

Resveratrol (3,4′,5-trihydroxy-*trans*-stilbene), a naturally occurring antioxidant and anti-inflammatory agent found in grapes, berries, peanuts, plums as well as red wine, has been shown to prevent the development or reduce the growth of tumors in multiple organs (Bishayee 2009). According to our study, dietary resveratrol reduced the incidence, total number, and multiplicity of hepatocyte nodules (Bishayee and Dhir 2009). Ancillary studies showed that resveratrol dose-dependently suppressed DENA-induced elevated expressions of hepatic inflammatory markers, such as iNOS, COX-2, and NF-κB, and attenuated the translocation of NF-κB to the nucleus by stabilizing IκB (Bishayee et al. 2010b, c). Additionally, we have also observed that resveratrol treatment reversed the DENA-induced alteration in the level and expression of hepatic TNF-α, IL-1β, and IL-6 (Mbimba et al. 2012).

Saikosaponin-d, a triterpene saponin, is extracted from *Bupleurum falcatum* L. (Umbelliferae). A recent study has investigated the chemopreventive potential of Saikosaponin-d against hepatocarcinogenesis and its possible molecular mechanism in vivo. The liver nodule formation, tumorous invasion to surrounding organs, and increased cellular atypia induced by DENA were markedly reduced by intraperitoneally injected saikosaponin-d. The immunohistochemical staining demonstrated that the expression of COX-2 and C/EBPβ (a protein involved in inflammation and carcinogenesis) was significantly increased in tumor cells and macrophages of liver tissue from DENA-treated rats, whereas the expression of these two proteins was markedly lowered in the saikosaponin-d plus DENA group (Lu et al. 2012).

Silymarin is a complex mixture of polyphenolic flavonoids present in the seeds of milk thistle (*Silybum marianum* L. Gaertner). Silibinin (also known as silybin) represents the major active component of silymarin. Silibinin reduced the growth transplanted HuH7 tumor through the inhibition of phosphatase and tensin homolog (PTEN)/p-Akt and ERK signaling and reduced the level of NF-κB (Cui et al. 2009). It has been showed time that both pre- and post-treatment of DENA-initiated rats with silymarin significantly inhibited the multiplicity and size of hepatic nodules (Ramakrishnan et al. 2006). A separate study from the same laboratory documented that dietary silymarin supplementation downregulated the hepatic expression of COX-2 during DENA-induced hepatic carcinogenesis (Ramakrishnan et al. 2008).

16.5.2 Synthetic Agents

Shimizu et al. (2011b) examined the effects of acyclic retinoid on the development of DENA-induced liver tumorigenesis in C57BLKS/J- +Lepr^{db}/+Lepr^{db} obese mice. The development of liver cell adenoma was significantly inhibited by acyclic retinoid which also markedly reduced the phosphorylation of ERK. The serum levels of TNF-α and the expression of levels of TNF-α, IL-1β, and IL-6 mRNA in the livers of DENA-treated mice were decreased by acyclic retinoid treatment, indicating attenuation of the chronic inflammation induced by excessive fatty deposits.

Aspirin (acetyl salicylic acid) significantly reduced the degree of highly metastatic HCC developed in rats by sequential treatment with DENA and *N*-nitrosomorpholine (NMOR). This effect was associated with aspirin-mediated downregulation of COX-2 in primary HCC (Futakuchi et al. 2002).

The chemopreventive effect of celecoxib, a specific COX-2 inhibitor, on the development of liver preneoplastic lesions in rats has been evaluated using a medium-term experimental hepatocarcinogenesis protocol. A reduction by 80 and 90 % both in the number and size of altered hepatic foci was observed in the group treated with celecoxib following carcinogen treatment, respectively. Neither COX-2 expression nor PGE2 production has been altered by the hepatocarcinogenic exposure or celecoxib treatment. Interestingly, celecoxib inhibited the translocation of Rel A/p65 to the nucleus from the cytoplasm with significant effect on stability of the repressor IκB-α (Márquez-Rosado et al. 2005).

The effect of etodolac ([±]-1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b] indole-1-acetic acid), a specific COX-2 inhibitor, on spontaneous development of HCC in fatty liver Shionogi mice has been evaluated. The development of HCC has been suppressed slightly in the high-dose group and suppressed markedly in the low-dose group, although the development of fatty liver has not been inhibited in either group. Plasma PGE2 levels were also decreased significantly in the low-dose group, consistent with the suppression of HCC (Liu et al. 2006).

Simile et al. (2005) have investigated the chemopreventive potential and possible mechanisms of action of fenretinide [*N*-(4-hydroxyphenyl)retinamide], a synthetic retinoid, using rats subjected to the "resistant hepatocyte" protocol that included initiation by DENA followed by 2-acetylaminofluorene (2-AAF) treatment and partial hepatectomy. Fenretinide suppressed the development of GST-P-positive foci, nodules, and HCC through inhibition of iNOS and inactivation of NF-κB.

Yamamoto et al. (2003) have investigated the inhibitory effects of JTE-522 [(4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide], a selective COX-2 inhibitor, on liver fibrosis and carcinogenesis induced by CDAA. JTE-522 significantly inhibited fibrosis and development of preneoplastic lesions in a dose-dependent manner and completely inhibited generation of cirrhosis and HCC at both low and high doses. Mechanistic studies indicated that the CDAA model displayed upregulation of several biomarkers, including COX-2 and PGE2, and increased the proportion of activated hepatic stellate cells, proliferating cell nuclear

antigen index, and CD45-positive inflammatory cells in the liver. JTE-522 effectively reversed all these changes.

The chemopreventive efficacy of nimesulide, a specific COX-2 inhibitor, has been tested in CDAA-induced rat hepatocarcinogenesis. Administration of nimesulide through diet decreased the number and size of preneoplastic, enzyme-altered liver foci, multiplicity of neoplastic nodules and hepatocellular carcinomas, and prevented the development of cirrhosis with reduced expression of COX-2 (Denda et al. 2002).

The effects of pitavastatin, a drug used for the treatment of hyperlipidemia, on the development of DENA-induced liver preneoplastic lesions have been examined in C57BL/KsJ-db/db (db/db) obese mice. Feeding of animals with 10 ppm pitavastatin significantly inhibited the development of hepatic premalignant lesions (foci of cellular alteration) as compared to the untreated group through inhibition of cell proliferation and induction of apoptosis. Pitavastatin improved liver steatosis, decreased free fatty acid and aminotransferases levels, while increasing adiponectin levels in the serum. Additionally, the serum levels of TNF-α and the expression of TNF-α and IL-6 mRNAs in the liver were decreased by pitavastatin treatment (Shimizu et al. 2011c).

Roxithromycin, a macrolide antibiotic, inhibited oxidative stress as measured by the level of thiobarbituric acid-reactive substances, NO production, and activation of NF-κB during DENA-induced hepatic carcinogenesis in rats. All these results were associated with a dose-dependent inhibition of hepatic tumor volume in experimental animals (Ueno et al. 2005).

SC-236, a selective COX-2 inhibitor, has been tested for its antihepatocarcinogenic potential using a choline-deficient, ethionine-supplemented (CDE) diet-induced rodent model of HCC. The test compound not only suppressed hepatocyte peri-cellular fibrosis and steatosis, but also inhibited the early stages of HCC (Davies et al. 2006).

Sodium selenite has been found to exert chemoprevention of DENA-initiated and 2-AAF-promoted hepatocarcinogenesis in rats as evidenced from histopathological observations with simultaneous inhibition of hepatic NF-κB expression (Alwahaibi et al. 2010).

Activation of Ras and its downstream signaling pathways are likely to contribute to the development of hepatocarcinoma. It has been shown that intraperitoneal injections of the *S-trans- trans*-farnesylthiosalicylic acid (FTS), a Ras inhibitor, blocks Ras activation and prevents heptocarcinoma development in rats challenged with DENA (Schneider-Merck et al. 2009). A follow-up study from the same laboratory showed that DENA-induced activation of NF-κB and STAT3 has been abrogated by FTS treatment. Although FTS treatment showed no effect on DENA-induced elevation of TNF-α, IL-6, and TLR4, it significantly reduced phosphorylation of the MAPK p38 and of the p70S6 kinase, a surrogate marker for mTOR activation, without affecting ERK and Akt phosphorylation (Stärkel et al. 2012).

TNP-470 (*O*-chloroacetyl-carbamoyl-fumagillol) is a synthetic derivative of fumagillin, a naturally secreted antibiotic from *Aspergillus fumigatus*. The expression of GST-P was significantly reduced in rats with hepatocarcinogenesis

receiving TNP-470 when compared to untreated animals. TNP-470 also inhibited oxidative stress, NO production, and NF-κB activation (Mauriz et al. 2003).

16.6 Conclusions and Future Directions

Emerging in vitro, in vivo, and clinical studies carried out during the last decade provide substantial evidence that activation of inflammatory signaling pathways plays a vital role in the pathogenesis and progression of liver cancer. It is also apparent that there are several mechanisms which contribute to the activation of inflammatory cascade in the liver in response to various etiological factors of liver cancer. There also exists the possibility of cross talk between inflammatory pathways and other signaling events in liver cancer. Since various inflammatory pathways are closely regulated at multiple cellular and subcellular levels, these pathways provide opportunities to develop novel preventive and therapeutic strategies for management of liver cancer. Based on current interest in inflammatory signaling pathways in liver cancer, it is conceivable that new signaling molecules and pathways of inflammation-linked HCC would be identified in the near future.

Several animal studies as presented in this chapter clearly demonstrate that various natural and synthetic compounds are capable of disrupting activated inflammatory signaling to halt or reverse the growth of a variety of transplanted HCC cells in vivo and inhibit the development and progression of chemically initiated, dietary-induced, or spontaneously occurring liver tumors in rodents. All these anti-hepatocarcinogenic effects could be possible due to inhibition of upstream activators of key inflammatory regulators, subunits of lead inflammatory mediators, activating kinases or target genes. The unique inflammation-hepatocarcinogenesis sequence in liver cancer clearly indicates that specific inhibitors of inflammatory pathways have the potential to block or disrupt the continuous transition from chronic liver injury to liver neoplasia. It is, indeed, noteworthy that all these structurally dissimilar compounds target nearly all known proinflammatory factors and signaling pathways in hepatic carcinogenesis. Since activation of inflammatory insult occurs during the early as well as late phases of multistage hepatocarcinogenesis, naturally occurring or synthetic anti-inflammatory agents could be effective in both chemoprevention and therapy of liver cancer.

Although a large number of preclinical and clinical studies underscore the importance of inflammation in liver cancer, the direct clinical application of this knowledge has not been fully realized. Similarly, despite the identification of a large number of natural as well as synthetic agents targeting inflammatory pathways during hepatocellular carcinogenesis, there remains a gap in the transition of these impressive results into clinical practice. Hence, future well-controlled clinical studies are needed to validate the promising preclinical results of blocking or diminishing liver cancer by interference with the inflammatory signaling by various natural and synthetic compounds. The safety of these agents also needs to be

established by appropriate clinical studies. Moreover, there are certain challenges as well as limitations of targeting inflammatory signaling. Several inflammatory pathways have a wide range of functions with complex cross talk and hence may function differently during hepatocarcinogenesis based on specific cell type and disease stage. Thus, inhibition of a signaling molecule in specific cell type within the liver would be more advantageous than global inhibition of the same target. An example of this premise is NF-κB. The tumor-specific suppression of NF-κB is beneficial. Nevertheless, generalized suppression of this inflammatory regulator may result in serious host toxicity with minimum effect on the tumor (Aggarwal and Sung 2011).

As presented here, various inflammatory signaling pathways are interconnected, and liver cancer may arise due to dysregulation of multiple pathways. Thus, agents that can suppress multiple pathways simultaneously may have better potential as liver cancer preventive and therapeutic drugs. The duration of therapy with anti-inflammatory drugs is another important consideration, and it is related to the extent of liver disease. In patients with severe fibrosis, cirrhosis or HCC, certain anti-inflammatory agents may trigger toxicity due to compromised liver function. Additionally, use of anti-inflammatory drugs in patients undergoing antiviral treatment, such as interferon therapy for HCV infection, may interfere with the clinical outcome of such treatment.

In conclusion, substantial experimental and clinical evidence as presented in this chapter strongly suggests that chronic inflammation fuels the development and progression of liver cancer and various proinflammatory molecules, and signaling pathways represent novel targets for the prevention and therapy of this devastating disease.

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