

Review

Insights into the Role of Oxidative Stress in Hepatocellular Carcinoma Development

Yuanyuan Li^{1,†}, Yang Yu^{1,†}, Lei Yang^{1,*}, Rui Wang^{2,*}¹Department of Medical Oncology, Affiliated Tumor Hospital, Nantong University, 226300 Nantong, Jiangsu, China²Department of Medical Oncology, Affiliated Jinling Hospital, Medical School of Nanjing University, 210016 Nanjing, Jiangsu, China*Correspondence: yanglei@ntu.edu.cn (Lei Yang); wangrui218@163.com (Rui Wang)

†These authors contributed equally.

Academic Editor: Giovanni Tossetta

Submitted: 19 April 2023 Revised: 18 July 2023 Accepted: 20 July 2023 Published: 8 November 2023

Abstract

Oxidative stress (OS) is linked to hepatocellular carcinoma (HCC) progression. HCC may develop as a result of genetic changes, including oxidative injury to both nuclear and mitochondrial DNA. Signaling pathways regulated by OS, such as Wnt/ β -catenin and Notch pathways, are vital regulators in developing HCC. OS-mediated activation of transcription factors, including nuclear factor- κ B and p53, among others, is capable of regulating the redox state of HCC cells. OS also affects the tumor microenvironment, which, in turn, regulates HCC progression. In HCC, reactive oxygen species (ROS) can potentially enhance tumor cell proliferation, metastasis, and resistance to treatment. However, elevated ROS levels can cause cytotoxicity and trigger apoptosis in HCC cells. This review highlights and explores potential oxidative stress-related treatment targets in HCC, offering novel insights for clinical therapies.

Keywords: oxidative stress; HCC; genetic changes; signaling pathways; transcription factors; tumor microenvironment; treatment targets

1. Introduction

Hepatocellular carcinoma (HCC) represents the predominant type of hepatic cancer, and is currently the sixth most frequently diagnosed cancer and the third leading contributor to cancer-associated mortalities, globally [1]. The progression of HCC is a complicated and multifaceted phenomenon, with its underlying mechanism still not fully understood [2]. Prominent risk factors for HCC include chronic infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV), exposure to aflatoxin, type 2 diabetes, liver cirrhosis due to excessive alcohol use, nonalcoholic fatty liver disease (NAFLD), which is linked to obesity, and smoking [3–5]. HCC progression involves multiple stages and several intricate pathways, such as phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR), Wnt/ β -catenin, Notch, and nuclear factor erythroid 2-related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (Keap1)/antioxidant response element (ARE) signaling pathways [6,7]. Oxidative stress (OS) significantly contributes to the onset and progression of HCC [8] and dysregulation of reactive oxygen species (ROS)-production and ROS-scavenging enzymes help drive HCC occurrence, which, in turn, leads to poor patient survival. If antioxidant systems are ineffective in mitigating cellular OS burden, then OS has the potential to induce genetic alterations in liver cells, ultimately leading to liver cancer [9,10]. Lately, the link between OS and the pathophysiology of liver cancer has been the subject of growing interest.

OS occurs when an imbalance develops between ROS production and accumulation following stimulation by harmful endogenous or exogenous factors. Free radicals, such as ROS and reactive nitrogen species (RNS), commonly function as metabolites in various redox reactions during normal cellular metabolism, and are increased upon OS initiation [11]. Both ROS and RNS include organic or inorganic molecules with an odd number of electrons and such molecules are produced during redox reactions within the body, and each exhibit high reactivity. Despite oxygen's crucial role as a substrate in oxidative metabolism, its partial reduction can lead to the formation of ROS [12]. ROS species generally include hydroxyl radical (OH^\cdot), superoxide anion ($\text{O}_2^{\cdot-}$), and hydrogen peroxide (H_2O_2) [13]. Among these, $\text{O}_2^{\cdot-}$ is produced by an oxidase (NADPH oxidase [NOX], superoxide dismutase [XO], and cytochrome P450 [CYP450]), and then can be dismutated to H_2O_2 by superoxide dismutase (SOD). And OH^\cdot is converted by H_2O_2 through a Fenton reaction in the presence of metal cations such as Fe^{2+} and Cu^+ [12,13]. When present at low levels, ROS functions as cell signaling molecule. Nonetheless, when present at high levels, these reactive molecules can cause damage to organelles, especially to the mitochondria. Such oxidative damage and related mitochondrial dysfunction may subsequently lead to depletion of cellular energy, accumulation of harmful mediators, and, ultimately, cell death [14]. Hence, understanding the association of stress adaptation with activation of cell death is crucial to obtain a deeper



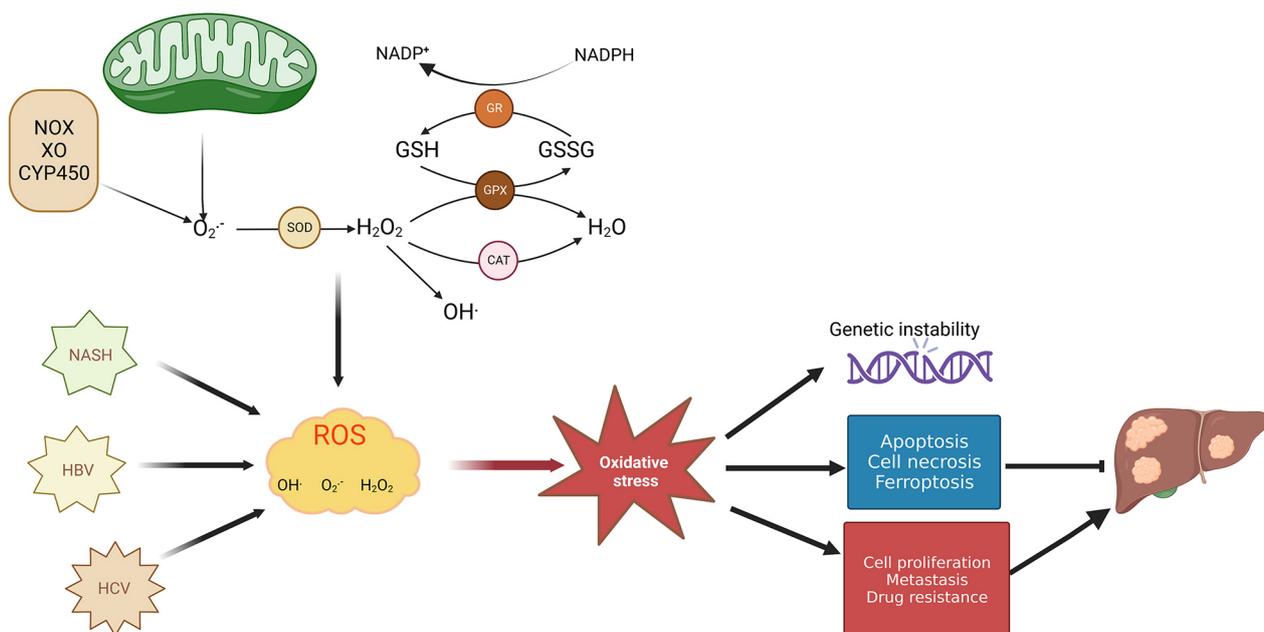


Fig. 1. Mechanism of redox balance–related HCC development. Both mitochondrial electron leakage and oxidase (NOX, XO, and CYP450) enzyme activity can produce superoxide anions ($O_2^{\bullet-}$). SOD converts $O_2^{\bullet-}$ into hydrogen peroxide (H_2O_2), which undergoes conversion into H_2O through CAT and GPX [19]. During the GPX reaction, GSH is oxidized to form GSSG, which can be reverted to GSH by GR following NADPH consumption [20]. NASH can promote ROS production through increased fat accumulation, which leads to the induction of OS. HBx in HBV and core proteins in HCV can cause ROS accumulation. ROS can trigger apoptosis, cell necrosis, and ferroptosis in liver cancer, but if the oxidant/antioxidant balance is disturbed, it can cause accumulation in DNA mutations, promote genetic instability, and result in liver cancer cell proliferation, metastasis, and drug resistance. Abbreviations used: CAT, catalase; GPX, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GSSG, glutathione disulfide; HBV, hepatitis B virus; HBx, hepatitis B virus x; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; NOX, NADPH oxidase; ROS, reactive oxygen species; SOD, superoxide dismutase; XO, xanthine oxidase.

comprehension of redox biology and disease pathogenesis. Mitochondrial dysfunction, including mitochondrial DNA (mtDNA) damage and abnormalities in oxidative phosphorylation (OXPHOS)–mediated ROS production can result in the onset and progression of several liver disorders such as liver cancer [15]. The progression of NAFLD into non-alcoholic steatohepatitis (NASH) causes an increase in mitochondrial ROS (mtROS), leading to oxidative mtDNA damage, structural abnormalities within the mitochondria, and lipid peroxidation [16]. mtROS and lipid peroxidation can also trigger the release of proinflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and IL-1 β , which are key mediators of NASH inflammation [17]. Additionally, increases in ROS also stimulate the accumulation of DNA mutations, which helps promote the transformation of NASH into HCC. Persistent HBV infection can also increase oxidative responses in affected patients, leading to abnormalities in the expression of *HBV* genes and further disruption of the oxidant/antioxidant balance and HCC development [18]. HBV and HCV infections can cause mitochondrial dysfunction and mtDNA damage, increasing ROS accumulation [18] (Fig. 1, Ref. [19,20]).

In different stages of cancer formation such as during tumor development, metastasis, and apoptosis, ROS activates various functions depending on cellular location, concentration, and duration within particular subcellular structures [21]. ROS's dual roles in cancer progression encompass ROS-driven malignant transformation and cell death induced by OS. ROS are capable of promoting alterations in genetic materials which help drive cancer occurrence, growth, and progression of both tumors and drug resistance. However, long-term overproduction of ROS is toxic to cells, and increased ROS may trigger apoptotic signals and consequently lead to cell death [22]. Particularly, ROS production at high levels is accompanied by cellular hyperproliferation within the tumor; however, tumor cells are capable of thriving under circumstances where the oxidative burden pushes redox balance away from a reduced state. This adaptability is achieved by tumor cells due to an enhanced antioxidant status, which optimizes ROS-fueled growth while avoiding ROS levels that would induce senescence, apoptosis, or ferroptosis [23] (Fig. 1). For example, oxidative stress may enhance glutaminolysis to promote synthesis of GSH and reduce oxidative stress [24]. How-

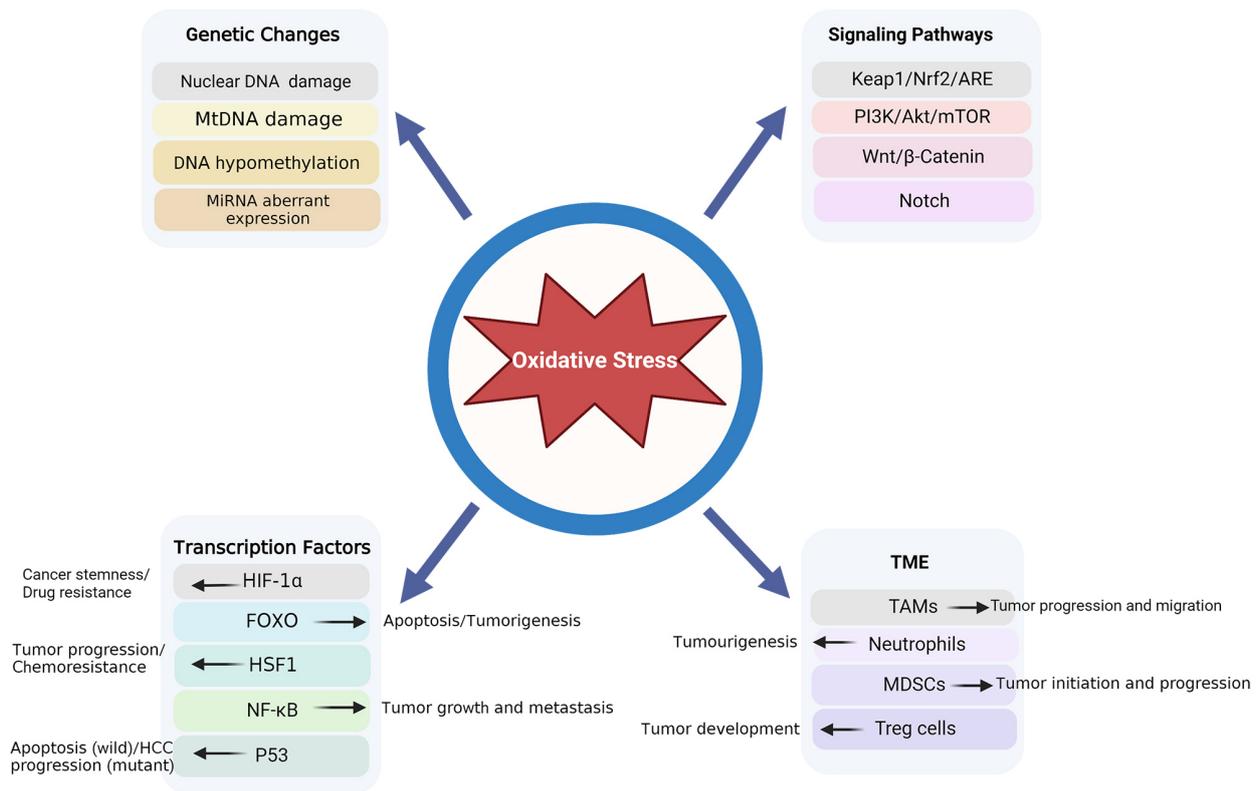


Fig. 2. OS-associated pathogenesis in HCC. HCC, hepatocellular carcinoma; OS, oxidative stress.

ever, studies have shown that excessive GSH promoted HCC tumor formation and growth [25]. Recent research demonstrates that tumor cells are capable of both glycolytic and OXPHOS metabolism, which renders them resistant to oxidative stress through enhanced antioxidant response and enhanced detoxification capacity [26]. In addition, changes in mitochondrial metabolism are closely related to the progression and metastasis of HCC [15]. In this review, we will highlight the effect of OS exerts on gene expression, signaling pathways, transcription factors, and tumor microenvironment (TME) in HCC development. Additionally, we will explore how OS functions in therapeutic treatment of liver cancer.

2. OS-Associated Pathogenesis in HCC

Four aspects are involved in the process via which OS results in HCC development: genetic alterations, signaling pathways, transcription factors, and the TME (Fig. 2).

2.1 OS-Regulated Genetic Changes in HCC

HCC can be induced by OS-associated genetic changes, including both oxidative nuclear and mitochondrial DNA damage, DNA hypomethylation, and aberrant microRNA expression. ROS-induced DNA damage and genetic instability are crucial developments in HCC onset and advancement [27,28]. 8-Hydroxydeoxyguanosine (8-OHdG), an oxidative DNA adduct, is a widely accepted marker for OS [29]. Ma-On *et al.* [30] studied the cellu-

lar response to OS and the level of DNA damage in human HCC tissues attributable to oxidation. They found that the 8-OHdG expression level was elevated in HCC tissues, particularly in HCC cell nuclei, and was linked to poor patient survival. *In vitro* experiments demonstrated that oxidative stress was induced by ROS, which substantially increased 8-OHdG expression levels in HCC cells. These outcomes indicate that ROS fosters an oxidative microenvironment in HCC cells, crucially promoting tumor progression.

Mitochondria can be impacted by various damaging factors, such as drugs, viruses, fat accumulation, and carcinogens [31]. When these factors exceed the mitochondria's coping ability, abnormalities in mitochondrial structure and function occur, for example, ROS accumulation following a disruption in the ROS scavenging system [18, 32]. MtDNA, which lacks histone protection, is vulnerable to damage caused by ROS [33,34]. Mitochondrial dysfunction contributes to ROS accumulation and mtDNA damage, potentially leading to HCC advancement. Shetty *et al.* [35,36] reported that mitochondrial ROS levels doubled at the time of the disease progression of nitrosodiethylamine-induced HCC in mice, resulting in DNA damage and proto-oncogene activation, and ultimately promoting tumorigenesis.

A high-calorie diet can cause fat accumulation, leading to metabolic stress and abnormalities in liver mitochondria [16]. When the condition progresses to NASH, the adaptability and flexibility of the mitochondria are reduced.

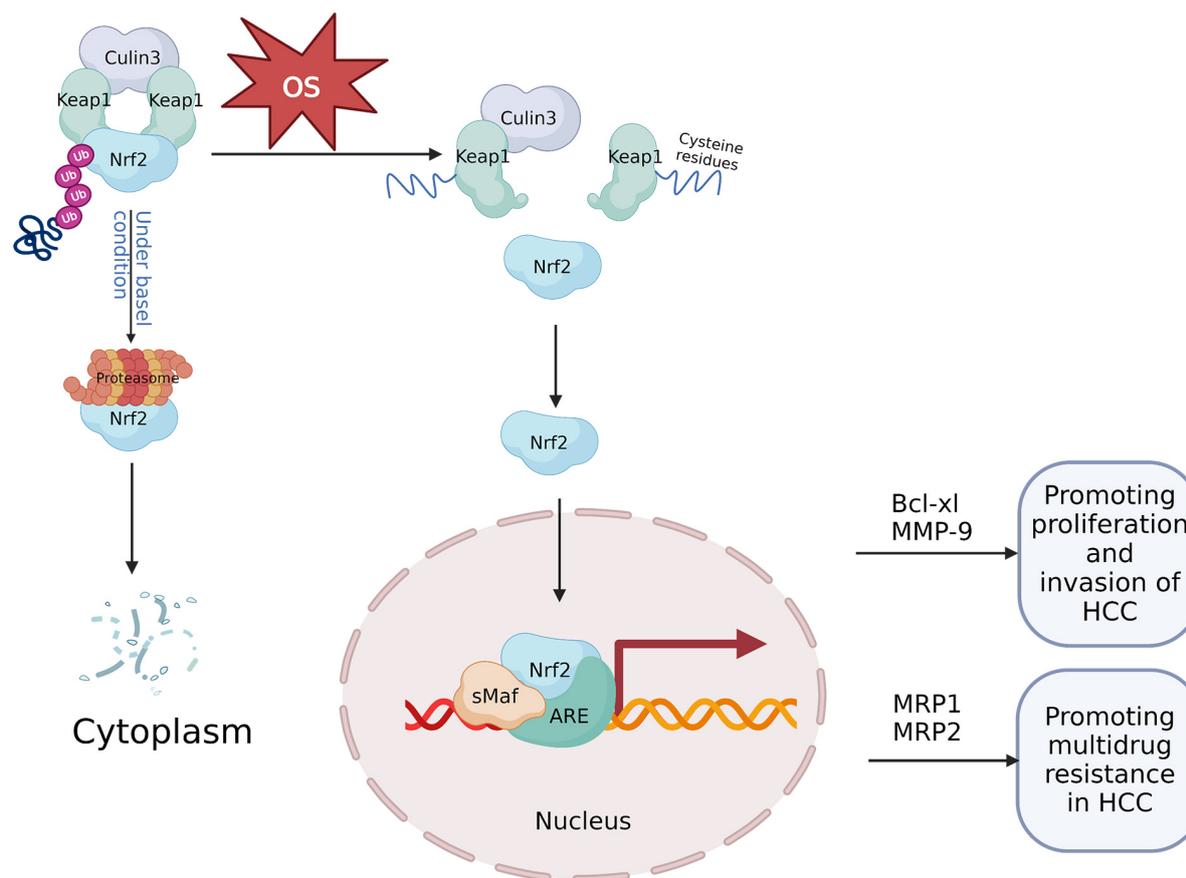


Fig. 3. Mechanism of the OS-mediated Keap1/Nrf2/ARE signaling axis in HCC. Under normal physiological circumstances, Keap1 binds to Nrf2 and the ubiquitin ligase Culin3, and forms a cytoplasmic complex. Keap1 reduces the stability of the Nrf2 protein through the ubiquitin-proteasome degradation, thereby negatively regulating Nrf2 and maintaining low cellular levels of Nrf2. However, during OS, cysteine residues within Keap1 are oxidized, Nrf2 is freed from its regulatory complex, resulting in stabilization of the Nrf2 protein and translocation to the nucleus where it forms a heterodimer with sMaf. Subsequently, Nrf2-sMaf heterodimers occupy ARE in the genome and activate target genes which contribute to cancer development. For example, Nrf2-dependent activation of Bcl-x1 and MMP-9 can enhance growth and invasiveness of cancerous hepatic cells. Further, increased expression of MRP1 and MRP2 mediated by Nrf2 can promote multidrug resistance in hepatocellular carcinoma. ARE, antioxidant response element; HCC, hepatocellular carcinoma; MMP, matrix metalloprotein; MRP, multidrug-associated protein; OS, oxidative stress.

As previously described, OS, mitochondrial malfunction, and oxidative mtDNA may facilitate the progression of NASH to HCC. Xie *et al.* [37] introduced the hepatitis B virus x (HBx) gene into the human liver cell line HL7702 and discovered that, in the presence of OS conditions, HBx triggered the inflammasome NLRP3 in HL7702 cells, as well as promoted pyroptosis via the mtROS pathway under OS conditions. The binding of the HBV protein HBx to the mitochondrial outer membrane enhances its permeability, resulting in the breakdown of mitochondrial membrane potential and increased ROS generation [38]. In addition, HBx directly binds to cytochrome c oxidase, thereby disrupting the mitochondrial respiratory chain and inducing increased ROS production [39]. HCV induces OS in liver cells, resulting in increased levels of ROS, including $O_2^{\cdot-}$, OH^{\cdot} , and H_2O_2 [40]. HCV core proteins inhibit the induction of ROS production through mitochondrial electron

transfer, which further induces both mitochondrial damage and ROS formation by enhancing CYP2E1 expression [41].

DNA methylation represents a significant epigenetic process that modulates gene expression, and is linked to the onset and advancement of differing cancer types [42]. This mechanism involves the covalent bonding of a methyl group, catalyzed by DNA methyltransferases (DNMTs), to the carbon at the 5th position of cytosine residues within CpG dinucleotides [42]. ROS can hinder this mechanism resulting in global DNA hypomethylation [43–45]. A link between chromosomal region abnormalities and DNA hypomethylation at repetitive DNA sequences has been observed, suggesting that global DNA hypomethylation could trigger chromosomal instability, ultimately contributing to hepatocarcinogenesis [46]. OS can change DNA methylation status by influencing the function of other enzymes that maintain epigenetic status including histone methy-

lases, and histone deacetylases (HDACs). Inducing OS in the HCC cells using hydrogen peroxide (H₂O₂) led to E-cadherin gene promoter hypermethylation stemming from enhanced Snail expression [47]. Snail triggers DNA methylation by recruiting HDAC1 and DNMT1 to sites of SNAIL occupancy. Human HCC also exhibit an association between ROS induction, E-cadherin downregulation, Snail upregulation, and E-cadherin promoter hypermethylation [47]. Recent findings revealed that increased ROS levels could upregulate Forkhead box C1 (FOXC1) expression via the ERK1/2-pELK1 pathway. FOXC1 subsequently elevates DNMT3B expression levels, resulting in DNA hypermethylation of the cystathionine γ -lyase (CTH) promoter and subsequent CTH gene silencing [48].

Micro RNAs (miRNAs) are responsible for regulating oncogenes and tumor suppressor genes in HCC, establishing a mechanistic link between epigenetics, inflammation, viral infection, and OS [49]. Both miRNAs and OS participate in the process of development of acute and chronic liver diseases, including viral hepatitis and oncogenesis, by affecting various signaling and metabolic pathways [50]. For example, miR483-3p may promote HCC metastasis via OS stimulation, uncovering a newly-discovered function of epigallocatechin-3-gallate for protection from miR483-3p-regulated HCC metastasis through the epigenetic modulation of miR483-3p [51]. Additionally, miR-33 deficiency improves mitochondrial function and reduces OS, and may represent an effective therapeutic approach for disease progression at different stages of HCC [52]. Overexpression of miR-92 and activation of telomerase activity are linked to the accumulation of ROS-mediated oxidative DNA damage during the development of chronic liver injury in HCC [53].

2.2 OS-Regulated Modifications in HCC Signaling Pathways

Numerous studies, including those on the Keap1/Nrf2/ARE, PI3K/AKT/mTOR, Wnt/ β -catenin, and Notch pathways have demonstrated the significance of redox modifications of components of these signaling pathways in HCC pathogenesis.

2.2.1 Keap1/Nrf2/ARE Pathway

The Nrf2 protein is a critical regulator of antioxidant response [54]. Under normal physiological circumstances, Keap1 functions as a Nrf2 inhibitor, maintaining basal cytoplasmic Nrf2 levels through ubiquitin-proteasomal system degradation of Nrf2 [55]. Conversely, during stress conditions, and most notably OS, Nrf2 expression increases. Cysteine residues within the Keap1 intervening region domain serve as redox sensors, and upon their oxidation, Nrf2 is liberated from its regulatory complex [56]. Further, under OS, the Nrf2 protein stabilizes and initiates a multistep activation process, including nuclear translocation and heterodimerization with its partner, small v-maf avian muscu-

loaponeurotic fibrosarcoma oncogene homolog (sMaf) proteins including MafG. Subsequently the complex recruits transcriptional co-activators and later attachment to target gene antioxidant response elements (AREs) [57]. The Nrf2-sMaf heterodimers occupy specific ARE sites within the genome, recruiting other transcriptional activators and inducing further Nrf2 transcription [58]. As Nrf2 shields cells from stress damage, it is formally classified as a tumor suppressor [59]; however, persistent oxidative stress during cancer development can result in Nrf2 hyperactivation, thus enhancing cancer cell survival [60] (Fig. 3).

In HCC, Nrf2 expression is associated with cell survival and various clinicopathological factors [61]. Nrf2 is abundantly expressed in cancerous cells and functions in tumor cell division and invasion. ROS significantly increases Nrf2 expression in liver cancer cells and creates an oxidative microenvironment in HCC, thus promoting further tumor development. The advancement of HCC due to ROS may be partially mediated through the activation of Nrf2 [62]. This suggests that stimulation of the Nrf2/Keap1/ARE signaling axis improves response to OS, which is advantageous for tumor cells in promoting liver cancer progression [30]. Thus, Nrf2 could be a potential prognostic indicator, and contribute to human HCC tumor cell proliferation and invasion partially by modulating Bcl-xL and matrix metalloproteinase-9 (MMP-9) expression [62] (Fig. 3).

The Keap1/Nrf2/ARE signaling axis is associated with chemotherapy resistance [62]. ROS-induced activation of Nrf2 controls sorafenib resistance in liver cancer cells [63]. Recent findings indicate that Nrf2 is overexpressed in chemoresistant HCC cells, thus contributing to the development of chemoresistance [64–66]. Ma *et al.* [67] demonstrated that Nrf2 expression was observed in three HCC cell lines, including HepG2, HepG3B, and SMMC-7721, and was associated with cisplatin (DDP) chemoresistance. Inhibiting dysregulated Nrf2 activation, particularly when combined with anticancer chemotherapeutics, is thought to be an effective strategy for overcoming multidrug resistance (MDR) and inhibiting tumor progression [68]. Nrf2 involvement in the MDR of HCC cells includes anti-apoptotic mechanisms and overexpression of Nrf2-regulated efflux transporters such as MDR-regulated proteins (MRPs), which enhance chemotherapy drug efflux and strengthen ROS defense systems. Niture *et al.* [69] reported that Nrf2 regulates Bcl-xL (an anti-apoptotic gene) expression by occupying a promoter in close proximity to Bcl-xL. This suggests that Nrf2 might contribute to anti-apoptotic protein expression and, thus, promote chemoresistance in HCC cells [69]. The expression of Nrf2-regulated MRPs, including MRP1 and MRP2, also increases, further contributing to chemoresistance in HCC cells [70] (Fig. 3). Gonzalez-Sanchez *et al.* [70] determined that Nrf2 activation reduced ROS levels stimulated by adriamycin, cisplatin, sorafenib, and SN-38 (an irinotecan metabolite with antineoplastic activity), leading to anti-

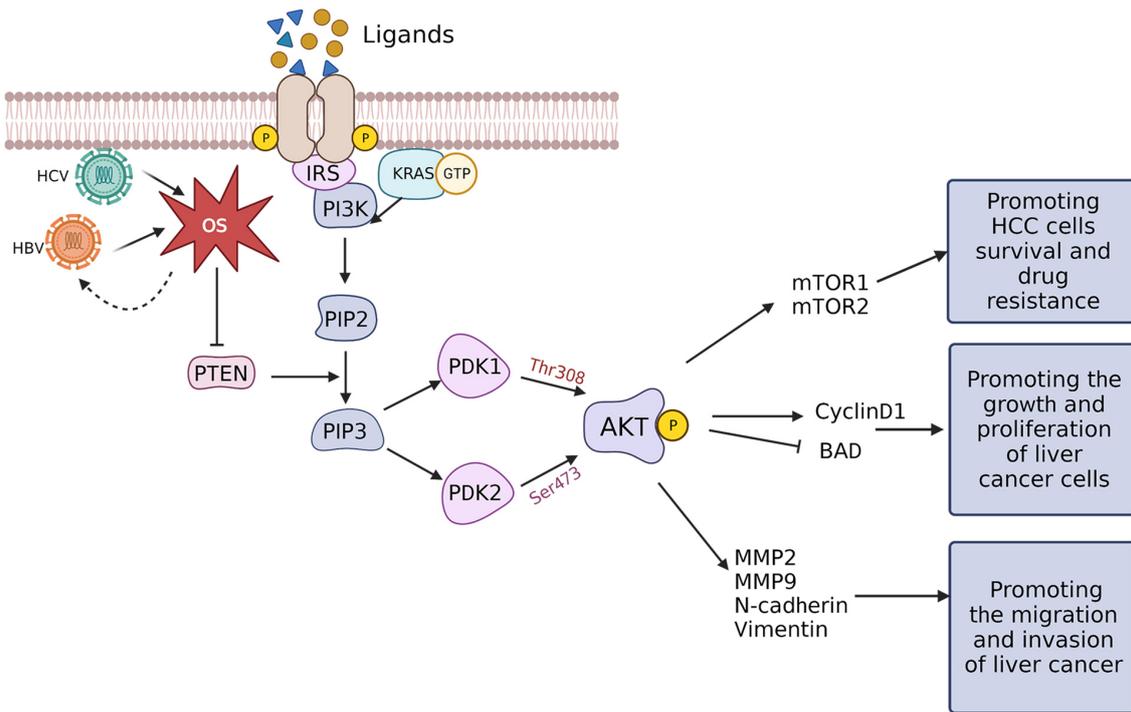


Fig. 4. Transduction mechanism of OS-controlled PI3K/AKT/mTOR signaling in HCC. When ligands, including growth factors, cytokines, and hormones, bind RTKs the RTKs undergo autophosphorylation and form homodimers. The activated RTKs can subsequently recruit PI3K, undergo direct activation via the regulatory subunits that bind to the G-protein KRAS, or are indirectly activated by IRS. Activated PI3K can phosphorylate PIP2 to form PIP3 which can, in turn, recruit PDK1 and PDK2. PDK1 and PDK2 phosphorylate Thr308 and Ser473 of the AKT regulatory region, respectively, thereby phosphorylating AKT. PTEN can dephosphorylate PIP3 to block AKT activation, while HBx and HCV core proteins can downregulate PTEN through ROS-mediated pathways to activate the PI3K/AKT/mTOR signaling. AKT can promote the survival and drug resistance of liver cancer cells by activating mTOR1/2 and can enhance the growth and proliferation of cancerous hepatic cells by upregulating cyclin D1 and blocking BAD. Furthermore, AKT can also upregulate EMT-related proteins such as MMP-2 and 9, N-cadherin, and vimentin, promoting liver cancer cells migration and invasion. BAD, Bcl-2-associated death; EMT, epithelial-mesenchymal transition; HBx, hepatitis B virus x; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MMP, matrix metalloproteins; mTOR, mammalian target of rapamycin; OS, oxidative stress; PTEN, phosphate and tensin homolog; RTK, receptor tyrosine kinase.

apoptosis and reducing the effectiveness of chemotherapy against HCC. Nrf2 is upregulated in response to low doses of ROS, and Nrf2 has been shown to increase telomerase activity, decrease oxidative stress, and promote the survival of liver cancer cells through regulating human telomerase reverse transcriptase (*hTERT*) gene expression [71]. Mitochondrial hTERT promotes drug resistance of tumor cells by reducing ROS production and Mitochondrial DNA damage, and playing a protective role on mitochondrial respiratory chain [72]. Recent clinical immunohistochemistry analysis of hTERT expression in 135 liver cancer tissues found that hTERT is mostly expressed in the cytoplasm of these tissues and is directly connected to oxidative stress [73].

2.2.2 PI3K/AKT/mTOR Pathway

The PI3K/AKT/mTOR pathway is a key intracellular signaling pathway that participates in regulating various cellular mechanisms, including cell cycle progres-

sion, cell proliferation, death, metabolism, and angiogenesis. It is stimulated in different cancer types due to dysregulation of receptor tyrosine kinases (RTKs) [74]. RTK monomers serve as high-affinity cell surface receptors for growth factors, cytokines, and hormones. Upon ligand binding, RTK monomers activate and dimerize, triggering autophosphorylation and subsequent activation of the PI3K/AKT/mTOR signaling axis [75,76]. Activated RTKs activate the lipid kinase PI3K, which catalyzes phosphorylation of phosphatidylinositol present within the internal leaflet of the plasma membrane. Direct activation of PI3K is achieved through binding to the regulatory region of RTKs or indirectly through adaptor molecules including insulin receptor substrates. Activated PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to form phosphatidylinositol-3,4,5-triphosphate (PIP3) [77, 78]. Subsequently, PIP3 interacts with phosphoinositide-dependent protein kinase 1 (PDK1) and AKT and recruits them to the plasma membrane. For AKT activation to

be complete, Thr308 and Ser473 residues within the AKT regulatory domain must be phosphorylated by PDK1 and PDK2, respectively [79]. The tumor suppressor phosphatase and tensin homolog (PTEN), is a phosphatase that catalyzes dephosphorylation of PIP3 to generate PIP2, which also regulates AKT. Two complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), are formed when several proteins bind to mTOR and activate it [80] (Fig. 4).

Stimulation of the PI3K/AKT/mTOR signaling pathway is linked proliferation, migration, invasion, and drug resistance of HCC cells [81–83]. The mTOR pathway is the major tumor-initiating pathway in HCC, and mTORC1 is upregulated in liver cancer, which is a possible pharmacological target for mitigating drug resistance in liver cancer [83]. Among the major factors for the abnormal stimulation of the AKT/mTOR signaling pathway is PTEN expression. Strong evidence for the crucial function of mTORC2 during liver tumor formation comes from how PTEN loss combines with c-Met to increase the development of HCC via the mTORC2 pathway [84].

The primary regulatory protein in HCC advancement is HBx, which is encoded by the HBV genome [85]. The oxidative inactivation of PTEN by HBx-stimulated ROS production activates the AKT pathway. Moreover, the positive regulatory loop that HBx and ROS maintain, which, through cyclin D1, contributes to hepatocellular carcinogenesis [86]. Hep3B cells and 293T cells overexpressing HBx stimulate AKT to phosphorylate I κ B kinase (IKK α) and drive its nuclear translocation, encouraging tumor cells to invade and migrate [87]. HBx also activates PI3K/AKT, leading to phosphorylation and blockade of the Bcl-2-associated death promoter (BAD), a pro-apoptotic protein that induces an opening of the mitochondrial permeability transition pore (MPTP). Phosphorylation of BAD thus inhibits apoptosis and promotes the proliferation of liver cancer cells [88]. Moreover, HCV downregulates PTEN through ROS-mediated pathways and stimulates the PI3K/AKT signaling pathway to counteract the growth inhibition stemming from p53 activity, thereby enhancing tumor cell growth and proliferation [89]. Further, targeting PTEN to activate the PI3K/AKT/mTOR signaling axis can lead to sorafenib resistance in liver cancer cells [90]. Recent research by Bataller *et al.* [91] showed that HCV core protein expression promoted growth in hepatic stellate cells in a manner dependent on RAS/ERK and PI3K/AKT. Another HCC study determined that ROS mediates apoptosis via suppression of the PI3K/AKT/mTOR signaling pathway [92], which is associated with ROS concentration, confirming a dual function for OS in cancer (Fig. 4). In addition, ROS participates in the regulation of cancer telomerase activity through activation of AKT signaling by activating telomerase to enhance HCC malignant potential [93,94].

HCC cell invasiveness induced by ROS is also believed to be mediated through the epithelial-mesenchymal transition (EMT), and is considered among the key regulatory factors for activating EMT [95]. Furthermore, EMT plays a significant part in HCC progression [96]. Stimulation of the PI3K/AKT/mTOR signaling pathway can induce EMT to promote HCC progression through MMP2, MMP9, N-cadherin, and vimentin [97] (Fig. 4).

2.2.3 Wnt/ β -Catenin Signaling Pathway

The Wnt/ β -catenin signaling pathway, which affects metastasis and treatment resistance, is another significant signaling pathway in HCC [98–100]. Tumor cell growth is caused by the ROS-dependent oxidation and inactivation of nucleoredoxin (NRX), a redox-sensitive regulator. This set of events is triggered by NADPH oxidase (NOX), stimulates the canonical Wnt/ β -catenin pathway [101]. Low-density lipoprotein receptor-related protein 5/6 (LRP5/6) phosphorylation primes the signal, which activates and recruits dishevelled (Dvl), forming an assembly platform for the LRP6 signalosome. These events are followed by ligand binding to the heterodimeric receptor complex generated by Frizzled (Fz) and LRP5/6 located on the plasma membrane. Wnt, Fz, Axin, phosphorylated LRP5/6, GSK3, and CK1 are all signalosome components, and this complex eventually enhances the stabilization and cytoplasmic accumulation of β -catenin. Myc, cyclin D1, and Axin2 are examples of Wnt target genes that can be promoted by free β -catenin following its translocation into the nucleus. Once in the nucleus, β -catenin forms a complex with the lymphoid enhancer factor/T-cell factor (LEF/TCF) transcription factor complex [102,103]. A destruction complex, which is made up of the scaffold protein Axin, APC, casein kinase 1 (CK1), and glycogen synthase kinase 3 β (GSK3 β), closely modulates the level of β -catenin in the cytoplasm. When Wnt ligands are absent, the destruction complex binds to and phosphorylates β -catenin, which is then recognized by the E3 ubiquitin ligase β -transducing repeats-containing protein (β -TRCP) followed by proteasomal degradation of β -catenin [103] and inhibition of the Wnt/ β -catenin pathway [104,105]. Phosphorylation of GSK3 β is upregulated by ROS and this results in the inactivation of GSK3 β via stimulation of the PI3K/AKT signaling pathway (Fig. 5, Ref. [106]). Moreover, meningioma-associated protein 30 (MAC30) speeds up the growth and infiltration of HCC cells by modulating Wnt/GSK3 β / β -catenin signaling [107]. Together, these findings demonstrate that the Wnt/ β -catenin pathway and the redox status of HCC cells are subject to bidirectional modulation and interactions between these regulatory mechanisms function in HCC pathophysiology.

The activation of EMT is a crucial step for HCC cells to acquire a malignant phenotype [108]. Among the primary signaling pathways that control the onset of EMT is the Wnt/ β -catenin pathway and this signaling axis is crucial

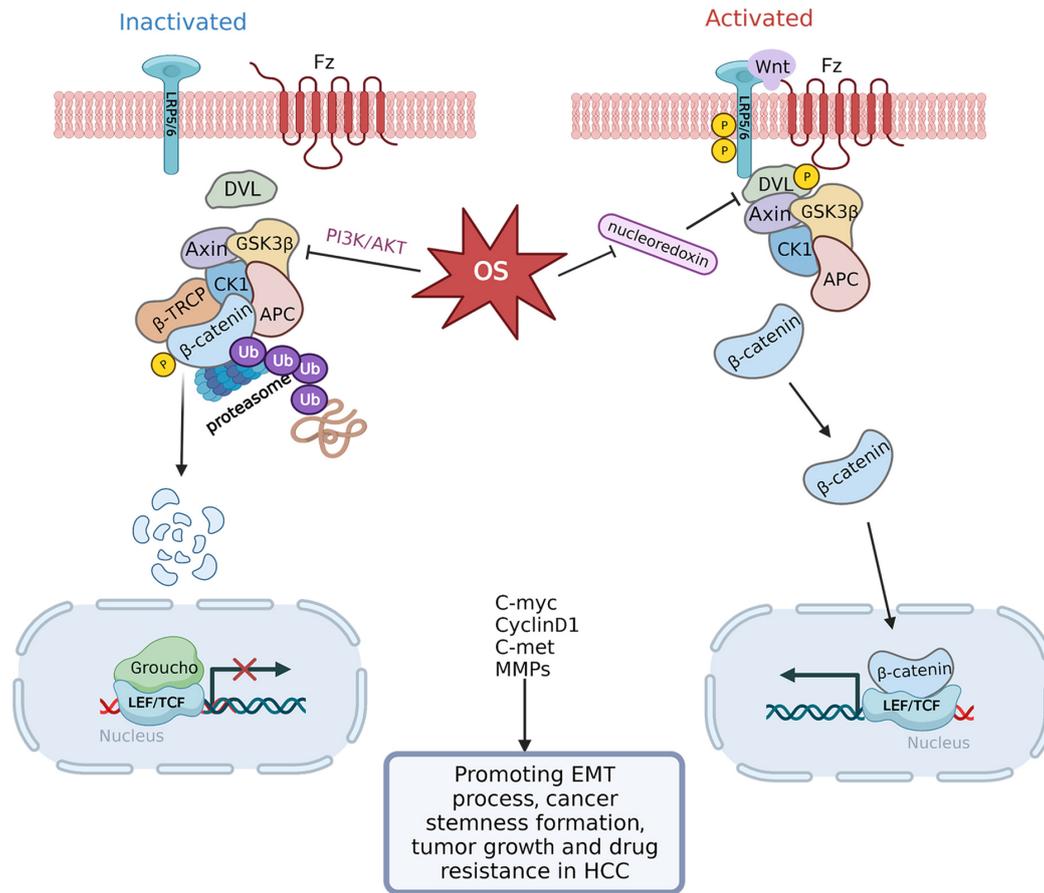


Fig. 5. Transduction mechanism controlling OS-regulated Wnt/ β -catenin signaling in HCC. The destruction complex is comprised of the proteins Axin, APC, CK1, and GSK3. When Wnt ligands are absent, the destruction complex captures and phosphorylates β -catenin present within the cytosol, which is subsequently identified by β -TRCP and targeted for proteasomal degradation. This prevents nuclear entry of β -catenin and thereby inhibits Wnt/ β -catenin signaling. The presence of Wnt ligands can induce Fz and LRP5/6 to form heterodimer complexes, and phosphorylated LRP5/6 can activate and recruit Dvl. Phosphorylated Dvl, however, can recruit Axin leading to disruption of the complex, thus promoting β -catenin stabilization and cytoplasmic accumulation. Free β -catenin enters the nucleus to displace Groucho and form a complex with the LEF/TCF transcription factor complex, promoting the activation of Wnt target genes such as c-Myc, cyclin D1, c-Met, MMPs. This also promotes EMT, cancer cell stemness, tumor growth, and drug resistance in HCC [106]. ROS can either cause phosphorylation and inactivation of GSK3 β through the PI3K/AKT pathway or inhibit Dvl by oxidizing and inactivating nucleoredoxin; thus, ROS can bidirectionally regulate the Wnt/ β -catenin pathway and redox status in HCC cells. Fz, frizzled; Dvl, dishevelled; HCC, hepatocellular carcinoma; LEF, lymphoid enhancer factor; MMP, matrix metalloprotein; OS, oxidative stress; ROS, reactive oxygen species; TCF, T-cell factor; β -TRCP, β -transducin repeats-containing protein.

for the modulation and maintenance of HCC stemness [109] (Fig. 5). A negative correlation exists between Wnt activity and T-cell signatures, specifically, by enhancing CD8⁺ T-cell infiltration in HCC, blocking Wnt/ β -catenin can improve anti-PD-1 immunotherapy [110]. In this way, inhibiting the Wnt pathway can make HCC cells more sensitive to chemotherapy [106].

2.2.4 Notch Signaling Pathway

Notch signaling has a link to steatosis and OS, specifically, H₂O₂ has been suggested to modulate the expression of Notch [111]. Alcohol-induced OS and buildup of lipids in HepG2 cells are reduced by the Notch1 inhibitor [112].

Moreover, triptolide (TP) promotes hepatotoxicity via initiation of OS. Shen *et al.* [113] reported that TP caused inhibition of Notch1 protein expression and the Notch intracellular domain thus blocking the possibility of conferring protection against TP-induced damage by active Notch signaling. The Notch signaling pathway is frequently linked to the onset and progression of tumors [114] and Notch1 suppresses the development of cancer cells and dysregulated angiogenesis [115]. Interestingly, MCUR1 promotes ROS-induced nuclear translocation of Nrf2 which, in turn, stimulates the Notch pathway and induces EMT and liver cancer metastasis [116]. Further, Notch signaling activation is linked to drug resistance in hepatoma cells. For example,

valproic acid reverses sorafenib resistance via suppression of Notch/AKT signaling in HCC [117], and inhibition of Notch signaling increased the sensitivity of HCC CD133+ cells to vincristine and 5-fluorouracil [118].

2.3 ROS-Regulated Modifications in Transcription Factors in HCC

ROS stimulates several transcription factors such as hypoxia-inducible factor-1 alpha (HIF-1 α), forkhead box O (FOXO), heat shock factor 1 (HSF1), NF- κ B, Nrf2, and p53. Activation of these molecules subsequently regulate the cellular redox state [119]. HCC is regulated by FOXO, HSF1, NF- κ B, and HIF-1 α under OS conditions.

FOXO family members including FOXO1, FOXO3, FOXO4, and FOXO6 are involved in supporting cellular homeostasis through various mechanisms [120]. These molecules enhance antioxidant status by inducing genes that eliminate ROS, improve mitochondrial redox, and inhibit levels of free transition metal ions by increasing metallothionein and ceruloplasmin abundance [121]. FOXOs respond to ROS, nutritional status, as well as genes implicated in apoptosis and cell cycle arrest like GADD45 [120]. ROS can activate AKT to directly phosphorylate FOXOs, which leads to the expulsion of FOXOs from the nucleus and suppression of their transcriptional activity. Inhibition of FOXO transcriptional activity could trigger apoptosis in HCC cells [122]. Since FOXOs cause cell cycle arrest and apoptosis, they were once characterized as tumor suppressors; however, mounting evidence indicates that FOXOs, particularly FOXO3, actually promote carcinogenesis. According to Lu *et al.* [123], FOXO3 expression accelerated carcinogenesis caused by hepatotoxin and the positive feedback loop between AKT and mTORC2 activation was activated when FOXO3 induced OS and DNA damage. It bears consideration that FOXO3, triggered by both ROS-promoting and ROS-eliminating systems, is linked to the activation of the pentose phosphate pathway (PPP).

Hypoxic response is largely regulated by hypoxia inducible factor-1 alpha (HIF-1 α), a transcription factor that is commonly expressed in numerous carcinomas, particularly HCC [124]. Low levels of oxygen result in an unbalanced flow of electrons in the electron transport chain which leads to the generation of ROS [125]. HIF-1 α is triggered in response to ROS accumulation and permits the transcription of genes that improve glycolysis within anaerobic environments [126,127]. For example, in hypoxic HCC cells, mitochondrial ubiquinol-cytochrome c reductase complex assembly factor 3 (UQCC3) creates a positive feedback loop with ROS generated in the mitochondria, which sustains UQCC3 expression and the production of ROS. As a result, mitochondrial structure and function is preserved and HIF-1 α improves glycolysis [128]. The transcriptional factor and stem cell marker NANOG facilitates the maintenance of stem cell capacity for self-renewal, pluripotency, and an undifferentiated phenotype [129], and NANOG can

modulate HIF-1 α . Of note, HIF-1 α or Toll-like receptor 4 (TLR4) can activate NANOG [130,131]. In HCC, NANOG activation through TLR4 increases fatty acid oxidation and suppresses mitochondrial oxidative phosphorylation. These processes result in the reduction of oxygen consumption rates and ROS formation [131]. This scenario further induces drug resistance and the maintenance of tumor-initiating stem-like cell capacity for self-renewal which can be resolved by restoring oxidative phosphorylation and suppressing fatty acid oxidation [131].

Heat Shock Transcription Factor 1 (HSF1) responds to protein misfolding-induced stressors through induction of genes encoding heat shock protein chaperones. HSF1 specifically responds to ROS via oxidation of internal Cys-35 and Cys-105 residues, and subsequent stimulation of antioxidant gene expression [132,133]. Upregulated HSF1 expression commonly occurs to protect tumor cells against diverse types of stresses [134] and increased expression of HSF1 activates a metabolic phenotype switch and chemoresistance in cancer cells. For example, HSF1/AMP-activated protein kinase α (AMPK α 2)-mediated alterations in the metabolic phenotypes confer enhanced oxaliplatin resistance in HCC cells [135]. In HSF1-knockdown HCC cells, glucose intake, lactate generation rates, and intercellular ROS levels were found to be reduced [136]. These findings indicate a positive correlation between ROS levels and HSF1 expression. Furthermore, liver carcinogenesis has been linked to the overexpression of inducible nitric oxide (NO) synthase and HSF-1, thus promoting tumor advancement [137].

By triggering cytokines, chemokines, and receptors that promote tissue healing, NF- κ B modulates an adaptive immune response aimed at eliminating invasive infections and NF- κ B also controls the expression of antioxidant genes [138]. By upregulating anti-apoptotic genes, cyclins, MMPs, cell adhesion, and pro-angiogenesis genes, NF- κ B facilitates tumor cell survival, growth, and metastasis [139]. NF- κ B also helps shift metabolism towards glycolysis and controls the TME by modulating primary immune cell functions [140]. NF- κ B serves as an anti-apoptotic factor, and multiple cancer cell types frequently exhibit dysregulated NF- κ B activity [141]. In HCC, ROS produced by the mitochondrial respiratory chain activates NF- κ B, which promotes tumor development and metastasis [142]. Cellular ROS levels are influenced by the transcriptional activity of NF- κ B-dependent genes, and NF- κ B levels are likewise influenced by ROS [138]. Thus, ROS can not only activate NF- κ B signaling but also inhibit NF- κ B. For example, NF- κ B activity is both inhibited by activated by mitochondrial ROS, which induces apoptosis in HCC cells [143].

P53 increases the antioxidant status of cells via transactivation of genes which encode proteins that scavenge ROS, support GSH production, enhance NADPH synthesis, detoxify xenobiotics, and promote pro-oxidant enzymes such as NO synthase 2 (NOS2) and cyclooxygenase 2

(COX2) [144,145]. Improvement in NADPH synthesis triggered by p53 occurs as a result of upregulation of the p53-induced glycolysis and apoptosis regulator TIGAR, which promotes DNA repair and reduces ROS to maintain redox balance [146]. Conversely, p53 also exhibits pro-oxidant activities through upregulation of p53-inducible genes (PIGs), such as PIG3 a quinone oxidoreductase/ ζ -crystallin synthesizing ROS via redox-cycling quinones, and p67phox which triggers formation of the NOX2 complex [147,148]. P53 provides defense against cancer by regulating cell cycle arrest, senescence, and apoptosis [149].

P53 promotes antioxidant genes under moderate OS conditions to aid in adaptability; however, under harsher circumstances, p53 modulates cancer cell death by promoting the generation of ROS. PIG3 and PIG6 are two p53 target genes that promote apoptosis, and mitochondrial proline dehydrogenases generate ROS via a mechanism that supplies carbon to various other mitochondrial dehydrogenases, which in turn produce ROS [148,150]. Genes encoding BAX, PUMA, and p66Shc are induced when p53 is activated by high levels of ROS. These genes disrupt the functioning of mitochondria, release cytochrome c, and enhance the generation of ROS [151]. Moreover, SOD2 and numerous Nrf2 target genes are repressed when p53 is active in proapoptotic scenarios [152]. OS induces changes in p53 activity and can upregulate p53 in HCC cells thereby inducing apoptosis of cancerous hepatic cells and inhibiting tumor proliferation and growth [153]. Furthermore, chronic infection with HBV and HCV contributes to ROS and RNS production, which can cause mutations in the *p53* gene and subsequent promotion of liver cancer [154].

2.4 ROS-Mediated Alterations in the TME in HCC

HCC is a form of cancer associated with inflammation, and most cases of HCC occur due to liver damage and chronic inflammation [155]. Prolonged and unresolved inflammation leads to the infiltration of immune cells into the liver which facilitates tissue remodeling [156]. The infiltration of immune cells results in a disturbance in the generation of chemokines and cytokines and a rise in the synthesis of ROS and RNS, which promote the development of fibrosis, cirrhosis, and, ultimately, the malignant transformation of liver cells [157]. The genesis, development, and therapeutic response in HCC tumors are all influenced by TME remodeling. By influencing various factors such as tumor-associated macrophages (TAMs), neutrophils, myeloid-derived suppressor cells (MDSCs), and Treg cells within the TME, OS plays a prominent role in modulating HCC development and progression.

TAMs within the TME mainly exert their function through secreted factors. Such factors include epidermal growth factor (EGF), cytokines (IL-6 and TNF- α), chemokines (CXCL17 and CCL24) which directly regulate the growth and metastasis of tumors [158]. TAMs can also increase the expression levels of IL-10 and transforming

growth factor β (TGF- β) within the TME as well as producing stromal and tumor cell activators such as EGF, basic fibroblast, vascular endothelial, platelet-derived growth factors, and TGF- β , all of which can regulate tumor development [159]. These findings suggest an interaction between factors secreted by TAMs and the TME that influence tumor progression. In hepatocytes, ROS are primarily produced by the mitochondria and released by complex I and/or complex III of the respiratory chain in response to TNF- α [160]. TNF- α -triggered synthesis of ROS stimulates NF- κ B, ultimately activating pro-survival signals, causing an increase in cell migration. OS induces TAMs to release cytokines such as TNF- α , IL-6, IL-10, and TGF- β which lead to HCC progression [104,161,162]. ROS production is critical for macrophage differentiation and continuous administration of the ROS inhibitor nanoliposome-loaded C6-ceramide (LipC6) in mouse models of hepatic malignancy effectively prevents TAM accumulation and significant inhibition of carcinogenesis [163].

Neutrophils are also becoming recognized as a significant player in the pathophysiology of HCC. Current evidence indicates that neutrophils are key mediators of the immunosuppressive environment as well as being drivers of tumor progression [164]. Growing evidence indicates that neutrophils function during the initial phases of carcinogenesis because they directly interact with HCC cells, mostly by producing ROS which leads to genomic instability [165]. S100A9, which belongs to a class of proteins termed damage-associated molecular patterns (DAMPs), displays upregulated expression when induced via HBV and has a direct impact on HCC cells by facilitating HCC progression and metastasis [166]. S100A9 affects neutrophil recruitment in acute and chronic hepatic damage in a mouse model, as well as promoting neutrophil stimulation and degranulation [166]. S100A9, which is also regulated by HBV, has an indirect impact on HCC malignancy by promoting the proliferation of neutrophil extracellular traps and activating neutrophils.

MDSCs induce the differentiation and expansion of Tregs during tumorigenesis, as well as producing OS [167]. The expansion of MDSCs can suppress immune function, as demonstrated by increased levels of arginase, NO, and ROS [168]. MDSCs also exhibit consistent alteration following a rise in the synthesis of ROS in response to therapy with Pam3CSK4 and Ro5-3335 [169]. Maintaining the immunological TME is crucial for MDSCs and promoting their polarization will enhance cancer immunotherapy. The immunosuppressive TME that enhances tumor onset and advancement can be alleviated by preventing the formation and recruitment of MDSCs within the liver. For example, long-term metformin therapy can prevent the accumulation of MDSCs in Ncoa5^{+/-} mouse livers displaying NASH, along with a decreased risk of developing HCC [170].

Factors involved in chronic liver disease influence Treg cells. Alcohol, high-fat diet, gut microbiota, and

metabolites are some examples of environmental stressors that can promote hepatic damage [18]. OS considerably contributes to the downregulation of Treg stimulation and their population, resulting in steatosis and fibrosis [171]. The progression of NASH toward tumor development increases the population of Tregs to establish a pro-tumorigenic TME. The development of NAFLD-linked HCC is aided by Tregs and neutrophils facilitating communication between the innate and adaptive immune systems. In work conducted by Hang *et al.* [172], isoallo-LCA increases FOXP3 expression levels which in turn triggers mitochondrial ROS generation and encourages Treg development. Fe-MnO₂/dihydroartemisinin (DHA) undergoes degradation within the TME, which induces ROS accumulation and subsequent triggering of ferroptosis and apoptosis of hepatoma cells [173]. DHA also acts as an immunomodulator to inhibit Tregs and systemic antitumor effects. Taken together, Fe-MnO₂/DHA offers a multimodal treatment for HCC that is triggered by ferroptosis, apoptosis, and immune activation and which substantially promotes synergistic chemotherapy for cancer.

These results suggest that a rise in ROS triggers alterations in the TME that promote carcinogenesis by changing the roles of MDSCs and TAMs and, coordinately, generating alterations in Tregs that may inhibit immunological reactions against tumor cells.

3. ROS-Mediated Autophagy in HCC

Autophagy, a catabolic process, eliminates defective and damaged cellular material via lysosomes. It is activated in response to a variety of stresses, including nutrient deprivation, hypoxia, and oxidative stress [174]. ROS can initiate the formation of Autophagosome and act as a cell Signaling molecule for autophagic degradation. Conversely, autophagy reduces oxidative damage and ROS levels by removing protein aggregates and damaged organelle such as mitochondria [175]. Additionally, autophagy has a dual influence, initially inhibiting the formation of tumours. Mitochondrial autophagy eliminates damaged mitochondria, preventing the accumulation of ROS and thereby reducing the effect of ROS on tumour formation [174]. But promoting cancer cell proliferation in already formed tumors, especially after chemotherapy with drugs, enhances autophagy, which may lead to tumor resistance and disease recurrence [176].

Under oxidative stress, Nrf2 activates and induces the autophagy pathway in cells, ultimately leading to the proliferation, migration, and invasion of HCC [177]. It is known that autophagy related protein p62 plays a key role in the modulation of Nrf2-Keap1 pathway [177,178]. In addition to Nrf2 activation, the carcinogenic signal transduction of p62 protein may affect other and multiple pathways, such as NF- κ B, Wnt/ β -catenin, mTOR, and c-Myc [178,179]. ROS leads to the up regulation of autophagic proteins, such as Beclin 1, autophagy related 5 (ATG5), microtubule as-

sociated protein1 light chain 3 (LC3)-II by inhibiting the AKT/mTOR pathway, and then increases the formation of Autophagosome, ultimately leading to the death of liver cancer cells. In addition, ROS can also promote autophagy by activating ERK1/2, p38, and c-Jun N-terminal kinase (JNK) phosphorylation in the mitogen-activated protein kinase (MAPK) pathway [180]. Recent studies have shown that some drugs, such as Coptisine, β -Thujaplicin and Mal-lotudin D can also promote autophagy in liver cancer cells by inhibiting the AKT/mTOR pathway, thereby achieving anticancer efficacy [181–183]. Notch1 mediated oxidative stress and mitochondrial dysfunction may be related to the autophagy pathway. The decrease in Notch1 levels may alleviate liver cell damage by reducing oxidative stress and promoting autophagy [184]. ROS can promote autophagy by activating the AMPK/mTOR/Unc-51-like kinase 1 (ULK1) pathway, effectively inhibiting the growth of HepG2 tumors transplanted into nude mice [185,186]. In addition, AMPK can also induce autophagy by promoting FOXO3 phosphorylation [187]. Hypoxia induced autophagy in liver cells and HCC tumor cells dependent on transcription factor HIF-1 α . Research shows that HIF-1 α . Upregulation of (adenovirus E1B 19 kDa protein-interacting protein 3) BNIP3 and BNIP3L proteins that bind to Bcl-2 protein. Under hypoxic conditions or after mitochondrial ROS generation, activation of Beclin 1 actively regulates autophagy, enabling cells to survive under hypoxic conditions [188]. Some non-coding RNAs are also associated with oxidative stress-induced autophagy. Circ-SPECC1 regulates autophagy under oxidative stress by sponging miR-33a, promoting the occurrence of HCC [189]. Targeting the mTOR pathway, upregulation of miR-7 can increase autophagy activity in HCC cell lines, thereby inhibiting cancer cell proliferation [190]. MiR-375 inhibits autophagy by downregulating ATG7 and inhibiting the conversion of LC3-I to LC3-II. Tumour growth in nude mice is greatly suppressed when cells expressing miR-375 are injected into the animals [191] (Fig. 6).

4. Possible OS-Associated Treatment Targets in HCC

Considering the importance of OS in promoting HCC, restoring the balance between oxidants and antioxidants is of significant therapeutic significance in HCC, and drugs that control OS are a key option for effective HCC therapy. Chemotherapeutic medications, organic compounds, traditional Chinese medicine, and nanoparticles have all recently drawn interest as these drugs can tackle abnormal OS in HCC in various ways. The majority of these substances, including vitamin C and trolox, enhance OS resulting in oxidative harm to DNA and a triggering of apoptosis in HCC cells. A few of these drugs, including 19- α -hydroxyurs-12(13)-ene-28-oic acid-3-*O*- β -D-glucopyranoside (HEG) and polydatin, activate antioxidant enzymes and decrease the synthesis of superoxides

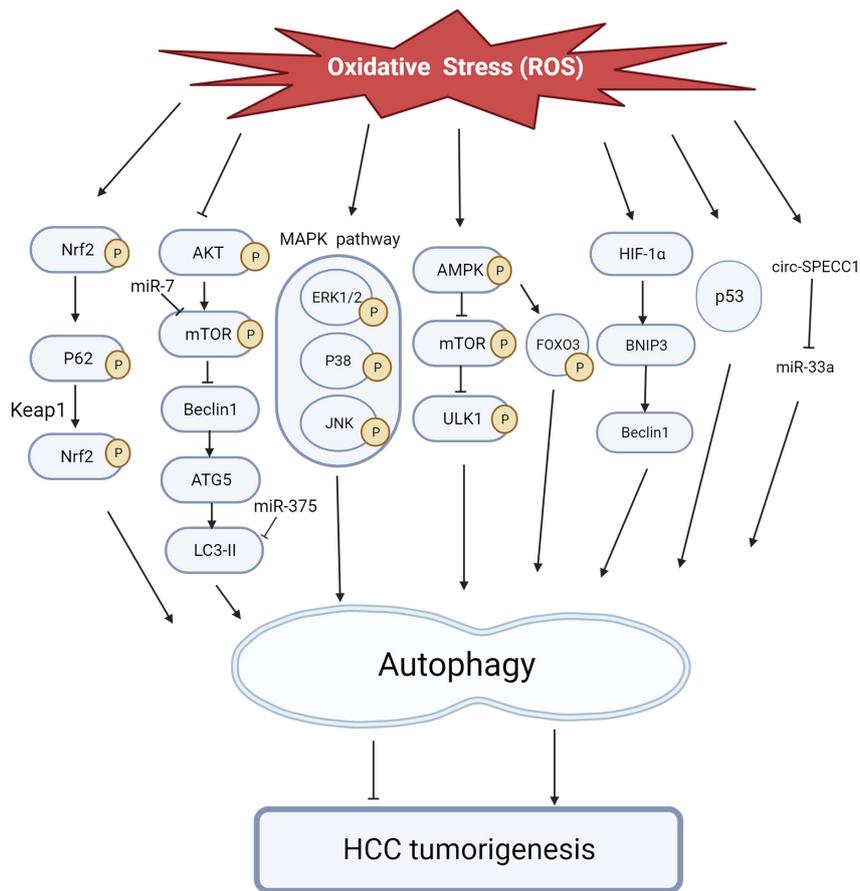


Fig. 6. The role of ROS-induced autophagy in HCC tumorigenesis. ROS regulates autophagy via the pathways, transcription factors, and non-coding RNAs depicted in the figure above, initiating or inhibiting liver cancer development.

for the purpose of reducing OS and inhibiting the proliferation, invasion, and migration of HCC cells. The three principal types of therapeutic drugs currently employed for treating patients with HCC are provided in Table 1 (Ref. [92,180,181,192–228]).

4.1 Chemotherapeutic Drugs

Chemotherapeutics cause OS, inflammation, apoptosis, and aberrations in neurotransmitter metabolism, all of which contribute to their toxicity. Oxazoline anthracyclines have drawn interest as potential signaling mediators of proliferation, differentiation, and death of cancer cells because they produce ROS and RNS [229]. High amounts of ROS are produced by platinum-containing complexes, alkylating agents, camptothecins, and arsenic agents. In contrast, low quantities of ROS are produced during response to taxanes, vinca alkaloids, nucleotide analogs, and antimetabolites such as antifolates and nucleosides [230]. 1-Methylpropyl 2-imidazolyl disulfide (PX-12), a thioredoxin 1 (Trx1) inhibitor, has been studied in various cancer types [231–233]. PX-12 therapy upregulates Bax expression and downregulates Bcl-2 expression, indicating that PX-12-mediated apoptosis occurs in a mitochondrion-dependent manner. PX-12 also synergizes with 5-fluorouracil to significantly

inhibit tumorigenicity both *in vitro* and *in vivo* [192]. The aminopeptidase N inhibitor 4cc synergistically acts with 5-fluorouracil to exert antitumor effects on cancerous human hepatocytes through ROS-regulated drug resistance, inhibition, as well as simultaneous triggering of the apoptotic mitochondrial pathways [193]. In addition, itraconazole exposure activates apoptosis, blocked cell cycle advance, and downregulated MMP in HepG2 cells [194]. Additionally, a link between intracellular ROS production and accelerated senescence triggered by cisplatin could be utilized as a prospective HCC target [234].

4.2 Natural Compounds and Chinese Herbal Medicines

HCC has been treated with various natural chemical extracts and Chinese herbal medications. For example, alnustone increased the synthesis of ROS in BEL-7402 and HepG2 cells, and downregulated proteins linked to apoptosis and PI3K/AKT/mTOR/p70S6K signaling [92]. Coptisine promotes autophagic cell death via the downregulation of proteins linked to PI3K/AKT/mTOR signaling and upregulation of ROS-regulated mitochondrial dysfunction in Hep3B cells [181]. Koumine suppresses HCC proliferation and enhances apoptosis. NF- κ B and ERK/p38 MAPK pathways both improve koumine activity through a mechanism

Table 1. Agents targeting OS in HCC.

Category	Materials	Cell lines/Animals	Trial	Targets	Mechanism	Effects	Refs.
Chemotherapeutic Drugs	PX-12	HepG2 and SMMC-7721 cells		Cleaved PARP \uparrow , Bax \uparrow , Bcl-2 \downarrow	ROS-dependent apoptosis	Inducing apoptosis, inhibiting proliferation	[192]
	APN inhibitor 4cc	PLC/PRF/5, HepG2, and H7402 cells		Bax \uparrow , Bcl-2 \downarrow	ROS-dependent apoptosis	Inducing apoptosis, inhibiting tumor growth	[193]
	Itraconazole	HepG2 and Bel-7405		Hedgehog pathway \downarrow , Wnt/ β -catenin signaling pathway \downarrow , PI3K/AKT/mTOR pathway \downarrow	ROS-mediated apoptosis	Inducing apoptosis, inhibiting proliferation	[194]
	Raddeanin A	QGY -7703 cells		P53 \uparrow , Bax \uparrow , Bcl-2 \downarrow , Survivin \downarrow	ROS-dependent apoptosis	Inducing apoptosis	[195]
	Caffeine	SMMC-7721 and Hep3B cells		Cleaved PARP \uparrow , Bcl-2 \downarrow , Bcl-xL \downarrow	ROS-mediated apoptosis	Inducing apoptosis, inhibiting proliferation	[196]
	Allicin	SK-Hep-1 and BEL-7402 cells		Cleaved Caspase-3 \uparrow , cleaved PARP \uparrow , Bcl-2 \downarrow	ROS-dependent apoptosis	Inducing apoptosis, inhibiting proliferation	[197]
	Galangin	HepG2 and Hep3B		Bax \uparrow , Caspase-3 \uparrow	ROS-dependent apoptosis	Inducing apoptosis	[198]
	Kaempferol	HepG2		Bax/Bcl-2 \uparrow , Caspase-3 \uparrow , Caspase-9 \uparrow	ROS apoptosis	Increasing apoptosis	[199]
	Vitamin C	HCC-LM3 and Huh7		Cleaved-Caspase-3 \uparrow , cleaved PARP \uparrow , p21 \uparrow	ROS-induced apoptosis and DNA damage	Inducing apoptosis, inhibiting proliferation, eradicating liver CSCs	[200]
	Naringenin	HepG2		P53 \uparrow , Bax \uparrow , Caspase-3 \uparrow , Bcl-2 \downarrow	ROS-dependent apoptosis	Inducing apoptosis, inhibiting proliferation	[201]
Natural compounds and Chinese medicines	Troloxerutin	Huh7		cleaved Caspase-3 \uparrow , cleaved PARP \uparrow , 8-OHdG \uparrow , Bax \uparrow , Bad \uparrow , Bcl-2 \downarrow	ROS-induced DNA damage	Inducing apoptosis, inhibiting proliferation	[202]
	Siegesbeckia Orientalis	Hepa1-6 and HepG2		IL-6 \uparrow , IL-1 β \uparrow , TNF- α \uparrow , catalase \downarrow , GPX1/2 \downarrow , SOD-1 \downarrow , Bcl-2 \downarrow , MMP-2, -7, -9 \downarrow , β -catenin \downarrow	ROS-induced apoptosis	Promoting inflammatory response, inducing apoptosis and inhibiting migration	[203]
	Giganteaside D	HepG2 and Bel-7402		Cleaved Caspase-3, -9 \uparrow , cleaved PARP \uparrow , cytochrome c \uparrow , p-JNK \uparrow , p-ERK \downarrow	ROS-mediated apoptosis	Inducing apoptosis, inhibiting proliferation	[204]
	Oleanolic acid	Huh7 and HepG2 cells		Cleaved PARP \uparrow , Mcl-1 \downarrow	ROS-induced cell death	Inducing apoptosis	[205]
	Linalool	HepG2		MAPK pathway \uparrow , PI3K/AKT/mTOR pathway \downarrow , RAS pathway \downarrow	ROS-dependent apoptosis	Inducing apoptosis, inhibiting proliferation	[206]
	Apigenin	SK-Hep-1 and BEL-7402 cells		Cleaved Caspase-3 \uparrow , cleaved PARP \uparrow , Bcl-2 \downarrow	ROS-mediated apoptosis	Inducing apoptosis, inhibiting tumor growth	[207]
	Alnustone	BEL-7402 and HepG2		PI3K/AKT/mTOR pathway \downarrow	ROS-mediated apoptosis	Inducing apoptosis, inhibiting tumor growth	[92]
	Coptisine	Hep3B cells		PI3K/AKT/mTOR pathway \downarrow	ROS-mediated mitochondrial dysfunction	Inducing autophagic cell death	[181]

Table 1. Continued.

Category	Materials	Cell lines/Animals	Trial	Targets	Mechanism	Effects	Refs.
	C0818	HepG2 and SK-Hep-1		P21↑, cleaved caspase-3, -7, -8, -9↑, cleaved PARP↑, Hsp90↓, Cdc2↓, P-Cdc2↓, cyclin B1↓, Cdc25c↓	ROS-dependent cytotoxicity	Inducing apoptosis, inhibiting proliferation	[208]
	Koumine	Huh-7 and SNU-449		NF-κB pathway↓, ERK/p38 MAPK pathway↓	ROS-dependent apoptosis	Inducing apoptosis, inhibiting proliferation	[209]
	Sanguinarine	Bel-7402 and Bel-7404 cells		APAF-1↑, AIF↑, cleaved PARP↑, Beclin 1↑, LC3↑, p62↑, cytochrome c↑, cleaved-caspase-3↑, Bax↑, Bak↑, Bcl-2↓, Mcl-1↓, Bcl-xL↓	ROS-dependent mitophagy and apoptosis	Inducing apoptosis, inhibiting proliferation	[210]
	Artesunate	PLC/PRF/5, HuH7, HepG2, Hep3B and HCCLM3 cells		P-ERK↑, p-STAT3↑, Bax/Bcl-2↑	ROS apoptosis	Inducing apoptosis, inhibiting proliferation	[211]
	Butyrate	Huh7 cells		AKT/mTOR pathway↓, MAPK pathway↑	ROS -induced autophagy	Inhibiting cell proliferation	[180]
	Notopterol	HepJ5 and Mahlavu cells, Female BALB/c nude mice		JAK2↓, ATF4↓, GPX1↓, SOD1↓, vimentin, snail, β-catenin and N-cadherin↓	OS-associated cell death	Attenuating HCC cell migration and invasive capacity, inhibiting HCC tumor development	[212]
	Chamaejasmenin E	Hep3B and SMMC-7721 cells, Male BALB/c nude mice		C-Met/Ras/Raf/MEK/ERK pathway↓	OS-regulated cell death	Inhibiting the proliferation of HCC cells, reducing HCC cells migration, triggering apoptosis and inhibiting tumor growth	[213]
	HEG	Huh7 and HepG2 cells		SOD↑, CAT↑, GSH↑, GPX↑, NF-κB pathway↓	OS↓	Inhibiting tumor growth	[214]
	Polydatin	SMMC-7721 and HepG2 cells		SOD↑, CAT↑, GSH↑, GPX↑, GR↑, HO-1↑, caspase-3↑, caspase-9↑, Bax↑, Bcl-2↓, Wnt/β-catenin pathway↓	OS↓	Inducing apoptosis, inhibiting proliferation, invasion and migration	[215]
	Coenzyme Q10		NCT01964001	SOD↑, CAT↑, GPX↑, hs-CRP↓, TNF-α↓, IL-6↓	OS↓	Protecting against the development of HCC	[216]
	Vitamin B-6		NCT01964001	Plasma homocysteine↓	OS↓	Protecting against the progression of HCC	[217]
	BCAA		Korenaga M <i>et al.</i> (2015)	BAP/dROM↑, CHOP↓, hepcidin↑, CPT1↑, SOD2↑	OS↓	Inhibiting HCC development in patients with cirrhosis	[218]
	MCTs	Mice		Lipid peroxidation↓	OS↓	Inhibition of oncogenesis and tumor growth	[219]
	CLT	Mice		AST↓, ALT↓, GGT↓, ALP↓, AFP↓, SOD↑, GPX↑, TNF-α, Il-1β, TGFβ, and Bcl-2↓, Bax↑, Bcl1c↑	OS↓	Inhibiting HCC growth	[220]

Table 1. Continued.

Category	Materials	Cell lines/Animals	Trial	Targets	Mechanism	Effects	Refs.
	Decalactone	Swiss Wistar rats		CAT, GSH, GPX and SOD↑, LPO↓, TNF- α , IL-1 β and IL-6↓ NF- κ B↓	OS↓	Suppressing the progression of HCC	[221]
	Daphnetin	Swiss albino Wistar rats		AFP, AST, ALP and ALT↓, SOD↑, CAT↑, GST↑, GPX↑, LPO↓	OS↓	Suppressing the development of hepatic cancer	[222]
	Genistein	Rats		Versican/PDGF/PKC signaling pathway↓, SOD, GSH and Nrf2↑	OS↓	Suppressing HCC development	[223]
	Bevacizumab and CCR2 Inhibitor Nanoparticles	HepG2 and Huh7 cells		CCR2↓	ROS-mediated apoptosis	Inducing apoptosis	[224]
	Cisplatin and Curcumin Co-loaded Nano-liposomes	HepG2 cells		P-ERK1/2↑, p53↑, caspase-3↑, Bax↑, Sp1↓, Bcl-2↓	ROS-dependent apoptosis	Inducing apoptosis	[225]
Nanoparticles	Cisplatin-oleanolic acid co-loaded calcium carbonate nanoparticles	HepG2 cells		P53 pathway↑, P13K/AKT/mTOR pathway↓, XIAP↓, Bcl-2↓	ROS-mediated apoptosis	Inducing apoptosis, inhibiting proliferation	[226]
	Silver Nanoparticles	HepG2 cells		AKT, MAPK and p53 signaling pathways↑	ROS-induced apoptosis and DNA damage	Inducing apoptosis, inhibiting proliferation	[227]
	ZnO nanoparticle-ferulic acid conjugate	Huh-7 and HepG2		γ H2AX↑, Bax↑, Bad↑, cleaved caspase 3↑, cleaved PARP↑, 8-OHdG↑, Bcl-2↓, Bcl-xL↓	ROS-induced apoptosis and DNA damage	Inducing apoptosis, inhibiting proliferation	[228]

PX-12, 1-methylpropyl 2-imidazolyl disulfide; PARP, poly ADP-ribose polymerase; APN, aminopeptidase N; 8-hydroxydeoxyguanosine, 8-OHdG; TNF- α , tumor necrosis factor- α ; IL, interleukin; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; Mcl-1, myeloid cell leukemia-1; MAPK, mitogen-activated protein kinase; C0818, 3,5-(E)-Bis(3-methoxy-4-hydroxybenzal)-4-piperidinone hydrochloride; Hsp90, heat shock protein 90; Cdc, cell division cycle; APAF-1, apoptotic protease activating factor-1; AIF, apoptosis-inducing factor; STAT3, signal transducer and activator of transcription 3; HEG, 19- α -hydroxyurs-12(13)-ene-28 oic acid-3-O- β -D-glucopyranoside; CCR2, CC chemokine receptor 2; Sp1, Specificity protein 1; XIAP, X-linked inhibitor of apoptotic protein; BCAA, Branched-chain amino acids; BAP, biological antioxidant potential; CHOP, CCAAT/enhancer-binding protein homology protein; dROM, derivatives of reactive oxygen metabolites; CPT1, carnitine palmitoyl transferase 1; MCTs, medium-chain triglycerides; CLT, dicinnamoyl-L-tartaric acid; JAK2, Janus kinase 2.

that is dependent on ROS [209]. In HCC cells, sanguinarine causes lysosomal dysfunction, ROS-mediated mitophagy, and death [210]. In HCC cells, artesunate elevated ROS levels which, in turn, enhanced Bax/Bcl-2 and the triggering of apoptosis [211]. A novel derivative of curcumin, 3,5-(E)-Bis(3-methoxy-4-hydroxybenzal)-4-piperidinone hydrochloride (C0818), has shown potency in inhibiting Hsp90 and exhibits good antitumor effectivity. Through a mitochondrially-regulated pathway, C0818 caused HCC cells to undergo apoptosis in a manner dependent on ROS and caspases [208]. The HCC-derived cell lines HepG2 and BEL-7402 exhibited a substantial growth inhibitory response following exposure to giganteaside D (GD). Moreover, in HCC cells GD also triggered ROS-mediated apoptosis [204]. Co-incubation of apigenin with 5-fluorouracil synergistically elevated the levels of ROS in HCC cells [207]. However, some therapeutic drugs such as decalactone, daphnetin, and genistein inhibit HCC proliferation by reducing OS [221–223]. Most of these agents can prevent tumor development by reducing inflammatory cytokines and boosting antioxidant enzyme abundance.

4.3 Nanoparticles

Due to their distinctive characteristics, including its significant drug-loading capacity, inherent anticancer actions, integrated diagnostic and therapeutic functions, and ease of surface engineering with targeting ligands, nanomedicines have received significant attention when attempting to discover and develop effective therapies for HCC [235]. Bevacizumab and CCR2 inhibitor-containing nanoparticles sensitize doxycycline-treated Huh-7 cells by activating ROS-stimulated apoptosis [224]. Lipid-coated cisplatin/oleanolic acid calcium carbonate nanoparticles (CDDP/OA-LCC NPs) were reported to induce tumor cell apoptosis via upregulation of proapoptotic proteins, downregulation of proteins associated with the PI3K/AKT/mTOR pathway, and upregulation of proteins linked to p53 proapoptotic functions [226]. Cisplatin and curcumin-loaded nano-liposomes (CDDP/CUR-Lip) act by elevating ROS levels in HCC cells [225] and can be used to co-deliver CDDP and CUR *in vitro* and *in vivo* to improve HCC treatment through synergistic effects with minimal toxicity.

Silver nanoparticles (AgNPs) have recently come to light as a cutting-edge method of treating tumors, particularly hepatocarcinoma. AgNP-induced apoptosis is dependent on ROS overproduction as well as the effects of MAPKs, AKT signaling, and DNA damage-mediated p53 phosphorylation to trigger HepG2 cell apoptosis [227]. ZnO nanoparticle–ferulic acid conjugate (ZnONPs-FAC) triggers cells to undergo apoptosis and results in the suppression of diethylnitrosamine (DEN)-induced HCC. ZnONPs-FAC can cause significant mitochondrial damage and generate ROS production, and it can also induce oxidative DNA damage in HCC cells [228]. There is little

doubt that nanomaterials will play a significant role in treating HCC when moving forward, particularly when paired with therapeutic drugs.

5. Conclusions and Future Prospects

A growing body of research highlights the vital function of OS in the onset and advancement of HCC. This occurs through genetic modifications, changes in signaling pathways, transcription factor alterations, and effects on the TME. Genetic changes induced by OS, such as oxidative damage, damage to nuclear and mitochondrial DNA, DNA hypomethylation, and irregular miRNA expression all can induce HCC progression. OS-mediated signaling pathways, including Keap1/Nrf2/ARE, PI3K/AKT/mTOR, Wnt/ β -catenin, and Notch, are important regulators of HCC progression. In particular, the Nrf2/Keap1/ARE pathway can enhance liver cancer progression and metastasis through mechanisms that are dependent on OS. Nrf2 expression is also linked to various clinicopathological factors and the prognosis of HCC individuals. Moreover, ROS-induced Nrf2 activation governs the multidrug resistance (MDR) mechanism in HCC. The PI3K/AKT/mTOR and Wnt/ β -catenin pathways, both of which are influenced by OS, contribute to HCC proliferation, migration, and chemoresistance. Transcription factors like p53, FOXO, HSF1, NF- κ B, and HIF-1 α are sensitive to ROS, and their redox modifications can impact HCC onset and progression. Lastly, OS influences HCC progression by influencing immune components including TAMs, neutrophils, MDSCs, and Treg cells within the TME. We also supplemented the relationship between oxidative stress and autophagy in HCC.

This review also focuses on four therapeutic approaches targeting abnormal OS in HCC: chemotherapeutic agents, natural compound extracts, Chinese herbal medicines, and nanoparticles. Their mechanisms of action may involve influencing oxidative DNA damage, modulating signaling pathways such as PI3K/AKT/mTOR and Wnt/ β -catenin, regulating transcription factors such as p53, and impacting components of the TME. These agents employ various strategies to address abnormal OS in HCC. Most of the agents promote OS to induce oxidative damage of DNA and trigger ROS-dependent apoptosis of HCC cells, whereas some agents can activate antioxidant enzymes and reduce superoxide generation to decrease OS. Notably, all agents serve to inhibit HCC cell proliferation, invasion, and migration. A complex relationship exists between HCC and OS, necessitating future clinical studies to fully understand this link.

Author Contributions

YL and YY designed, wrote and revised the manuscript. YL prepared figures of the manuscript. YY contributed to making table of the manuscript. YL and YY participated in collecting data of the manuscript. LY

and RW made significant revisions and proofread the manuscript. LY and RW also provided support for the publication of the manuscript. All authors contributed to the article and approved the final version.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Figures created with BioRender.com (<https://www.biorender.com>).

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*. 2021; 71: 209–249.
- [2] Zhang XL, Lu Y, Yang S, Peng QL, Wang J, Xie L, *et al.* An updated meta-analysis between the association of XRCC1 Arg399Gln polymorphism and hepatocellular carcinoma risk. *Asian Pacific Journal of Cancer Prevention*. 2014; 15: 3273–3278.
- [3] Bao J, Lu Y, Deng Y, Rong C, Liu Y, Huang X, *et al.* Association between IL-18 polymorphisms, serum levels, and HBV-related hepatocellular carcinoma in a Chinese population: a retrospective case-control study. *Cancer Cell International*. 2015; 15: 72.
- [4] Sun Y, Lu Y, Li T, Xie L, Deng Y, Li S, *et al.* Interferon Gamma +874T/A Polymorphism Increases the Risk of Hepatitis Virus-Related Diseases: Evidence from a Meta-Analysis. *PLoS ONE*. 2015; 10: e0121168.
- [5] Dastjerdi MN, Kavooosi F, Valiani A, Esfandiari E, Sanaei M, Sobhanian S, *et al.* Inhibitory Effect of Genistein on PLC/PRF5 Hepatocellular Carcinoma Cell Line. *International Journal of Preventive Medicine*. 2015; 6: 54.
- [6] Garcia-Lezana T, Lopez-Canovas JL, Villanueva A. Signaling pathways in hepatocellular carcinoma. *Advances in Cancer Research*. 2021; 149: 63–101.
- [7] Haque E, Karim MR, Salam Teeli A, Śmiech M, Leszczynski P, Winiarczyk D, *et al.* Molecular Mechanisms Underlying Hepatocellular Carcinoma Induction by Aberrant NRF2 Activation-Mediated Transcription Networks: Interaction of NRF2-KEAP1 Controls the Fate of Hepatocarcinogenesis. *International Journal of Molecular Sciences*. 2020; 21: 5378.
- [8] Gabbia D, Cannella L, De Martin S. The Role of Oxidative Stress in NAFLD-NASH-HCC Transition-Focus on NADPH Oxidases. *Biomedicines*. 2021; 9: 687.
- [9] Li S, Tan HY, Wang N, Zhang ZJ, Lao L, Wong CW, *et al.* The Role of Oxidative Stress and Antioxidants in Liver Diseases. *International Journal of Molecular Sciences*. 2015; 16: 26087–26124.
- [10] Uchida D, Takaki A, Oyama A, Adachi T, Wada N, Onishi H, *et al.* Oxidative Stress Management in Chronic Liver Diseases and Hepatocellular Carcinoma. *Nutrients*. 2020; 12: 1576.
- [11] Wang Z, Li Z, Ye Y, Xie L, Li W. Oxidative Stress and Liver Cancer: Etiology and Therapeutic Targets. *Oxidative Medicine and Cellular Longevity*. 2016; 2016: 7891574.
- [12] Ozben T. Oxidative stress and apoptosis: impact on cancer therapy. *Journal of Pharmaceutical Sciences*. 2007; 96: 2181–2196.
- [13] Zou Z, Chang H, Li H, Wang S. Induction of reactive oxygen species: an emerging approach for cancer therapy. *Apoptosis*. 2017; 22: 1321–1335.
- [14] Lee J, Giordano S, Zhang J. Autophagy, mitochondria and oxidative stress: cross-talk and redox signalling. *The Biochemical Journal*. 2012; 441: 523–540.
- [15] Lee HY, Nga HT, Tian J, Yi HS. Mitochondrial Metabolic Signatures in Hepatocellular Carcinoma. *Cells*. 2021; 10: 1901.
- [16] Léveillé M, Estall JL. Mitochondrial Dysfunction in the Transition from NASH to HCC. *Metabolites*. 2019; 9: 233.
- [17] Raza S, Rajak S, Upadhyay A, Tewari A, Anthony Sinha R. Current treatment paradigms and emerging therapies for NAFLD/NASH. *Frontiers in Bioscience (Landmark Edition)*. 2021; 26: 206–237.
- [18] Mansouri A, Gattolliat CH, Asselah T. Mitochondrial Dysfunction and Signaling in Chronic Liver Diseases. *Gastroenterology*. 2018; 155: 629–647.
- [19] Elejalde E, Villarán MC, Alonso RM. Grape polyphenols supplementation for exercise-induced oxidative stress. *Journal of the International Society of Sports Nutrition*. 2021; 18: 3.
- [20] Narayanankutty A, Job JT, Narayanankutty V. Glutathione, an Antioxidant Tripeptide: Dual Roles in Carcinogenesis and Chemoprevention. *Current Protein & Peptide Science*. 2019; 20: 907–917.
- [21] Wang Y, Qi H, Liu Y, Duan C, Liu X, Xia T, *et al.* The double-edged roles of ROS in cancer prevention and therapy. *Theranostics*. 2021; 11: 4839–4857.
- [22] Moloney JN, Cotter TG. ROS signalling in the biology of cancer. *Seminars in Cell & Developmental Biology*. 2018; 80: 50–64.
- [23] Klaunig JE. Oxidative Stress and Cancer. *Current Pharmaceutical Design*. 2018; 24: 4771–4778.
- [24] Shiau JP, Chuang YT, Cheng YB, Tang JY, Hou MF, Yen CY, *et al.* Impacts of Oxidative Stress and PI3K/AKT/mTOR on Metabolism and the Future Direction of Investigating Fucoidan-Modulated Metabolism. *Antioxidants*. 2022; 11: 911.
- [25] Zhang VX, Sze KMF, Chan LK, Ho DWH, Tsui YM, Chiu YT, *et al.* Antioxidant supplements promote tumor formation and growth and confer drug resistance in hepatocellular carcinoma by reducing intracellular ROS and induction of TMBIM1. *Cell & Bioscience*. 2021; 11: 217.
- [26] Arfin S, Jha NK, Jha SK, Kesari KK, Ruokolainen J, Roychoudhury S, *et al.* Oxidative Stress in Cancer Cell Metabolism. *Antioxidants*. 2021; 10: 642.
- [27] Matuz-Mares D, Vázquez-Meza H, Vilchis-Landeros MM. NOX as a Therapeutic Target in Liver Disease. *Antioxidants*. 2022; 11: 2038.
- [28] Zhang D, Guo S, Schrodi SJ. Mechanisms of DNA Methylation in Virus-Host Interaction in Hepatitis B Infection: Pathogenesis and Oncogenetic Properties. *International Journal of Molecular Sciences*. 2021; 22: 9858.
- [29] Ye W, Zhang Y, Hu W, Wang L, Zhang Y, Wang P. A Sensitive FRET Biosensor Based on Carbon Dots-Modified Nanoporous Membrane for 8-hydroxy-2'-Deoxyguanosine (8-OHdG) Detection with Au@ZIF-8 Nanoparticles as Signal Quenchers. *Nanomaterials*. 2020; 10: 2044.
- [30] Ma-On C, Sanpavat A, Whongsiri P, Suwannasin S, Hirankarn N, Tangkijvanich P, *et al.* Oxidative stress indicated by elevated expression of Nrf2 and 8-OHdG promotes hepatocellular carcinoma progression. *Medical Oncology*. 2017; 34: 57.
- [31] Xue C, Gu X, Li G, Bao Z, Li L. Mitochondrial Mechanisms of Necroptosis in Liver Diseases. *International Journal of Molecular Sciences*. 2020; 22: 66.

- [32] Fuhrmann DC, Brüne B. Mitochondrial composition and function under the control of hypoxia. *Redox Biology*. 2017; 12: 208–215.
- [33] Grattagliano I, Russmann S, Diogo C, Bonfrate L, Oliveira PJ, Wang DQH, *et al*. Mitochondria in chronic liver disease. *Current Drug Targets*. 2011; 12: 879–893.
- [34] Sorrentino V, Menzies KJ, Auwerx J. Repairing Mitochondrial Dysfunction in Disease. *Annual Review of Pharmacology and Toxicology*. 2018; 58: 353–389.
- [35] Shetty S, Kumar R, Bharati S. Mito-TEMPO, a mitochondria-targeted antioxidant, prevents N-nitrosodiethylamine-induced hepatocarcinogenesis in mice. *Free Radical Biology & Medicine*. 2019; 136: 76–86.
- [36] Shetty S, Anushree U, Kumar R, Bharati S. Mitochondria-targeted antioxidant, mito-TEMPO mitigates initiation phase of N-Nitrosodiethylamine-induced hepatocarcinogenesis. *Mitochondrion*. 2021; 58: 123–130.
- [37] Xie WH, Ding J, Xie XX, Yang XH, Wu XF, Chen ZX, *et al*. Hepatitis B virus X protein promotes liver cell pyroptosis under oxidative stress through NLRP3 inflammasome activation. *Inflammation Research*. 2020; 69: 683–696.
- [38] Lee HR, Cho YY, Lee GY, You DG, Yoo YD, Kim YJ. A direct role for hepatitis B virus X protein in inducing mitochondrial membrane permeabilization. *Journal of Viral Hepatitis*. 2018; 25: 412–420.
- [39] Ling LR, Zheng DH, Zhang ZY, Xie WH, Huang YH, Chen ZX, *et al*. Effect of HBx on inflammation and mitochondrial oxidative stress in mouse hepatocytes. *Oncology Letters*. 2020; 19: 2861–2869.
- [40] Hino K, Nishina S, Sasaki K, Hara Y. Mitochondrial damage and iron metabolic dysregulation in hepatitis C virus infection. *Free Radical Biology & Medicine*. 2019; 133: 193–199.
- [41] Ivanov AV, Smirnova OA, Petrushanko IY, Ivanova ON, Karpenko IL, Alekseeva E, *et al*. HCV core protein uses multiple mechanisms to induce oxidative stress in human hepatoma Huh7 cells. *Viruses*. 2015; 7: 2745–2770.
- [42] Ehrlich M. DNA hypomethylation in cancer cells. *Epigenomics*. 2009; 1: 239–259.
- [43] Wu Q, Ni X. ROS-mediated DNA methylation pattern alterations in carcinogenesis. *Current Drug Targets*. 2015; 16: 13–19.
- [44] Maltseva DV, Baykov AA, Jeltsch A, Gromova ES. Impact of 7,8-dihydro-8-oxoguanine on methylation of the CpG site by Dnmt3a. *Biochemistry*. 2009; 48: 1361–1368.
- [45] Koczor CA, Ludlow I, Fields E, Jiao Z, Ludaway T, Russ R, *et al*. Mitochondrial polymerase gamma dysfunction and aging cause cardiac nuclear DNA methylation changes. *Physiological Genomics*. 2016; 48: 274–280.
- [46] Nishida N, Kudo M, Nishimura T, Arizumi T, Takita M, Kitai S, *et al*. Unique association between global DNA hypomethylation and chromosomal alterations in human hepatocellular carcinoma. *PLoS ONE*. 2013; 8: e72312.
- [47] Lim SO, Gu JM, Kim MS, Kim HS, Park YN, Park CK, *et al*. Epigenetic changes induced by reactive oxygen species in hepatocellular carcinoma: methylation of the E-cadherin promoter. *Gastroenterology*. 2008; 135: 2128–2140.e21408.
- [48] Lin Z, Huang W, He Q, Li D, Wang Z, Feng Y, *et al*. FOXC1 promotes HCC proliferation and metastasis by Upregulating DNMT3B to induce DNA Hypermethylation of CTH promoter. *Journal of Experimental & Clinical Cancer Research*. 2021; 40: 50.
- [49] Sartorius K, Sartorius B, Winkler C, Chuturgoon A, Makarova J. The biological and diagnostic role of miRNA's in hepatocellular carcinoma. *Frontiers in Bioscience (Landmark Edition)*. 2018; 23: 1701–1720.
- [50] Klieser E, Mayr C, Kiesslich T, Wissniowski T, Fazio PD, Neureiter D, *et al*. The Crosstalk of miRNA and Oxidative Stress in the Liver: From Physiology to Pathology and Clinical Implications. *International Journal of Molecular Sciences*. 2019; 20: 5266.
- [51] Kang Q, Tong Y, Gowd V, Wang M, Chen F, Cheng KW. Oral administration of EGCG solution equivalent to daily achievable dosages of regular tea drinkers effectively suppresses miR483-3p induced metastasis of hepatocellular carcinoma cells in mice. *Food & Function*. 2021; 12: 3381–3392.
- [52] Fernández-Tussy P, Sun J, Cardelo MP, Price NL, Goedeke L, Xirouchaki CE, *et al*. Hepatocyte-specific miR-33 deletion attenuates NAFLD-NASH-HCC progression. *bioRxiv*. 2023. (preprint)
- [53] Cardin R, Piciocchi M, Sinigaglia A, Lavezzo E, Bortolami M, Kotsafti A, *et al*. Oxidative DNA damage correlates with cell immortalization and mir-92 expression in hepatocellular carcinoma. *BMC Cancer*. 2012; 12: 177.
- [54] Ma Q. Role of nrf2 in oxidative stress and toxicity. *Annual Review of Pharmacology and Toxicology*. 2013; 53: 401–426.
- [55] Liu Y, Tao S, Liao L, Li Y, Li H, Li Z, *et al*. TRIM25 promotes the cell survival and growth of hepatocellular carcinoma through targeting Keap1-Nrf2 pathway. *Nature Communications*. 2020; 11: 348.
- [56] Abed DA, Goldstein M, Albanyan H, Jin H, Hu L. Discovery of direct inhibitors of Keap1-Nrf2 protein-protein interaction as potential therapeutic and preventive agents. *Acta Pharmaceutica Sinica B*. 2015; 5: 285–299.
- [57] Suzuki T, Motohashi H, Yamamoto M. Toward clinical application of the Keap1-Nrf2 pathway. *Trends in Pharmacological Sciences*. 2013; 34: 340–346.
- [58] Raghunath A, Sundarraj K, Nagarajan R, Arfuso F, Bian J, Kumar AP, *et al*. Antioxidant response elements: Discovery, classes, regulation and potential applications. *Redox Biology*. 2018; 17: 297–314.
- [59] Taguchi K, Yamamoto M. The KEAP1-NRF2 System as a Molecular Target of Cancer Treatment. *Cancers*. 2020; 13: 46.
- [60] Raghunath A, Sundarraj K, Arfuso F, Sethi G, Perumal E. Dysregulation of Nrf2 in Hepatocellular Carcinoma: Role in Cancer Progression and Chemoresistance. *Cancers*. 2018; 10: 481.
- [61] Lee K, Kim S, Lee Y, Lee H, Lee Y, Park H, *et al*. The Clinicopathological and Prognostic Significance of Nrf2 and Keap1 Expression in Hepatocellular Carcinoma. *Cancers*. 2020; 12: 2128.
- [62] Zhang M, Zhang C, Zhang L, Yang Q, Zhou S, Wen Q, *et al*. Nrf2 is a potential prognostic marker and promotes proliferation and invasion in human hepatocellular carcinoma. *BMC Cancer*. 2015; 15: 531.
- [63] Leung HW, Lau EYT, Leung CON, Lei MML, Mok EHK, Ma VWS, *et al*. NRF2/SHH signaling cascade promotes tumor-initiating cell lineage and drug resistance in hepatocellular carcinoma. *Cancer Letters*. 2020; 476: 48–56.
- [64] Gao AM, Ke ZP, Wang JN, Yang JY, Chen SY, Chen H. Apigenin sensitizes doxorubicin-resistant hepatocellular carcinoma BEL-7402/ADM cells to doxorubicin via inhibiting PI3K/Akt/Nrf2 pathway. *Carcinogenesis*. 2013; 34: 1806–1814.
- [65] Wu S, Zhang T, Du J. Ursolic acid sensitizes cisplatin-resistant HepG2/DDP cells to cisplatin via inhibiting Nrf2/ARE pathway. *Drug Design, Development and Therapy*. 2016; 10: 3471–3481.
- [66] Zhou S, Ye W, Zhang Y, Yu D, Shao Q, Liang J, *et al*. miR-144 reverses chemoresistance of hepatocellular carcinoma cell lines by targeting Nrf2-dependent antioxidant pathway. *American Journal of Translational Research*. 2016; 8: 2992–3002.
- [67] Ma RQ, Zhang MX, Wang JS, Cai H, Yeer MK, Duan XY. Expression and distribution of Nrf2 in several hepatocellular carcinoma cell lines. *Chinese Journal of Cellular and Molecular Immunology*. 2011; 27: 608–610.
- [68] Jeddi F, Soozangar N, Sadeghi MR, Somi MH, Samadi N. Con-

- tradiictory roles of Nrf2/Keap1 signaling pathway in cancer prevention/promotion and chemoresistance. *DNA Repair*. 2017; 54: 13–21.
- [69] Niture SK, Jaiswal AK. Nrf2-induced antiapoptotic Bel-xL protein enhances cell survival and drug resistance. *Free Radical Biology & Medicine*. 2013; 57: 119–131.
- [70] Gonzalez-Sanchez E, Marin JGG, Perez MJ. The expression of genes involved in hepatocellular carcinoma chemoresistance is affected by mitochondrial genome depletion. *Molecular Pharmacetics*. 2014; 11: 1856–1868.
- [71] Moghadam D, Zarei R, Vakili S, Ghoghghi R, Zarezade V, Veisi A, *et al.* The effect of natural polyphenols Resveratrol, Gallic acid, and Kuromanin chloride on human telomerase reverse transcriptase (hTERT) expression in HepG2 hepatocellular carcinoma: role of SIRT1/Nrf2 signaling pathway and oxidative stress. *Molecular Biology Reports*. 2023; 50: 77–84.
- [72] Yan J, Zhou Y, Chen D, Li L, Yang X, You Y, *et al.* Effects of mitochondrial translocation of telomerase on drug resistance in hepatocellular carcinoma cells. *Journal of Cancer*. 2015; 6: 151–159.
- [73] Nishi Y, Aoki T, Shimizu T, Sato S, Matsumoto T, Shiraki T, *et al.* Significance of cytoplasmic expression of telomerase reverse transcriptase in patients with hepatocellular carcinoma undergoing liver resection. *Molecular and Clinical Oncology*. 2021; 15: 244.
- [74] Sever R, Brugge JS. Signal transduction in cancer. *Cold Spring Harbor Perspectives in Medicine*. 2015; 5: a006098.
- [75] Khan KH, Yap TA, Yan L, Cunningham D. Targeting the PI3K-AKT-mTOR signaling network in cancer. *Chinese Journal of Cancer*. 2013; 32: 253–265.
- [76] Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. *Cell*. 2010; 141: 1117–1134.
- [77] Czech MP. PIP2 and PIP3: complex roles at the cell surface. *Cell*. 2000; 100: 603–606.
- [78] Maehama T, Dixon JE. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. *The Journal of Biological Chemistry*. 1998; 273: 13375–13378.
- [79] Gao Y, Moten A, Lin HK. Akt: a new activation mechanism. *Cell Research*. 2014; 24: 785–786.
- [80] Szwed A, Kim E, Jacinto E. Regulation and metabolic functions of mTORC1 and mTORC2. *Physiological Reviews*. 2021; 101: 1371–1426.
- [81] Pu Z, Duda DG, Zhu Y, Pei S, Wang X, Huang Y, *et al.* VCP interaction with HMGB1 promotes hepatocellular carcinoma progression by activating the PI3K/AKT/mTOR pathway. *Journal of Translational Medicine*. 2022; 20: 212.
- [82] Du A, Li S, Zhou Y, Disoma C, Liao Y, Zhang Y, *et al.* M6A-mediated upregulation of circMDK promotes tumorigenesis and acts as a nanotherapeutic target in hepatocellular carcinoma. *Molecular Cancer*. 2022; 21: 109.
- [83] Akula SM, Abrams SL, Steelman LS, Emma MR, Augello G, Cusimano A, *et al.* RAS/RAF/MEK/ERK, PI3K/PTEN/AKT/mTORC1 and TP53 pathways and regulatory miRs as therapeutic targets in hepatocellular carcinoma. *Expert Opinion on Therapeutic Targets*. 2019; 23: 915–929.
- [84] Xu Z, Hu J, Cao H, Pilo MG, Cigliano A, Shao Z, *et al.* Loss of Pten synergizes with c-Met to promote hepatocellular carcinoma development via mTORC2 pathway. *Experimental & Molecular Medicine*. 2018; 50: e417.
- [85] Zheng C, Liu M, Ge Y, Qian Y, Fan H. HBx increases chromatin accessibility and ETV4 expression to regulate dishevelled-2 and promote HCC progression. *Cell Death & Disease*. 2022; 13: 116.
- [86] Ha HL, Yu DY. HBx-induced reactive oxygen species activates hepatocellular carcinogenesis via dysregulation of PTEN/Akt pathway. *World Journal of Gastroenterology*. 2010; 16: 4932–4937.
- [87] Huang WC, Chen WS, Chen YJ, Wang LY, Hsu SC, Chen CC, *et al.* Hepatitis B virus X protein induces IKK α nuclear translocation via Akt-dependent phosphorylation to promote the motility of hepatocarcinoma cells. *Journal of Cellular Physiology*. 2012; 227: 1446–1454.
- [88] Lee YI, Kang-Park S, Do SI, Lee YI. The hepatitis B virus-X protein activates a phosphatidylinositol 3-kinase-dependent survival signaling cascade. *The Journal of Biological Chemistry*. 2001; 276: 16969–16977.
- [89] Cheng D, Zhang L, Yang G, Zhao L, Peng F, Tian Y, *et al.* Hepatitis C virus NS5A drives a PTEN-PI3K/Akt feedback loop to support cell survival. *Liver International*. 2015; 35: 1682–1691.
- [90] Cheng Z, Ni Q, Qin L, Shi Y. MicroRNA-92b augments sorafenib resistance in hepatocellular carcinoma via targeting PTEN to activate PI3K/AKT/mTOR signaling. *Brazilian Journal of Medical and Biological Research*. 2021; 54: e10390.
- [91] Batailler R, Paik YH, Lindquist JN, Lemasters JJ, Brenner DA. Hepatitis C virus core and nonstructural proteins induce fibrogenic effects in hepatic stellate cells. *Gastroenterology*. 2004; 126: 529–540.
- [92] Wang L, Cheng L, Ma L, Ahmad Farooqi A, Qiao G, Zhang Y, *et al.* Alnustone inhibits the growth of hepatocellular carcinoma via ROS-mediated PI3K/Akt/mTOR/p70S6K axis. *Phytotherapy Research*. 2022; 36: 525–542.
- [93] Li P, Wu M, Wang J, Sui Y, Liu S, Shi D. NAC selectively inhibit cancer telomerase activity: A higher redox homeostasis threshold exists in cancer cells. *Redox Biology*. 2016; 8: 91–97.
- [94] Nishikawa T, Nakajima T, Katagishi T, Okada Y, Jo M, Kagawa K, *et al.* Oxidative stress may enhance the malignant potential of human hepatocellular carcinoma by telomerase activation. *Liver International*. 2009; 29: 846–856.
- [95] Giannoni E, Parri M, Chiarugi P. EMT and oxidative stress: a bidirectional interplay affecting tumor malignancy. *Antioxidants & Redox Signaling*. 2012; 16: 1248–1263.
- [96] Jayachandran A, Dhungel B, Steel JC. Epithelial-to-mesenchymal plasticity of cancer stem cells: therapeutic targets in hepatocellular carcinoma. *Journal of Hematology & Oncology*. 2016; 9: 74.
- [97] Luo X, Cao M, Gao F, He X. YTHDF1 promotes hepatocellular carcinoma progression via activating PI3K/AKT/mTOR signaling pathway and inducing epithelial-mesenchymal transition. *Experimental Hematology & Oncology*. 2021; 10: 35.
- [98] Deldar Abad Paskeh M, Mirzaei S, Ashrafzadeh M, Zarrabi A, Sethi G. Wnt/ β -Catenin Signaling as a Driver of Hepatocellular Carcinoma Progression: An Emphasis on Molecular Pathways. *Journal of Hepatocellular Carcinoma*. 2021; 8: 1415–1444.
- [99] Vilchez V, Turcios L, Marti F, Gedaly R. Targeting Wnt/ β -catenin pathway in hepatocellular carcinoma treatment. *World Journal of Gastroenterology*. 2016; 22: 823–832.
- [100] Cui H, Guo D, Zhang X, Zhu Y, Wang Z, Jin Y, *et al.* ENO3 Inhibits Growth and Metastasis of Hepatocellular Carcinoma via Wnt/ β -Catenin Signaling Pathway. *Frontiers in Cell and Developmental Biology*. 2021; 9: 797102.
- [101] Vallée A, Lecarpentier Y. Crosstalk Between Peroxisome Proliferator-Activated Receptor Gamma and the Canonical WNT/ β -Catenin Pathway in Chronic Inflammation and Oxidative Stress During Carcinogenesis. *Frontiers in Immunology*. 2018; 9: 745.
- [102] Nusse R, Clevers H. Wnt/ β -Catenin Signaling, Disease, and Emerging Therapeutic Modalities. *Cell*. 2017; 169: 985–999.
- [103] Li Q, Sun M, Wang M, Feng M, Yang F, Li L, *et al.* Dysregulation of Wnt/ β -catenin signaling by protein kinases in hepatocellular carcinoma and its therapeutic application. *Cancer Science*. 2021; 112: 1695–1706.

- [104] Mao J, Wang D, Wang Z, Tian W, Li X, Duan J, *et al.* Combretastatin A-1 phosphate, a microtubule inhibitor, acts on both hepatocellular carcinoma cells and tumor-associated macrophages by inhibiting the Wnt/ β -catenin pathway. *Cancer Letters*. 2016; 380: 134–143.
- [105] Maurya BK, Trigun SK. Fisetin Attenuates AKT Associated Growth Promoting Events in AflatoxinB1 Induced Hepatocellular Carcinoma. *Anti-cancer Agents in Medicinal Chemistry*. 2018; 18: 1885–1891.
- [106] Leung RW, Lee TKW. Wnt/ β -Catenin Signaling as a Driver of Stemness and Metabolic Reprogramming in Hepatocellular Carcinoma. *Cancers*. 2022; 14: 5468.
- [107] Zhang Y, Li H, Wang J, Geng X, Hai J. Meningioma-associated protein 30 accelerates the proliferation and invasion of hepatocellular carcinoma by modulating Wnt/GSK-3 β / β -catenin signaling. *Journal of Bioenergetics and Biomembranes*. 2021; 53: 73–83.
- [108] Gurzu S, Kobori L, Fodor D, Jung I. Epithelial Mesenchymal and Endothelial Mesenchymal Transitions in Hepatocellular Carcinoma: A Review. *BioMed Research International*. 2019; 2019: 2962580.
- [109] Chen D, Yu D, Wang X, Liu Y, He Y, Deng R, *et al.* Epithelial to mesenchymal transition is involved in ethanol promoted hepatocellular carcinoma cells metastasis and stemness. *Molecular Carcinogenesis*. 2018; 57: 1358–1370.
- [110] Zhu GQ, Wang Y, Wang B, Liu WR, Dong SS, Chen EB, *et al.* Targeting HNRNPM Inhibits Cancer Stemness and Enhances Antitumor Immunity in Wnt-activated Hepatocellular Carcinoma. *Cellular and Molecular Gastroenterology and Hepatology*. 2022; 13: 1413–1447.
- [111] Marinho HS, Real C, Cyrne L, Soares H, Antunes F. Hydrogen peroxide sensing, signaling and regulation of transcription factors. *Redox Biology*. 2014; 2: 535–562.
- [112] Wang C, Li X, Wang H, Xie Q, Xu Y. Notch1-nuclear factor κ B involves in oxidative stress-induced alcoholic steatohepatitis. *Alcohol and Alcoholism*. 2014; 49: 10–16.
- [113] Shen F, Xiong Z, Kong J, Wang L, Cheng Y, Jin J, *et al.* Triptolide impairs thioredoxin system by suppressing Notch1-mediated PTEN/Akt/Txnip signaling in hepatocytes. *Toxicology Letters*. 2019; 300: 105–115.
- [114] Nowell CS, Radtke F. Notch as a tumour suppressor. *Nature Reviews. Cancer*. 2017; 17: 145–159.
- [115] Wu Y, Cain-Hom C, Choy L, Hagenbeek TJ, de Leon GP, Chen Y, *et al.* Therapeutic antibody targeting of individual Notch receptors. *Nature*. 2010; 464: 1052–1057.
- [116] Jin M, Wang J, Ji X, Cao H, Zhu J, Chen Y, *et al.* MCUR1 facilitates epithelial-mesenchymal transition and metastasis via the mitochondrial calcium dependent ROS/Nrf2/Notch pathway in hepatocellular carcinoma. *Journal of Experimental & Clinical Cancer Research*. 2019; 38: 136.
- [117] Yang X, Liu J, Liang Q, Sun G. Valproic acid reverses sorafenib resistance through inhibiting activated Notch/Akt signaling pathway in hepatocellular carcinoma. *Fundamental & Clinical Pharmacology*. 2021; 35: 690–699.
- [118] Hemati H, Kaur J, Sobti RC, Trehanpati N. Inhibition of NOTCH signaling pathway chemosensitizes HCC CD133⁺ cells to vincristine and 5-fluorouracil through upregulation of BBC3. *Biochemical and Biophysical Research Communications*. 2020; 525: 941–947.
- [119] Hayes JD, Dinkova-Kostova AT, Tew KD. Oxidative Stress in Cancer. *Cancer Cell*. 2020; 38: 167–197.
- [120] Eijkelenboom A, Burgering BMT. FOXOs: signalling integrators for homeostasis maintenance. *Nature Reviews. Molecular Cell Biology*. 2013; 14: 83–97.
- [121] Klotz LO, Sánchez-Ramos C, Prieto-Arroyo I, Urbánec P, Steinbrenner H, Monsalve M. Redox regulation of FoxO transcription factors. *Redox Biology*. 2015; 6: 51–72.
- [122] Hou YQ, Yao Y, Bao YL, Song ZB, Yang C, Gao XL, *et al.* Juglanthraquinone C Induces Intracellular ROS Increase and Apoptosis by Activating the Akt/Foxo Signal Pathway in HCC Cells. *Oxidative Medicine and Cellular Longevity*. 2016; 2016: 4941623.
- [123] Lu M, Hartmann D, Braren R, Gupta A, Wang B, Wang Y, *et al.* Oncogenic Akt-FOXO3 loop favors tumor-promoting modes and enhances oxidative damage-associated hepatocellular carcinogenesis. *BMC Cancer*. 2019; 19: 887.
- [124] Chen C, Lou T. Hypoxia inducible factors in hepatocellular carcinoma. *Oncotarget*. 2017; 8: 46691–46703.
- [125] Semenza GL. Hypoxia-inducible factors in physiology and medicine. *Cell*. 2012; 148: 399–408.
- [126] Zhou Y, Huang Y, Hu K, Zhang Z, Yang J, Wang Z. HIF1A activates the transcription of lncRNA RAET1K to modulate hypoxia-induced glycolysis in hepatocellular carcinoma cells via miR-100-5p. *Cell Death & Disease*. 2020; 11: 176.
- [127] Guo Y, Xiao Z, Yang L, Gao Y, Zhu Q, Hu L, *et al.* Hypoxia inducible factors in hepatocellular carcinoma (Review). *Oncology Reports*. 2020; 43: 3–15.
- [128] Yang Y, Zhang G, Guo F, Li Q, Luo H, Shu Y, *et al.* Mitochondrial UQC3 Modulates Hypoxia Adaptation by Orchestrating OXPPOS and Glycolysis in Hepatocellular Carcinoma. *Cell Reports*. 2020; 33: 108340.
- [129] Zhao L, Liu J, Chen S, Fang C, Zhang X, Luo Z. Prognostic significance of NANOG expression in solid tumors: a meta-analysis. *OncoTargets and Therapy*. 2018; 11: 5515–5526.
- [130] Gong S, Li Q, Jeter CR, Fan Q, Tang DG, Liu B. Regulation of NANOG in cancer cells. *Molecular Carcinogenesis*. 2015; 54: 679–687.
- [131] Chen CL, Uthaya Kumar DB, Punj V, Xu J, Sher L, Tahara SM, *et al.* NANOG Metabolically Reprograms Tumor-Initiating Stem-like Cells through Tumorigenic Changes in Oxidative Phosphorylation and Fatty Acid Metabolism. *Cell Metabolism*. 2016; 23: 206–219.
- [132] Ahn SG, Thiele DJ. Redox regulation of mammalian heat shock factor 1 is essential for Hsp gene activation and protection from stress. *Genes & Development*. 2003; 17: 516–528.
- [133] Kovács D, Sigmund T, Hotzi B, Bohár B, Fazekas D, Deák V, *et al.* HSF1Base: A Comprehensive Database of HSF1 (Heat Shock Factor 1) Target Genes. *International Journal of Molecular Sciences*. 2019; 20: 5815.
- [134] Dong B, Jaeger AM, Thiele DJ. Inhibiting Heat Shock Factor 1 in Cancer: A Unique Therapeutic Opportunity. *Trends in Pharmacological Sciences*. 2019; 40: 986–1005.
- [135] Shen JH, Chen PH, Liu HD, Huang DA, Li MM, Guo K. HSF1/AMPK α 2 mediated alteration of metabolic phenotypes confers increased oxaliplatin resistance in HCC cells. *American Journal of Cancer Research*. 2019; 9: 2349–2363.
- [136] Liu HT, Huang DA, Li MM, Liu HD, Guo K. HSF1: a mediator in metabolic alteration of hepatocellular carcinoma cells in cross-talking with tumor-associated macrophages. *American Journal of Translational Research*. 2019; 11: 5054–5064.
- [137] Moreira AJ, Rodrigues GR, Bona S, Fratta LXS, Weber GR, Picada JN, *et al.* Ductular reaction, cytokeratin 7 positivity, and gamma-glutamyl transferase in multistage hepatocarcinogenesis in rats. *Protoplasma*. 2017; 254: 911–920.
- [138] Morgan MJ, Liu ZG. Crosstalk of reactive oxygen species and NF- κ B signaling. *Cell Research*. 2011; 21: 103–115.
- [139] Perkins ND. The diverse and complex roles of NF- κ B subunits in cancer. *Nature Reviews. Cancer*. 2012; 12: 121–132.
- [140] Taniguchi K, Karin M. NF- κ B, inflammation, immunity and cancer: coming of age. *Nature Reviews. Immunology*. 2018; 18: 309–324.
- [141] Chen WT, Hsu FT, Liu YC, Chen CH, Hsu LC, Lin SS. Flu-

- oxetine Induces Apoptosis through Extrinsic/Intrinsic Pathways and Inhibits ERK/NF- κ B-Modulated Anti-Apoptotic and Invasive Potential in Hepatocellular Carcinoma Cells *In Vitro*. *International Journal of Molecular Sciences*. 2019; 20: 757.
- [142] Chang H, Li J, Qu K, Wan Y, Liu S, Zheng W, *et al*. CRIF1 overexpression facilitates tumor growth and metastasis through inducing ROS/NF κ B pathway in hepatocellular carcinoma. *Cell Death & Disease*. 2020; 11: 332.
- [143] Mu W, Cheng X, Zhang X, Liu Y, Lv Q, Liu G, *et al*. Hinokiflavone induces apoptosis via activating mitochondrial ROS/JNK/caspase pathway and inhibiting NF- κ B activity in hepatocellular carcinoma. *Journal of Cellular and Molecular Medicine*. 2020; 24: 8151–8165.
- [144] Maillot A, Pervaiz S. Redox regulation of p53, redox effectors regulated by p53: a subtle balance. *Antioxidants & Redox Signaling*. 2012; 16: 1285–1294.
- [145] Nguyen TAT, Grimm SA, Bushel PR, Li J, Li Y, Bennett BD, *et al*. Revealing a human p53 universe. *Nucleic Acids Research*. 2018; 46: 8153–8167.
- [146] Cheung EC, Athineos D, Lee P, Ridgway RA, Lambie W, Nixon C, *et al*. TIGAR is required for efficient intestinal regeneration and tumorigenesis. *Developmental Cell*. 2013; 25: 463–477.
- [147] Italiano D, Lena AM, Melino G, Candi E. Identification of NCF2/p67phox as a novel p53 target gene. *Cell Cycle*. 2012; 11: 4589–4596.
- [148] Porté S, Valencia E, Yakovtseva EA, Borràs E, Shafqat N, Debreczeny JÉ, *et al*. Three-dimensional structure and enzymatic function of proapoptotic human p53-inducible quinone oxidoreductase PIG3. *The Journal of Biological Chemistry*. 2009; 284: 17194–17205.
- [149] Biegging KT, Mello SS, Attardi LD. Unravelling mechanisms of p53-mediated tumour suppression. *Nature Reviews. Cancer*. 2014; 14: 359–370.
- [150] Goncalves RLS, Rothschild DE, Quinlan CL, Scott GK, Benz CC, Brand MD. Sources of superoxide/H₂O₂ during mitochondrial proline oxidation. *Redox Biology*. 2014; 2: 901–909.
- [151] Liu D, Xu Y. p53, oxidative stress, and aging. *Antioxidants & Redox Signaling*. 2011; 15: 1669–1678.
- [152] Faraonio R, Vergara P, Di Marzo D, Pierantoni MG, Napolitano M, Russo T, *et al*. p53 suppresses the Nrf2-dependent transcription of antioxidant response genes. *The Journal of Biological Chemistry*. 2006; 281: 39776–39784.
- [153] Guo L, Tan K, Wang H, Zhang X. Pterostilbene inhibits hepatocellular carcinoma through p53/SOD2/ROS-mediated mitochondrial apoptosis. *Oncology Reports*. 2016; 36: 3233–3240.
- [154] Hussain SP, Schwank J, Staib F, Wang XW, Harris CC. TP53 mutations and hepatocellular carcinoma: insights into the etiology and pathogenesis of liver cancer. *Oncogene*. 2007; 26: 2166–2176.
- [155] Yu LX, Ling Y, Wang HY. Role of nonresolving inflammation in hepatocellular carcinoma development and progression. *NPJ Precision Oncology*. 2018; 2: 6.
- [156] Landskron G, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic inflammation and cytokines in the tumor microenvironment. *Journal of Immunology Research*. 2014; 2014: 149185.
- [157] El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*. 2007; 132: 2557–2576.
- [158] Kim J, Bae JS. Tumor-Associated Macrophages and Neutrophils in Tumor Microenvironment. *Mediators of Inflammation*. 2016; 2016: 6058147.
- [159] Yang M, Li J, Gu P, Fan X. The application of nanoparticles in cancer immunotherapy: Targeting tumor microenvironment. *Bioactive Materials*. 2020; 6: 1973–1987.
- [160] Kastl L, Sauer SW, Ruppert T, Beissbarth T, Becker MS, Süß D, *et al*. TNF- α mediates mitochondrial uncoupling and enhances ROS-dependent cell migration via NF- κ B activation in liver cells. *FEBS Letters*. 2014; 588: 175–183.
- [161] Wan S, Zhao E, Kryczek I, Vatan L, Sadovskaya A, Ludema G, *et al*. Tumor-associated macrophages produce interleukin 6 and signal via STAT3 to promote expansion of human hepatocellular carcinoma stem cells. *Gastroenterology*. 2014; 147: 1393–1404.
- [162] Ye YC, Zhao JL, Lu YT, Gao CC, Yang Y, Liang SQ, *et al*. NOTCH Signaling via WNT Regulates the Proliferation of Alternative, CCR2-Independent Tumor-Associated Macrophages in Hepatocellular Carcinoma. *Cancer Research*. 2019; 79: 4160–4172.
- [163] Li G, Liu D, Kimchi ET, Kaifi JT, Qi X, Manjunath Y, *et al*. Nanoliposome C6-Ceramide Increases the Anti-tumor Immune Response and Slows Growth of Liver Tumors in Mice. *Gastroenterology*. 2018; 154: 1024–1036.e9.
- [164] Geh D, Leslie J, Rummey R, Reeves HL, Bird TG, Mann DA. Neutrophils as potential therapeutic targets in hepatocellular carcinoma. *Nature Reviews. Gastroenterology & Hepatology*. 2022; 19: 257–273.
- [165] Lluçh P, Segarra G, Tosca J, Navarro L, Navarrete-Navarro J, Herrera G, *et al*. Oxidative and Nitrosative Pattern in Circulating Leukocytes of Very Early/Early Hepatocellular Carcinoma Patients. *Anticancer Research*. 2020; 40: 6853–6861.
- [166] Zhan X, Wu R, Kong XH, You Y, He K, Sun XY, *et al*. Elevated neutrophil extracellular traps by HBV-mediated S100A9-TLR4/RAGE-ROS cascade facilitate the growth and metastasis of hepatocellular carcinoma. *Cancer Communications*. 2023; 43: 225–245.
- [167] Lu C, Rong D, Zhang B, Zheng W, Wang X, Chen Z, *et al*. Current perspectives on the immunosuppressive tumor microenvironment in hepatocellular carcinoma: challenges and opportunities. *Molecular Cancer*. 2019; 18: 130.
- [168] Xu M, Zhao Z, Song J, Lan X, Lu S, Chen M, *et al*. Interactions between interleukin-6 and myeloid-derived suppressor cells drive the chemoresistant phenotype of hepatocellular cancer. *Experimental Cell Research*. 2017; 351: 142–149.
- [169] Li S, Li F, Xu L, Liu X, Zhu X, Gao W, *et al*. TLR2 agonist promotes myeloid-derived suppressor cell polarization via Runx1 in hepatocellular carcinoma. *International Immunopharmacology*. 2022; 111: 109168.
- [170] Williams M, Liu X, Zhang Y, Reske J, Bahal D, Gohl TG, *et al*. NCOA5 deficiency promotes a unique liver protumorigenic microenvironment through p21^{WAF1/CIP1} overexpression, which is reversed by metformin. *Oncogene*. 2020; 39: 3821–3836.
- [171] Riaz F, Wei P, Pan F. Fine-tuning of regulatory T cells is indispensable for the metabolic steatosis-related hepatocellular carcinoma: A review. *Frontiers in Cell and Developmental Biology*. 2022; 10: 949603.
- [172] Hang S, Paik D, Yao L, Kim E, Trinath J, Lu J, *et al*. Bile acid metabolites control T_H17 and T_{reg} cell differentiation. *Nature*. 2019; 576: 143–148.
- [173] Huang D, Xu D, Chen W, Wu R, Wen Y, Liu A, *et al*. Fe-MnO₂ nanosheets loading dihydroartemisinin for ferroptosis and immunotherapy. *Biomedicine & Pharmacotherapy*. 2023; 161: 114431.
- [174] Hasan A, Rizvi SF, Parveen S, Pathak N, Nazir A, Mir SS. Crosstalk Between ROS and Autophagy in Tumorigenesis: Understanding the Multifaceted Paradox. *Frontiers in Oncology*. 2022; 12: 852424.
- [175] Elmansi A, El-Karef A, Shishtawy M, Eissa L. Hepatoprotective Effect of Curcumin on Hepatocellular Carcinoma Through Autophagic and Apoptotic Pathways. *Annals of Hepatology*. 2017; 16: 607–618.

- [176] Buchser WJ, Laskow TC, Pavlik PJ, Lin HM, Lotze MT. Cell-mediated autophagy promotes cancer cell survival. *Cancer Research*. 2012; 72: 2970–2979.
- [177] Zhou J, Zhang X, Tang H, Yu J, Zu X, Xie Z, *et al.* Nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2) in autophagy-induced hepatocellular carcinoma. *Clinica Chimica Acta; International Journal of Clinical Chemistry*. 2020; 506: 1–8.
- [178] Bartolini D, Dallaglio K, Torquato P, Piroddi M, Galli F. Nrf2-p62 autophagy pathway and its response to oxidative stress in hepatocellular carcinoma. *Translational Research*. 2018; 193: 54–71.
- [179] Umemura A, He F, Taniguchi K, Nakagawa H, Yamachika S, Font-Burgada J, *et al.* p62, Upregulated during Preneoplasia, Induces Hepatocellular Carcinogenesis by Maintaining Survival of Stressed HCC-Initiating Cells. *Cancer Cell*. 2016; 29: 935–948.
- [180] Pant K, Saraya A, Venugopal SK. Oxidative stress plays a key role in butyrate-mediated autophagy via Akt/mTOR pathway in hepatoma cells. *Chemico-Biological Interactions*. 2017; 273: 99–106.
- [181] Kim SY, Hwangbo H, Kim MY, Ji SY, Lee H, Kim GY, *et al.* Coptisine induces autophagic cell death through down-regulation of PI3K/Akt/mTOR signaling pathway and up-regulation of ROS-mediated mitochondrial dysfunction in hepatocellular carcinoma Hep3B cells. *Archives of Biochemistry and Biophysics*. 2021; 697: 108688.
- [182] Zhang G, He J, Ye X, Zhu J, Hu X, Shen M, *et al.* β -Thujaplicin induces autophagic cell death, apoptosis, and cell cycle arrest through ROS-mediated Akt and p38/ERK MAPK signaling in human hepatocellular carcinoma. *Cell Death & Disease*. 2019; 10: 255.
- [183] Dai X, Sun F, Deng K, Lin G, Yin W, Chen H, *et al.* Mal-lotucin D, a Clerodane Diterpenoid from *Croton crassifolius*, Suppresses HepG2 Cell Growth via Inducing Autophagic Cell Death and Pyroptosis. *International Journal of Molecular Sciences*. 2022; 23: 14217.
- [184] Xu H, Wang L. The Role of Notch Signaling Pathway in Non-Alcoholic Fatty Liver Disease. *Frontiers in Molecular Biosciences*. 2021; 8: 792667.
- [185] Xiao X, Hu Q, Deng X, Shi K, Zhang W, Jiang Y, *et al.* Old wine in new bottles: Kaempferol is a promising agent for treating the trilogy of liver diseases. *Pharmacological Research*. 2022; 175: 106005.
- [186] Yin X, Li W, Zhang J, Zhao W, Cai H, Zhang C, *et al.* AMPK-Mediated Metabolic Switching Is High Effective for Phytochemical Levo-Tetrahydropalmatine (l-THP) to Reduce Hepatocellular Carcinoma Tumor Growth. *Metabolites*. 2021; 11: 811.
- [187] Xu Y, Ji Y, Li X, Ding J, Chen L, Huang Y, *et al.* URI1 suppresses irradiation-induced reactive oxygen species (ROS) by activating autophagy in hepatocellular carcinoma cells. *International Journal of Biological Sciences*. 2021; 17: 3091–3103.
- [188] Yazdani HO, Huang H, Tsung A. Autophagy: Dual Response in the Development of Hepatocellular Carcinoma. *Cells*. 2019; 8: 91.
- [189] Zhang B, Liu Z, Cao K, Shan W, Liu J, Wen Q, *et al.* Circ-SPECC1 modulates TGF β 2 and autophagy under oxidative stress by sponging miR-33a to promote hepatocellular carcinoma tumorigenesis. *Cancer Medicine*. 2020; 9: 5999–6008.
- [190] Wang Y, Wang Q, Song J. Inhibition of autophagy potentiates the proliferation inhibition activity of microRNA-7 in human hepatocellular carcinoma cells. *Oncology Letters*. 2017; 14: 3566–3572.
- [191] Chang Y, Yan W, He X, Zhang L, Li C, Huang H, *et al.* miR-375 inhibits autophagy and reduces viability of hepatocellular carcinoma cells under hypoxic conditions. *Gastroenterology*. 2012; 143: 177–187.e8.
- [192] Li GZ, Liang HF, Liao B, Zhang L, Ni YA, Zhou HH, *et al.* PX-12 inhibits the growth of hepatocellular carcinoma by inducing S-phase arrest, ROS-dependent apoptosis and enhances 5-FU cytotoxicity. *American Journal of Translational Research*. 2015; 7: 1528–1540.
- [193] Sun ZP, Zhang J, Shi LH, Zhang XR, Duan Y, Xu WF, *et al.* Aminopeptidase N inhibitor 4cc synergizes antitumor effects of 5-fluorouracil on human liver cancer cells through ROS-dependent CD13 inhibition. *Biomedicine & Pharmacotherapy*. 2015; 76: 65–72.
- [194] Wang W, Dong X, Liu Y, Ni B, Sai N, You L, *et al.* Itraconazole exerts anti-liver cancer potential through the Wnt, PI3K/AKT/mTOR, and ROS pathways. *Biomedicine & Pharmacotherapy*. 2020; 131: 110661.
- [195] Li JN, Yu Y, Zhang YF, Li ZM, Cai GZ, Gong JY. Synergy of Raddeanin A and cisplatin induced therapeutic effect enhancement in human hepatocellular carcinoma. *Biochemical and Biophysical Research Communications*. 2017; 485: 335–341.
- [196] Wang Z, Gu C, Wang X, Lang Y, Wu Y, Wu X, *et al.* Caffeine enhances the anti-tumor effect of 5-fluorouracil via increasing the production of reactive oxygen species in hepatocellular carcinoma. *Medical Oncology*. 2019; 36: 97.
- [197] Zou X, Liang J, Sun J, Hu X, Lei L, Wu D, *et al.* Allicin sensitizes hepatocellular cancer cells to anti-tumor activity of 5-fluorouracil through ROS-mediated mitochondrial pathway. *Journal of Pharmacological Sciences*. 2016; 131: 233–240.
- [198] Fang D, Xiong Z, Xu J, Yin J, Luo R. Chemopreventive mechanisms of galangin against hepatocellular carcinoma: A review. *Biomedicine & Pharmacotherapy*. 2019; 109: 2054–2061.
- [199] Zhang Q, Cheng G, Qiu H, Zhu L, Ren Z, Zhao W, *et al.* The p53-inducible gene 3 involved in flavonoid-induced cytotoxicity through the reactive oxygen species-mediated mitochondrial apoptotic pathway in human hepatoma cells. *Food & Function*. 2015; 6: 1518–1525.
- [200] Lv H, Wang C, Fang T, Li T, Lv G, Han Q, *et al.* Vitamin C preferentially kills cancer stem cells in hepatocellular carcinoma via SVCT-2. *NPJ Precision Oncology*. 2018; 2: 1.
- [201] Arul D, Subramanian P. Naringenin (citrus flavonone) induces growth inhibition, cell cycle arrest and apoptosis in human hepatocellular carcinoma cells. *Pathology Oncology Research*. 2013; 19: 763–770.
- [202] Subastri A, Suyavaran A, Preedia Babu E, Nithyanathan S, Barathidasan R, Thirunavukkarasu C. Troxerutin with copper generates oxidative stress in cancer cells: Its possible chemotherapeutic mechanism against hepatocellular carcinoma. *Journal of Cellular Physiology*. 2018; 233: 1775–1790.
- [203] Chen TH, Chang CC, Houg JY, Chang TH, Chen YL, Hsu CC, *et al.* Suppressive Effects of *Siegesbeckia orientalis* Ethanolic Extract on Proliferation and Migration of Hepatocellular Carcinoma Cells through Promoting Oxidative Stress, Apoptosis and Inflammatory Responses. *Pharmaceuticals*. 2022; 15: 826.
- [204] Liu J, Wei X, Wu Y, Wang Y, Qiu Y, Shi J, *et al.* Giganteaside D induces ROS-mediated apoptosis in human hepatocellular carcinoma cells through the MAPK pathway. *Cellular Oncology*. 2016; 39: 333–342.
- [205] Liese J, Hinrichs TM, Lange M, Fulda S. Cotreatment with sorafenib and oleonic acid induces reactive oxygen species-dependent and mitochondrial-mediated apoptotic cell death in hepatocellular carcinoma cells. *Anti-Cancer Drugs*. 2019; 30: 209–217.
- [206] Rodenak-Kladniew B, Castro A, Stärkel P, De Saeger C, Garcia de Bravo M, Crespo R. Linalool induces cell cycle arrest and apoptosis in HepG2 cells through oxidative stress generation and modulation of Ras/MAPK and Akt/mTOR pathways. *Life Sciences*. 2018; 199: 48–59.
- [207] Hu XY, Liang JY, Guo XJ, Liu L, Guo YB. 5-Fluorouracil combined with apigenin enhances anticancer activity through

mitochondrial membrane potential ($\Delta\Psi_m$)-mediated apoptosis in hepatocellular carcinoma. *Clinical and Experimental Pharmacology & Physiology*. 2015; 42: 146–153.

- [208] Abdelmoaty AAA, Zhang P, Lin W, Fan YJ, Ye SN, Xu JH. C0818, a novel curcumin derivative, induces ROS-dependent cytotoxicity in human hepatocellular carcinoma cells *in vitro* via disruption of Hsp90 function. *Acta Pharmacologica Sinica*. 2022; 43: 446–456.
- [209] Yuan Z, Liang Z, Yi J, Chen X, Li R, Wu J, *et al.* Koumine Promotes ROS Production to Suppress Hepatocellular Carcinoma Cell Proliferation Via NF- κ B and ERK/p38 MAPK Signaling. *Biomolecules*. 2019; 9: 559.
- [210] Wang J, Su Q, Wu Q, Chen K, Ullah A, Ghauri MA, *et al.* Sanguinarine impairs lysosomal function and induces ROS-dependent mitophagy and apoptosis in human hepatocellular carcinoma cells. *Archives of Pharmacol Research*. 2021; 44: 1025–1036.
- [211] Yao X, Zhao CR, Yin H, Wang K, Gao JJ. Synergistic antitumor activity of sorafenib and artesunate in hepatocellular carcinoma cells. *Acta Pharmacologica Sinica*. 2020; 41: 1609–1620.
- [212] Huang TY, Yang CK, Chen MY, Yadav VK, Fong IH, Yeh CT, *et al.* Furanocoumarin Notopterol: Inhibition of Hepatocellular Carcinogenesis through Suppression of Cancer Stemness Signaling and Induction of Oxidative Stress-Associated Cell Death. *Nutrients*. 2023; 15: 2447.
- [213] Yu XQ, Yan QL, Shen S, Cheng ZY, Huang XX, Yao GD, *et al.* Chamaejasmenin E from *Stellera chamaejasme* induces apoptosis of hepatocellular carcinoma cells by targeting c-Met *in vitro* and *in vivo*. *Bioorganic Chemistry*. 2022; 119: 105509.
- [214] Verma A, Singh D, Anwar F, Bhatt PC, Al-Abbasi F, Kumar V. Triterpenoids principle of *Wedelia calendulacea* attenuated diethylnitrosamine-induced hepatocellular carcinoma via down-regulating oxidative stress, inflammation and pathology via NF- κ B pathway. *Inflammopharmacology*. 2018; 26: 133–146.
- [215] Tang D, Zhang Q, Duan H, Ye X, Liu J, Peng W, *et al.* Polydatin: A Critical Promising Natural Agent for Liver Protection via Antioxidative Stress. *Oxidative Medicine and Cellular Longevity*. 2022; 2022: 9218738.
- [216] Liu HT, Huang YC, Cheng SB, Huang YT, Lin PT. Effects of coenzyme Q10 supplementation on antioxidant capacity and inflammation in hepatocellular carcinoma patients after surgery: a randomized, placebo-controlled trial. *Nutrition Journal*. 2016; 15: 85.
- [217] Cheng SB, Lin PT, Liu HT, Peng YS, Huang SC, Huang YC. Vitamin B-6 Supplementation Could Mediate Antioxidant Capacity by Reducing Plasma Homocysteine Concentration in Patients with Hepatocellular Carcinoma after Tumor Resection. *BioMed Research International*. 2016; 2016: 7658981.
- [218] Korenaga M, Nishina S, Korenaga K, Tomiyama Y, Yoshioka N, Hara Y, *et al.* Branched-chain amino acids reduce hepatic iron accumulation and oxidative stress in hepatitis C virus polyprotein-expressing mice. *Liver International*. 2015; 35: 1303–1314.
- [219] Wakana H, Kono H, Fukushima H, Nakata Y, Akazawa Y, Maruyama S, *et al.* Effects of Medium-chain Triglycerides Administration in Chemically-induced Carcinogenesis in Mice. *Anticancer Research*. 2019; 39: 6653–6660.
- [220] Elmetwalli A, Hashish SM, Hassan MG, El-Magd MA, El-Naggar SA, Tolba AM, *et al.* Modulation of the oxidative damage, inflammation, and apoptosis-related genes by dicinnamoyl-L-tartaric acid in liver cancer. *Naunyn-Schmiedeberg's Archives of Pharmacology*. 2023. (online ahead of print)
- [221] Shen H, Li Q, Yu Y. Chemoprotective Effect of Decalactone on Hepatic Cancer via Diminishing the Inflammatory Response and Oxidative Stress. *Journal of Oleo Science*. 2022; 71: 1327–1335.
- [222] Li T, Yang G, Hao Q, Zhang X, Zhang X. Daphnetin Ameliorates the Expansion of Chemically Induced Hepatocellular Carcinoma via Reduction of Inflammation and Oxidative Stress. *Journal of Oleo Science*. 2022; 71: 575–585.
- [223] El-Far YM, Khodir AE, Emarah ZA, Ebrahim MA, Al-Gayyar MMH. Chemopreventive and hepatoprotective effects of genistein via inhibition of oxidative stress and the versican/PDGF/PKC signaling pathway in experimentally induced hepatocellular carcinoma in rats by thioacetamide. *Redox Report: Communications in Free Radical Research*. 2022; 27: 9–20.
- [224] Abd-Rabou AA, Ahmed HH. Bevacizumab and CCR2 Inhibitor Nanoparticles Induce Cytotoxicity-Mediated Apoptosis in Doxorubicin-Treated Hepatic and Non-Small Lung Cancer Cells. *Asian Pacific Journal of Cancer Prevention*. 2019; 20: 2225–2238.
- [225] Cheng Y, Zhao P, Wu S, Yang T, Chen Y, Zhang X, *et al.* Cisplatin and curcumin co-loaded nano-liposomes for the treatment of hepatocellular carcinoma. *International Journal of Pharmaceutics*. 2018; 545: 261–273.
- [226] Khan MW, Zhao P, Khan A, Raza F, Raza SM, Sarfraz M, *et al.* Synergism of cisplatin-oleanolic acid co-loaded calcium carbonate nanoparticles on hepatocellular carcinoma cells for enhanced apoptosis and reduced hepatotoxicity. *International Journal of Nanomedicine*. 2019; 14: 3753–3771.
- [227] Zhu B, Li Y, Lin Z, Zhao M, Xu T, Wang C, *et al.* Silver Nanoparticles Induce HePG-2 Cells Apoptosis Through ROS-Mediated Signaling Pathways. *Nanoscale Research Letters*. 2016; 11: 198.
- [228] Ezhuthupurakkal PB, Ariraman S, Arumugam S, Subramaniyan N, Muthuvel SK, Kumpati P, *et al.* Anticancer potential of ZnO nanoparticle-ferulic acid conjugate on Huh-7 and HepG2 cells and diethyl nitrosamine induced hepatocellular cancer on Wistar albino rat. *Nanomedicine: Nanotechnology, Biology, and Medicine*. 2018; 14: 415–428.
- [229] Rogalska A, Gajek A, Łukawska M, Oszczapowicz I, Marczak A. Novel oxazolinoanthracyclines as tumor cell growth inhibitors-Contribution of autophagy and apoptosis in solid tumor cells death. *PLoS ONE*. 2018; 13: e0201296.
- [230] Yang H, Villani RM, Wang H, Simpson MJ, Roberts MS, Tang M, *et al.* The role of cellular reactive oxygen species in cancer chemotherapy. *Journal of Experimental & Clinical Cancer Research: CR*. 2018; 37: 266.
- [231] Li C, Thompson MA, Tamayo AT, Zuo Z, Lee J, Vega F, *et al.* Over-expression of Thioredoxin-1 mediates growth, survival, and chemoresistance and is a druggable target in diffuse large B-cell lymphoma. *Oncotarget*. 2012; 3: 314–326.
- [232] Shin HR, You BR, Park WH. PX-12-induced HeLa cell death is associated with oxidative stress and GSH depletion. *Oncology Letters*. 2013; 6: 1804–1810.
- [233] You BR, Shin HR, Park WH. PX-12 inhibits the growth of A549 lung cancer cells via G2/M phase arrest and ROS-dependent apoptosis. *International Journal of Oncology*. 2014; 44: 301–308.
- [234] Qu K, Lin T, Wang Z, Liu S, Chang H, Xu X, *et al.* Reactive oxygen species generation is essential for cisplatin-induced accelerated senescence in hepatocellular carcinoma. *Frontiers of Medicine*. 2014; 8: 227–235.
- [235] Lu J, Wang J, Ling D. Surface Engineering of Nanoparticles for Targeted Delivery to Hepatocellular Carcinoma. *Small*. 2018; 14.