



Mechanisms of resistance to chemotherapy and radiotherapy in hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is an inflammation-related malignant tumor that develops from underlying cirrhosis. As HCC is a common tumor seen in clinical practice, its prevention and treatment attract considerable attention. There is no doubt that surgical interventions, such as resection and transplantation, are the best methods of addressing early HCC. However, because HCC is difficult to diagnose early in the disease course, and most patients tend to be diagnosed at advanced stages and cannot undergo surgery. In terms of advanced HCC, conservative treatment strategies are usually useful. However, chemotherapy, such as local chemoembolization and targeted immunization, and radiotherapy, such as stereotactic body radiation therapy, meet the treatment bottlenecks caused by increased resistance, indicating that considerable effort is still needed to treat HCC due to its high morbidity and mortality. In addition, treatment efficacy depends on our ability to study the related mechanisms of resistance and develop new approaches for advanced HCC. Studies have focused on the variety of possible mechanisms of resistance in HCC, and some progress has been made in recent years. However, further exploration of the relationships and crosstalk between associated molecular factors may deepen the understanding of underlying pathogenic mechanisms to help overcome HCC resistance.

Keywords: Hepatocellular carcinoma (HCC); radiotherapy; chemotherapy; resistance; mechanism

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Introduction

Hepatocellular carcinoma (HCC) is a common malignant tumor locating at hepatic or hepatobiliary cells and presents a high mortality rate. The incidence of HCC morbidity is approximately 850,000 new cases per year (1). Epidemiological statistics in recent years have shown that over 80% of HCC occurred in eastern Asia and southern Africa, where the morbidity exceeds 2%. In developed countries, the average morbidity is 1–2% in southern

Europe, while it is less than 0.5% in northern Europe, Oceania and America (2–4).

The development of HCC is a multistage procedure which performs as a symptomatic disease in the initial stages while leads to a late diagnosis eventually. The American Association for the Study of Liver Disease (AASLD) (5) and the European Association for the Study of the Liver (EASL) (6) signed the document of Barcelona Clinic Liver Cancer Classification (BCLC), which has been most widely applied all over the world (7) and recommended the

guidance of liver cancer administration. BCLC clarifies the treatment decision model of HCC in early stage and divides the HCC into several stages as following: very early stage (0), early stage (BCLC, A), intermediate stage (BCLC, B), advanced stage (BCLC, C), terminal stage (BCLC, D).

Treatment

Treatment of HCC is adjusted according to the characteristics of the tumor, stage of disease and patient characteristics, including age, physical strength and complications. In the clinic, liver resection, liver transplantation or radiofrequency ablation are usually used for patients at BCLC stage 0 or A disease. The 5-year survival rates of patients with BCLC stage 0 disease are approximately 80–90% after resection or transplantation and approximately 70% after local ablation (8,9). However, reports have shown that liver transplantation is suitable for only 5% of patients with early HCC with a single tumor less than 5 cm in diameter or with multiple tumors less than 3 cm in diameter (10). Despite this, approximately 50% of patients still have liver cirrhosis after liver transplantation. Moreover, the 5-year recurrence rate of patients treated with resection at very early stages was as much as 68%, and the 5-year survival rates of patients with stage A disease was approximately 50–70% (11,12). Patients with stage BCLC B disease tend to be treated with radiotherapy or chemotherapy (13) and the median survival time is 36–45 months (14). Until now, Transcatheter arterial chemoembolization (TACE) has been widely used to treat HCC in different stages and plays an important role in the treatment of unresectable HCC (15,16). In cases of TACE resistance or advanced stage HCC (stage C) with compatible residual liver function, systemic chemotherapy is indicated. Sorafenib was used to treat HCC patients with BCLC stage C disease in 2006, and had been regarded as the only standard systemic treatment available in the past few years (15). Unfortunately, it prolonged survival on average of only 3 months and the response rate was low (17), suggesting it was of limited benefit. In addition, cytotoxic drugs, such as oxaliplatin, gemcitabine and 5-fluorouracil, have been used in advanced HCC following doxorubicin, which is one of the first reported chemotherapeutic drugs to be used for HCC and showed interesting results (18). BCLC stage D disease indicates a worse prognosis, and most patients at this stage survive for only 3–4 months, and only 11% survive as long as 1 year (19). Recently, late-model molecular targeting drugs have been researched and applied as trial treatments for HCC (20), such drugs include angiogenesis inhibitors, such

as sunitinib, cediranib and bevacizumab; anti-EGFR drugs, such as cetuximab; EGFR inhibitors, such as lapatinib; MEK inhibitors, such as selumetinib; mTOR inhibitors, such as everolimus; and tyrosine kinase inhibitors, such as nintedanib.

In recent years, immunotherapy for cancer treatment has eventually progressed from bench to bed (21) and many new drugs of antibody therapy have been tested as an alternative in the treatment of HCC. Unlike conventional chemotherapy or molecular targeted therapy, antibody therapy improves the potency of attack on cancer cells by restoring the function of the innate anticancer immune system. For example, the safety profile of monotherapy with the antibodies against programmed cell death 1 (anti-PD-1) antibody demonstrated satisfying and promising results against HCC. Feng *et al.* (22) showed that nivolumab could achieve acceptable outcome in HCC patients and might serve as a relatively safe treatment, especially for patients who failed to gain a benefit from routine treatments. Besides, clinical studies are currently ongoing to aggressively evaluate the utility of the antibodies against cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4) antibodies ipilimumab and tremelimumab (23,24). The efficacy of combination therapy with pembrolizumab and lenvatinib in HCC is being tested in Japan.

Data imply that radiotherapy plays a vital role in managing HCC. Historically, the use of radiotherapy has been limited for treating HCC owing to the low tolerance of the whole liver to radiotherapy. In addition, radiation-induced liver disease reduces the sensitivity of HCC to radiotherapy. However, as techniques have developed, there is new hope for the treatment of HCC with radiotherapy expect for the side-effect because several methods are applied to the HCC. For example, 3-dimensional conformal radiotherapy (3DCRT) (25,26) can minimize the irradiation of normal tissue and improve the target irradiation dose to HCC; this technology for the treatment of advanced HCC has gradually been recognized and proved to be useful by several studies. Intensity-modulated radiotherapy (IMRT) is typically administered on a conventional or hypofractionated schedule. In addition, stereotactic body radiotherapy (SBRT) is increasingly used for a number of different oncologic indications, including the treatment of primary and metastatic tumors (27-29).

Resistance to radiotherapy and chemotherapy in HCC

While resection is the best method of treatment for HCC,

less than half of patients can benefit from this modality because of undetected disease and the invasive nature of this treatment (30), suggesting that the majority of HCC patients are deprived of the chance of surgery at the time of diagnosis. In this case, chemotherapy or radiotherapy are used as conservative treatments (5,31). Conservative treatment methods are increasingly used in patients with advanced HCC; however, the resistance to chemotherapy and radiation and the attenuation of efficacy in HCC remain problematic (32). HCC is a complex solid tumor at the gene and molecular level and has a tendency to mutate, which is suggestive of its variety of associated drug-resistance mechanisms.

In terms of the severe resistance to drugs in HCC, systemic chemotherapy can rarely achieve the anticipated effect. Nevertheless, given that the majority of HCC patients can hardly benefit from surgery, traditional chemotherapy is still used in HCC as a palliative treatment modality to attenuate symptoms caused by HCC and improve patients' life quality. Although systemic chemotherapy for HCC does not prolong the overall survival and responses are observed in less than 10% of patients treated with this method, doxorubicin is still one of the most commonly used chemotherapeutics. Cisplatin has also been used for the treatment of HCC alone or in combination (33,34). In addition, other drugs such as mitoxantrone, paclitaxel, irinotecan, gemcitabine and capecitabine have been used alone or in combination to treat HCC, but these treatments lack efficacy (35,36). Sorafenib is a new style of drug that targets the RAF-MEK-ERK/MAPK signaling pathway and has been the most effective drug to treat HCC. However, the long-term survival time is merely 2–3 months, and related resistance has been reported. A randomized controlled trial has revealed that although chemotherapeutics used in combination lead to better responses in HCC patients, overall survival does not improve due to multiple drug resistance (MDR) (37,38). In addition to MDR, a variety of other factors restrict the use of chemotherapy to treat HCC including the short half-life of chemotherapeutics, the narrow treatment window, the low targeted specificity of chemotherapeutics and a series of side effects (39). In summary, chemotherapeutic treatment of HCC is fraught with inevitable difficulties.

In addition to chemotherapy, great progress has been made in radiotherapy for the treatment of HCC treatment, but it also has a limited role due to resistance (40). Further investigation of the underlying mechanisms in radioresistant HCC cells is warranted. HCC has been

regarded as a radioresistant tumor for a long time because a variety of cellular processes that involve essential proteins are activated in radiotherapy, which make a difference in its curative effects (41). In addition, the susceptibility and resistance of HCC to radiotherapy is related to the heterogeneity of HCC and regulation of the *P53* gene or other proliferation and apoptosis-related proteins (42,43). Complete understanding of the radio-resistance of HCC is also essential.

Mechanisms of HCC resistance to chemotherapy and radiotherapy

Data show that tumor stem cells, hepatic stellate cells, hepatic viruses and so on participate in the resistance of HCC to chemotherapy and radiotherapy, and the inhibition of apoptosis or the decrease in susceptibility to apoptosis is an essential mechanism. Numerous studies have revealed that the resistance of HCC to chemotherapy and radiotherapy is related to the overexpression of transmembrane transporters, epithelial-mesenchymal transition (44), signal transduction pathways (45), DNA damage and repair (46,47), the induction of autophagy (48), and epigenetic factors (49). Recently, some new factors, such as noncoding RNA (50), the immunosuppressive microenvironment (51), and signaling pathways, that make resistance more complex have been identified. The following discussion explains the probable reasons for resistance that are related to these factors.

Changes in the tumor microenvironment in HCC

Tumor growth and infiltration benefits from stromal cells and secreted proteins in the tumor microenvironment. Chronic inflammatory irritation induces liver tissue fibrillation, which gradually develops into HCC. In HCC microenvironment, the liver tumor cells, tumor-associated macrophage, lymphocyte, CD4+ and CD8+ T cell, PD1 positivity in CD8+ T cells, natural killer (NK) cell, regulatory T cells (Tregs), plasma cells, neutrophils, dendritic cells (DCs), hepatic stellate cells and the specific immunocyte live together, which acts as important components and creates beneficial condition for liver cancer cells' proliferation, immune escape and angiogenesis. The HCC immune microenvironment was classified into three major distinct immunosubtypes in Yutaka Kurebayashi's research, facilitating investigation of how the immune microenvironment changes during focal progression of

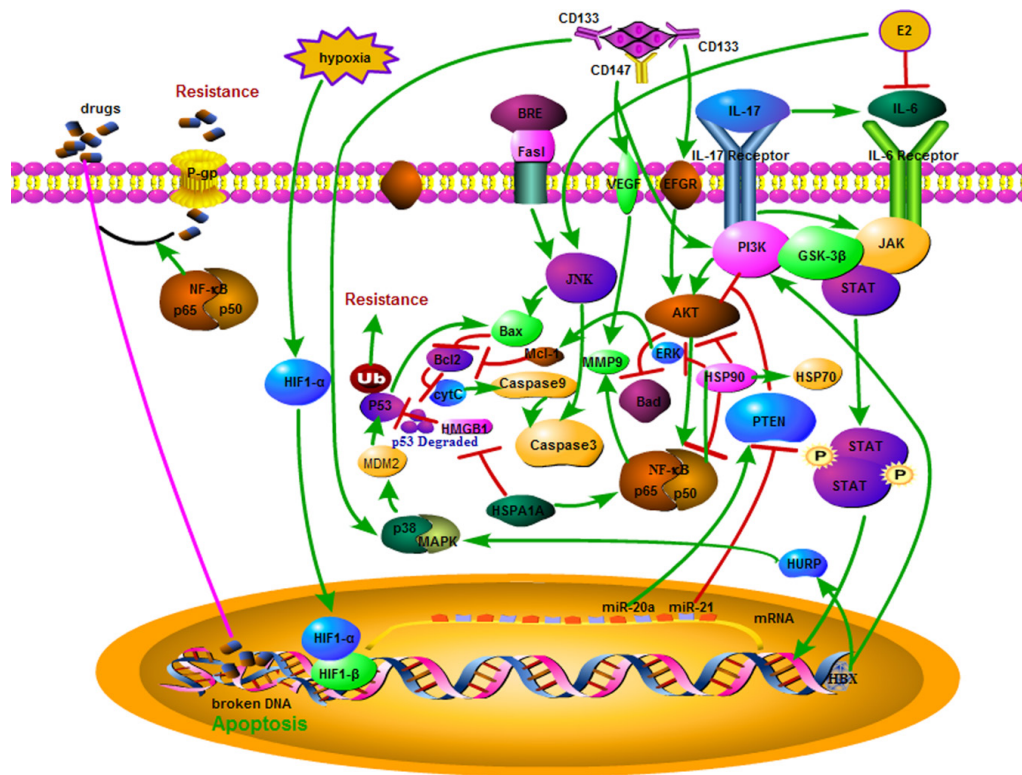


Figure 1 Mechanisms by which signaling pathway or molecular activated on HCC cells are shown to resistance to radiotherapy and chemotherapy. HCC is one of the common tumors in clinical. HCC has commonly been regarded as a radiotherapy and chemotherapy resistant tumor for a long time, because varieties of cellular processes are activated in therapy involving essential molecular which make a difference in the curative effects. HCC, hepatocellular carcinoma.

HCC (52). In liver cancer tissue, the newly formed abnormal blood vessels have abnormal function and are anoxic. As the *Figure 1* showed, when hypoxia occurs, the expression of nuclear transcription factor HIF-1 increases and upregulates resistant genes, thus causing the resistance of liver cancer cells to multiple drugs (53). There are studies that have shown that epithelial-mesenchymal transition can enhance the invasiveness of liver cancer cells and that it is involved in tumor resistance associated with CD29 (54).

Adhesion molecules in the microenvironment can also induce resistance of liver cancer cells to drugs by connecting them directly with the extracellular matrix, interstitial cells and other liver cancer cells (55,56). In addition, there is crosstalk between the activated hepatic stellate cells and liver cancer cells. In particular, the hepatic stellate cells participate in the remodeling of the tumor microenvironment and in promoting the development of liver cancer via Ln-332 and TGF- β , thus inducing resistance to sorafenib (57,58). In addition, in the formation of liver

cancer, the microenvironment alters signal transduction, which also leads to hepatocarcinoma resistance.

Tumor immune responses depend on the balance between tumor antigens and the tumor microenvironment. Immunotherapy is not as effective for advanced HCC as previously thought. In general, there are genetic mutations in HCC that enhance the tumor antigenicity of liver cancer cells, and the tumor cells can escape from the immune system by changing the molecules that present antigens and the signaling pathway. Furthermore, tissue hypoxia can also cause oxaliplatin-resistance and radio-resistance in liver cancer cells because it induces specific cytokines, chemical factors and immunosuppressive molecules that decrease tumor proliferation and disable angiogenesis in tumor tissue. In addition, tumor tissues release some cytokines during hypoxia to attack Treg cells and form an immunosuppressive environment. The stability of immune targeted therapy for advanced tumors is only 12–41% (59), which is not very encouraging, even though some tumors

are sensitive to this therapy. Hence, the liver cancer microenvironment may induce tolerance to radiotherapy and chemotherapy, suggesting that regulating the tumor microenvironment may be instrumental in maintaining normal antitumor immunity.

Transmembrane transporters can pump chemotherapeutic drugs out of cells

P-glycoprotein (P-gp), which is the typical representative of ATP-binding cassette transporters in tumor cells, can pump chemotherapeutic drugs out of cells and reduce the concentration of these drugs, thus affecting their efficacy. P-gp is encoded by the *MDR1* gene, which is activated by NF- κ B and located at the cell membrane; *Figure 1* described that the P-gp pumps chemotherapeutic drugs out of liver cancer cells and affects the activity of Caspase-3, further decreasing cellular apoptosis (60). In addition, anti-P-gp-ribozyme is reported to reverse sorafenib resistance in HCC cells (61,62). However, the expression of P-gp in HCC has great individual differences, and its role in liver cancer is also controversial. On the one hand, some studies have shown that P-gp is closely related to the progression of HCC; when it is overexpressed in human or rat liver cancer tissues, it is associated with decreased survival rates. On the other hand, the expression of P-gp is independent of malignant classification and survival rate in some liver cancers, and it is no use to regulate P-gp with verapamil for reversing the chemoresistance of HCC.

Abnormal expression of noncoding RNAs

Yin *et al.* (63) have demonstrated that aberrant expression of noncoding RNA is related to the oxaliplatin-resistant profile; 421 differentially expressed mRNAs, 228 upregulated mRNAs and 193 downregulated mRNAs in oxaliplatin-resistant (MHCC97H-OXA) cells were identified and appeared to be related to resistance to oxaliplatin.

microRNA is a noncoding RNA. As a marker of clinical diagnosis and prognosis, it provides a new reference for the clinical evaluation of tumor progression and treatment intervention (64). miRNAs regulate drug transport by inhibiting or degrading drug transport proteins when binding to mRNA (65). Considerable evidence suggests that the abnormal expression of miRNAs plays an important biological role in the regulation of tumor stem cells, including those in HCC. In the formation of liver cancer,

miRNAs have dual roles in inhibiting and promoting tumorigenesis; miR-21, miR-224, miR-34a, miR-221/222, miR-106a, miR-203, miR-125a and miR-150 are involved in these processes (66). miR-122 is specifically expressed in HCC cells and can increase the sensitivity of HCC to chemotherapeutic drugs by prolonging the G2/M phase of the cell cycle (67). Both miR-106b and miR-490-3p are upregulated in HCC cells and promote the proliferation of HCC by influencing the cell cycle and promoting epithelial-mesenchymal transition. MiR-223 can cause doxorubicin tolerance in tumor cells by modulating P-gp transcription (68). In HepG2 cells, miR-379 can act on MRP2 to induce rifampicin-resistance (69).

miRNAs not only affect chemo-resistance in tumor cells but also radiosensitivity. For example, in *Figure 1*, miR-20a induces radio-resistance in HCC cells when exposed to 6-MV X-rays by activating the PTEN/PI3K/AKT signaling pathway (70). In addition, miRNAs not only regulate tumor-related signaling pathways and the cell cycle but also affect the process of DNA damage and repair, which is an area that requires further study to elucidate tumor resistance to radiotherapy and chemotherapy.

Influence of hepatitis B virus infection

The hepatitis virus protein HBX plays a vital role in the development of HCC; in particular, during treatment with chemotherapy and radiation, HBV-DNA and HBeAg in HCC cells may be reactivated, resulting in treatment failure (71,72). In light of the few mechanisms of radio-resistance that have been reported, we will mainly discuss chemotherapy resistance. HCC associated with HBV infection is less sensitive to chemotherapy because HBX-encoded proteins can promote the direct or indirect development of liver cancer from hepatitis. The evidence is as follows.

Overexpression of HBX in HepG2 cells can enhance the activity of NF- κ B, which can lead to an obvious decrease in apoptosis (73). Studies have shown that the stable expression of HBX activates PI3K in Hep3B cells and inhibits TGF- β -induced apoptosis, namely, chemotherapy tolerance (74). In addition, the oncogene-encoded protein hepatoma upregulated protein (HURP), is highly expressed in most cases of HCC. When the mRNA and protein levels of HURP in Hep3B cells are increased, these HCC cells were resistant to cisplatin (*Figure 1*), while HURP knockout cells were more sensitive to chemotherapy even though

they still carried HBX (75). HBX activates the p38/MAPK signaling pathway and exerts antiapoptotic biological effects via special AT-rich sequence-binding protein 1 (SATB1) and HURP, and in this process, HURP promotes the ubiquitination of P53 by upregulating the tumor anchored protein E3 ubiquitin ligase MDM2, and then promotes tumor growth once it is degraded by proteasomes, thus inducing chemotherapy resistance in HCC cells.

Cytokine-induced chemoradiotherapy resistance

Certain cytokines, such as IL-6, that are secreted by tumor cells and released into the tumor microenvironment can promote cell proliferation and induce cellular tolerance to radiotherapy and chemotherapy (76). High concentrations of IL-6 are detected in the microenvironment of a variety of cancers including liver cancer and contribute to tumor growth by regulating cellular apoptosis, proliferation, angiogenesis, invasion, metastasis and metabolism-related tumor markers, as well as by acting in multiple signaling pathways. Furthermore, IL-6 protects HCC cells from DNA damage, hypoxia and apoptosis and promotes the transduction of antiapoptotic signaling pathways. This leads to the resistance of HCC to chemotherapy and radiotherapy. High levels of serum IL-6 and the signal transcription factor STAT3 are detected in patients with HCC. Inside, IL-6 is able to enhance the invasion of HCC cells, which can be inhibited by E2. The *Figure 1* implied the related mechanism is that the phosphorylation of STAT3 in HCC cells is reduced by E2, suggesting that downregulating the IL-6/STAT3 signaling pathway inhibits the proliferation of anoikis-resistant HCC cells (77). Moreover, under the influence of E2, the G2/M phase of the HCC cell cycle is static, and caspase-3, -9 and PARP are activated by phosphorylated c-Jun N-terminal kinase (JNK). This is one of the important reasons why E2 can promote apoptosis of HCC cells.

In addition to IL-6, IL-17 is closely related to inflammatory diseases, HCC included. Once IL-17 binds to IL-17R, the signal is transduced into cells, resulting in cell synthesis and release of cytokines such as TGF- β , TNF- α , IL-1 β , which have considerable biological effects. It has been reported in the literature that IL-17 is highly expressed in a variety of tumors associated with chronic inflammation. During the course of oxaliplatin treatment for liver cancer, high expression of IL-17 and IL-17R tend to decrease the survival rate and increase the recurrence rate.

In terms of radioresistance, IL-17 is reported to be able to

induce radiation tolerance in low dose pre-irradiated tumor cells (78). In addition, Solberg *et al.* (79) found that HCC cells that survived after radiotherapy could secrete vascular endothelial growth factor (VEGF) to reduce apoptosis and stimulate the proliferation of tumor cells, leading to the resistance. They treated HCC cells with SBRT and then observed that CD147 was highly expressed and induced the expression of the VEGF. Therefore, CD147 is also associated with resistance to radiation in HCC cells which was shown in *Figure 1*. HAb18G/CD147 is closely related to the metastatic potential of tumors. HCC cells with HAb18G/CD147 knockout express P53 when irradiated using X-ray or Co γ -ray irradiation, which halts the cell cycle at stage G0–G1, upregulating the apoptotic sensitivity to irradiation. Integrin b1 has been confirmed to participate in HAb18G/CD147 to enhance the radio-resistance of HCC cells (80). TGF- β is plays two roles in HCC apoptosis because it can simultaneously induce cell death and activate antiapoptotic proteins. TGF- β is better at activating antiapoptotic proteins in HCC cells than it is at inducing cell death, and it induces resistance to radiotherapy and chemotherapy in HCC (81). The abovementioned studies have shown that cytokines directly or indirectly lead to the resistance of HCC.

Induction of tumor stem cells

Cancer stem cells (CSCs) consist of a group of cells that constantly renew and differentiate themselves. They have a close relationship to the heterogeneity, metastasis, recurrence, chemo-resistance and radio-resistance of HCC (82,83). It is well-known that tumor heterogeneity leads to tumor development, metastasis and resistance (84).

CD133 is a marker of tumor stem cells, and it is closely related to tumor resistance (85). An example is JNK activity, which is related to the CD133 expression level and is inversely correlated with the therapeutic response to the sorafenib (86,87). Jang *et al.* (88) pointed out that CD133 (+) cells were more likely to differentiate into tumor cell clusters; furthermore, the chemo-resistance, metastatic potential and tumor formation of these cells were more prominent than those of CD133(–) cells. HCC cells positive for CD133 may abnormally express EGFR, activating the EGFR-AKT signaling pathway (shown in *Figure 1*), which contributes to tumor growth. However, HCC cells that are positive for CD133 but not for are EGFR have been reported to be more susceptible to antitumor drugs and more likely to fail in forming tumor cell clusters.

That is to say that CD133 promotes tumorigenesis via the EGFR-AKT signaling pathway in HCC. Patients with overexpression of CD133 and epithelial cell adhesion molecules (EpCAM) have a poor prognosis because the two molecules may exacerbate HCC. In addition, CD133 can induce radio-resistance in HCC cells via the MAPK/PI3K signaling pathway during radiotherapy. Zhu *et al.* (89) found that a subpopulation of CD133(+) CD44(+) double-positive cells displayed enhanced tumorigenic capacity, increased resistance to chemotherapy and increased expression of stemness genes.

CSCs have been deemed to be derived from normal stem cells. However, there is another hypothesis about CSCs that considers that ordinary tumor cells obtain CSC specialties via “dedifferentiation” and conversion to CSCs after ionizing radiation (90,91). Further scientific evidence for this hypothesis is that the proportion of CSCs increase in tumor tissues after radiotherapy. CSCs upregulate the expression of DNA repair genes in different proportions in cells in different phases of the cell cycle and then cause radio-resistance (92). Specifically, CSCs are more sensitive to radiation during the G2 phase, rather than during the S phase. Then, we speculated that CSCs are increased in irradiated HCC; during radiotherapy, CSCs are stagnated in the G2/M phase, reducing the susceptibility to gamma rays, thus escaping from radiation damage.

Chromosomal variations and DNA damage

Chromosomal variations can lead to HCC. SATB1, which is as a component of chromosomes, participates in the regulation of genes and the stabilization of chromosomes. Studies have indicated that SATB1 not only promotes the survival and metastasis of tumor cells but also inhibits cellular apoptosis and induces drug resistance (93).

A variety of external factors can stimulate genetic mutations and induce HCC, such as HBV and HCV infections and chronic hepatitis (94,95). Numerous HCC-related proteins encoded by mutated genes have been discovered, including P53, P73, P16, APC, PTEN, BRCA2, DLC-1, IGF-2, SOCS-1, c-myc, β -catenin, cyclinD1 and so on (33,96-101). Among these, P53 mutations have vital roles (41,102), because the most common pathologies of liver cancer cells at the molecular level are TP53 mutations and P53 abnormalities (103).

Under normal conditions, the concentration of P53 in cells is very low; however, when cells are exposed to external stimuli, such as hypoxia, DNA damage or cell

cycle inhibition, P53 transcription is activated to maintain the stability of the cell cycle, participate in DNA repair, and maintain a balance between cellular proliferation and apoptosis. P53 can act directly on the cell cycle and stagnate it at the G1 phase and repair chemical or radioactive damage; if such damage remains unrepaired, the cells will directly undergo apoptosis.

P53 can indirectly regulate cellular apoptosis by activating the downstream P21, which suppresses tumor growth by inhibiting the cell cycle-dependent protein kinases. Except for P21, the cell cycle-related protein cyclin G is another target of P53 that leads to induced apoptosis (104). In addition, there is a negative feedback mechanism between the P53 and MDM2, which is expressed highly in 7% of human tumors and promotes tumor progression by suppressing P53; in *Figure 1*, MDM2 can promote phosphorylation/degradation of the P53 protein, while P53 can activate the expression of MDM2 (105,106), ultimately leading to the development of tumors. P53 mutations are important factors in the recurrence of HCC. Some patients have a long survival period but obvious resistance to arterial infusion chemotherapy and radiation (107,108) because P53 normally induces apoptosis after radiotherapy and chemotherapy. In particular, mutations of the *TP53* gene and the downregulation of BCL2 family proteins have attracted much more attention. Hence, low expression of P53 or the presence of mutated P53 in tumor cells is one reason for resistance in and poor efficacy of traditional radiotherapy and chemotherapy in liver cancer. Details were shown in *Figure 1* (109).

He *et al.* (110) have demonstrated that CP-31398 inhibits the growth of P53-mutated liver cancer cells and reactivates wild-type P53 function in P53-mutated HCC cells, resulting in induction of cell-cycle arrest and apoptosis. They have also confirmed that CP-31398 induced desired phenotypic changes in P53-mutated HCC cells *in vitro* and *in vivo*, suggesting that CP-31398 could be developed as a therapeutic candidate for patients with HCC harboring P53 mutations. Moreover, Wang *et al.* (111) reported that miR 215 was upregulated in ADM treatment of HCC cells exhibiting mutated P53, which caused insensitivity to ADM and worsened the prognosis of patients. In addition, the PcG family proteins are present in P53-wild-type HepG2 cells but not in Hep3B or PLC/PRF5 cells with P53 deletions or mutations. Gao *et al.* (112) have previously reported that PcG regulates P53 transcription and that expression of PcG is negatively correlated with P53 in HCC. They treated HepG2 (p53 wild-type) cells,

PLC/PRF5 (P53 mutant) cells and Hep3B (P53 null) cells with MMC and EPB. They unexpectedly found that the expression of PcG in HepG2 cells was decreased, while it was increased in PLC/PRF5 cells exposed to MMC and EPB; however, no obvious changes were observed in Hep3B cells. Phenotypically, this study finally revealed that HepG2 cells were more sensitive than Hep3B and PLC/PRF5 cells to either MMC or EPB. In terms of radiotherapy, Williams *et al.* (113) concluded that tumor cells that expressed wtTP53 were more sensitive to radiotherapy than cells that expressed mutTP53 at doses of 2 Gy. Even though they did not evaluate HCC cells in their research, we hypothesize that the same results would be found in HCC. According to the abovementioned reports, we speculate that mutant p53 target therapy may be effective for HCC treatment.

Ionizing radiation mainly attacks DNA in tumor cells, breaking the double strands or separating the single strand out to kill these cells. Numerous studies have shown that inhibiting the response to DNA damage is a mechanism to kill tumor cells and inhibit their growth. DNA-dependent protein kinase catalytic subunit (DNA-PKcs), which is involved in DNA damage repair, is promising a new target for antitumor therapy. The following studies have evaluated DNA-PKcs. The expression level of DNA-PKcs is markedly upregulated in several kinds of tumors including HCC, which predicts a poor prognosis. Moreover, DNA-PKcs protects tumor cells from DNA damage, the tumor microenvironment, chemotherapeutic drugs and ionizing radiation and ensures that tumor cells proliferate independently without DNA repair (113).

Decreased HCC-related protein 1 (HCRP1) expression in HCC cells

The expression of HCRP1 is decreased in numerous tumors. It has been reported that HCRP1 expression is negatively correlated with epidermal growth factor receptor (EGFR) in breast cancer and can induce resistance of ovarian cancer cells to cetuximab. HCRP1 expression affects the prognosis of HCC patients, but its mechanism of action was previously unknown.

Xu *et al.* (114) studied the expression of HCRP1 in 101 cases of HCC diagnosed based on immunohistochemistry and analyzed the clinical significance. The results implied that the expression level of HCRP1 was decreased in partial HCC and was related to age, pathological grade, recurrence and mortality, but not to cirrhosis, tumor volume, or distant metastasis, while its expression level was increased in both

benign and normal liver tissues. The research revealed that low expression of HCRP1 was an independent risk factor for the prognosis of liver cancer because decreased expression of HCRP1 promoted cancer cell proliferation, metastasis and invasion, upregulated EGFR expression and activated the EMT phenotype, further activating the phosphorylation of AKT in HepG2 cells. However, increased expression of HCRP1 had the opposite effects. Obviously, decreased HCRP1 expression affects the prognosis of HCC.

High expression of HSP

Heat shock proteins (HSPs) are a highly conserved family of proteins that are expressed at low levels in physiological states but are strongly expressed when exposed to stress, hypoxia, cytotoxic drugs, or malnutrition, to ensure that cells adapt to adverse conditions (115-117). As a molecular chaperone protein, the main function of HSP is to ensure the correct folding of proteins, prevent improper assemblage and regulate cell signal transduction (118). However, this vital factor is expressed highly in certain tumors that are resistant to traditional therapy.

Studies have revealed that HSP27 inhibits cisplatin-induced apoptosis by activating protein responses and the autophagy. In chemotherapy, the expression of HSP27 can be induced by 5-FU and carboplatin in Hep3B and HepG2 cells, inducing chemoresistance, while inhibiting HSP27 with siRNA or OGX-427 can largely improve the therapeutic efficacy (119,120). As it was shown in Figure, Inhibiting HSP90 in HepG2 and Hep3B cells can attenuate extracellular signal-regulated kinase (ERK)-mediated autophagy and the accumulation of Mcl-1 and enhances the efficacy of Bcl-2 inhibitors, which leads to increased cell apoptosis (121). Similarly, inhibiting HSP90 in HepG2 and Huh-7 cells can block rapamycin-induced activation of AKT and NF- κ B, thus improving therapeutic efficacy. Intracellular HSP70 is a protective protein, but the role of extracellular HSP70 in tumor cells is still undefined. Wu *et al.* (122) studied the effects of extracellular HSPA1A on tumor proliferation and found that the HSPA1A, which is a stress protein in the HSP70 family, promoted H22 cell proliferation by activating TLR2 and TLR4 signaling pathways and enhanced the resistance of H22 to mitomycin C via NF- κ B. In contrast, the promotion of proliferation correspondingly disappeared.

HSPs is a highly conserved protein family that expresses lowly at physiological state while expresses obviously when exposed to stress, hypoxia, cytotoxic drugs, malnutrition

to ensure the cells adapt to the adverse conditions. As a molecular chaperone protein, the main function of HSP is to ensure the correct folding of proteins, prevent improper assemblage and regulate the cell signal transduction. However, such a vital factor expresses highly in a certain of tumors resisting to the traditional therapy.

Studies revealed that HSP27 inhibited the cisplatin-induced apoptosis through activating the protein response and the autophagy. In chemotherapy, the expression of HSP27 could be induced by 5-FU and carboplatin in Hep3B and HepG2 cells, which would induce chemoresistance. While inhibiting the HSP27 by siRNA or OGX-427 could largely improve the therapeutic efficacy. Inhibiting HSP90 in HepG2 and Hep3B cells could attenuate the ERK-mediated autophagy and accumulation of Mcl-1, and enhanced the efficacy of Bcl-2 inhibitors, which meant more cell apoptosis. Similarly, inhibiting HSP90 in HepG2 and Huh-7 cells could block rapamycin-induced activation of AKT and NF- κ B, thus improving the efficacy. Intracellular HSP70 was a protective protein, but the role of extracellular HSP70 in tumor cells was still indefinite. The HSPA1A, as a stress protein in the HSP70 family, could promote H22 cell proliferation through activating the TLR2 and TLR4 signaling pathway, and enhanced the resistance of H22 to mitomycin C via NF- κ B. On the contrary, the proliferation promotion would correspondingly disappear.

High levels of HSF1 and HSP70 have been associated with tumor prognosis, metastasis, and treatment tolerance (123,124). Elevated levels of HSP are not only beneficial to the survival of tumor cells but also indirectly protect against radiation-induced apoptosis. HSP90 inhibitors might enhance tumor cell sensitivity to radiotherapy and activate HSF1 (125,126), which induces the synthesis of the protective factor HSP70, thus leading to resistance of HCC cells to radiotherapy (127). Once HSPA1A acts on tumor cells, even if it is dislodged, it still promotes proliferation. The possible mechanism is that HSPA1A activates TLR4 in tumor cells and simultaneously reduces intracellular HMGB1 levels, further affecting the sensitivity of tumor cells to radiotherapy (Figure 1).

Excessive activation of autophagy

Autophagy is a self-metabolic process of eukaryotes that occurs by degrading damaged intracellular organelles or macromolecules via lysosomal digestion when exposed to nutritional deficiencies, hypoxia or drug stimulation.

Autophagy, including macroautophagy, microautophagy and chaperone-mediated autophagy, is an essential regulatory mechanism for maintaining cell growth, differentiation and death. It is a reversible process that can promote tumor cell death or survival and is closely associated with multiple human diseases, including carcinoma.

Beclin-1, which is an autophagy-related gene, is homogeneous with yeast ATG6/vps30. The antiapoptotic protein Bcl-2 is the most relevant in terms of tumor resistance to treatment because it can inhibit caspase protease activation via cytochrome C or by forcing glutathione to enter the nucleus. Beclin-1 decreases cell death mainly by interacting with Bcl-2. Autophagy, therefore, is a resistance mechanism that contributes to cell viability (128). Previously, various molecular-targeted drugs have led to the evaluation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in tumor cells. Lim *et al.* (129) studied the mechanism of TRAIL resistance (HepG2-TR) in HepG2 cells. The results showed that HepG2-TR expressed resistance to rhTRAIL, induced autophagy, and died due to toxicity with rhTRAIL, which was prevented by 3-MA or ATG5 inhibitors, indicating that autophagy played a role in HepG2-TR drug resistance. In addition, rhTRAIL-induced autophagy occurred in HepG2-TR under treatment with DR4 but not in HepG2 cells. In addition, JNK is also engaged in DR4-mediated autophagy in HepG2-TR cells and causes therapeutic resistance.

Beclin-1, an autophagy-related gene, is homogeneous with yeast ATG6/vps30. The anti-apoptosis protein Bcl-2 is the most relevant with the formation of tumor resistance, which can inhibit caspase protease activation via cytochrome C or through forcing glutathione to enter into the nucleus. The Beclin-1 decreases cell death mainly through interaction with Bcl-2. Autophagy therefore be taken as a resistant mechanism contributing to cells viability. Previously, various of targeted-molecule drugs lead to drug-fast in tumor cells to TRAIL. Lim *et al.* studied the mechanism of HepG2 cells with TRAIL resistance (HepG2-TR). The results showed that the HepG2-TR expresses resistance to rhTRAIL and induce related autophagy, while died of the toxicity of rhTRAIL which inhibited by 3-MA or ATG5 inhibitor, indicating that autophagy functioned in HepG2-TR drug resistance. In addition, the rhTRAIL-induced autophagy is produced by HepG2-TR under the care of DR4 but not by HepG2 cell. Besides, the JNK also engages in the DR4-mediated autophagy in HepG2-TR cells and causes therapeutic resistance.

Depending on the tumor type and microenvironment,

autophagy may increase or decrease resistance to radiotherapy in different tumors. Despite numerous reports that autophagy can protect cells from radiotherapy, the underlying mechanism has not been fully elucidated. Various studies have indicated that autophagy plays a key role in improving survival of tumor cells after radiotherapy (130,131). The sensitivity of tumor cells to radiotherapy was increased when RNAi was used to knock out autophagy-related genes, including Atg4B, Atg5 and Atg12, delaying the repair process of breaks in the DNA double strand (132). In addition, the autophagy inhibitors 3-MA and chloroquine can alleviate the apoptotic sensitivity of HCC cells to ionizing radiation (133,134), indicating the role of autophagy regulation in the resistance of HCC.

Abnormal activation of signaling pathways

Neoplastic transformation of liver cells is a complex and diverse process. Signaling pathways regulate each step of tumor cell proliferation, angiogenesis, invasion, metastasis and down-regulation. Almost every signaling pathway involved in liver cancer, such as the PI3K/PTEN/Akt/mTOR pathway (135), the RAS/MAPK pathway (136), the Wnt/b-Catenin pathway (137), and the JAK/STAT pathway (138) is altered, ultimately leading to inhomogeneity in HCC biology and clinical phenotypes (139).

The JAK/STAT signaling pathway is activated abnormally and expressed remarkably in multiple tumor tissues, regulating the expression of various apoptosis-related genes including the antiapoptotic genes Bcl-xl and Bcl-2, the pro-apoptotic genes Bax and BH3, as well as caspase-3 and caspase-9 in the mitochondrial apoptosis pathway. There were evidence demonstrating that JAK2/STAT3 pathway could induce chemo-resistance in HCC. However, GL63 could suppress the phosphorylation of nuclear transcription factors in JAK2/STAT3 pathway to reduce proliferation of hepatoma cells (140). When JAK/STAT signaling pathway was upregulated, the STAT3 phosphorylation activation concerning angiogenesis and cell differentiation can be detected in 50–100% cases of HCC. Therefore, the JAK2/STAT3 pathway was hoped to be a target for HCC therapy (141,142).

Modifications in the PI3K/AKT signaling pathway in liver cancer cells can also induce acquired sorafenib-resistance in HCC (143). Defective or abnormal expression of the PTEN gene is one of the factors involved in tolerance in HCC cells (99). Relevant studies have confirmed that the AKT pathway participates in clusterin-induced resistance

in HCC to antitumor drugs, such as sorafenib, doxorubicin, kinasamycin and oxaliplatin (144). Moreover, the PI3K/AKT signaling pathway, which stimulates the cell survival and prevents apoptosis, is also involved in resistance to radiotherapy. It has been confirmed that PI3K/AKT inhibitors sensitize tumor cells to radiotherapy (145). On one hand, radiotherapy activates the FAK-PI3K/AKT pathway. On the other hand, HCC cells that resist radiation and survive will multiply. Naturally, inhibitors of FAK and PI3K can accelerate radiation-induced cell death. In addition, the PI3K/AKT/NF- κ B signaling pathway in HCC can also be triggered by MMP-9 during radiotherapy, enhancing the cell tolerance and aggressiveness.

The ERK signaling pathway plays an essential role in tumor cell viability and proliferation. In HCC, the ERK pathway is correlated with epithelial-mesenchymal transition (146), attenuating the effects of chemotherapy. In addition, the MEK/ERK/NF- κ B signaling pathway affects the sensitivity of HCC to radiotherapy to HCC (147). Hence, the ERK pathway has widespread appeal as a target.

Excessive activation of the Wnt/ β -catenin pathway in HCC contributes to cell growth and metastasis and leads to tumor tolerance (148). β -catenin encoded by genes with a missense mutation of exon-3 is highly expressed in approximately 10–50% of HCC cells, and is responsible for increased invasion and poor prognosis in HCC patients (149).

There are many other factors that affect HCC progression, such as modulation of cell viability and proliferation, angiogenic factors secreted by tumor cells, and the activation of proto-oncogene receptors and growth factor receptors. The abnormal activation of signaling pathways associated with cell growth in HCC hinder cellular apoptosis and lead to chemoresistance. Among these factors, some autocrine signaling factors have attracted considerable attention. For example, epidermal growth factor (EGF) stimulates tyrosine kinase and transformed the communication from cytomembrane into nucleus. EGF can also protect HCC cells from external stimuli, physiological factors and chemotherapeutic drugs by binding with EGFR. Another example is P60C-src, which is expressed highly in HCC cells and decreases the susceptibility of HCC to TRAIL (150).

Increasing evidence indicates that glycogen synthase kinase (GSK-3 β) is excessively activated in multiple tumors and is involved in tumor proliferation and aggressiveness by regulating signaling pathways. In addition, the *Figure 1* described that GSK-3 β -induced tolerance of tumor cells can facilitate resistance to chemotherapy, radiotherapy and

targeted therapy; thus, it is becoming a concerning target (151).

In addition, other mechanisms and second messengers are engaged in HCC progression, such as RAS/MAPK. HCC is a hypervascular solid tumor under the influence of widely scattered VEGF. The MAPK signaling pathway is related to angiogenesis, which has biological effects on HCC proliferation and differentiation (152,153). Jin *et al.* (153) showed that the TUC338/RASAL1 pathway was related to sorafenib resistance; *in vitro* inhibition by a noncoding RNA of TUC338 led to sensitization to sorafenib.

As second messengers, calcium ions play a pivotal role. Cell signaling pathways are regulated by intracellular calcium. Multiple phosphorylated kinases, calcium binding proteins, transcription factors and calcium-dependent channels must function in a complex manner to ensure intricate signal transduction. Recent studies have found that different tumors modulate calcium channels and pumps differently (154); transient receptor potential canonical (TRPC) has been highlighted because of its close relationship to tumor proliferation, metastasis and invasion (155). TRPC5 has been reported to be necessary for P-gp-induced tumor resistance (156). TRPC6 and TRPC1 are involved in proliferation in HCC (157); in particular, TRPC6 is obviously expressed in HCC cells but is expressed at low levels in normal liver cells (158). Other studies have pointed out that tolerance mechanisms, such as EMT, the Hif1- α pathway, and DNA damage repair, in HCC cells rely on calcium-regulated signal transduction which were shown in *Figure 1* (159). Epigenetic-related DNA methylation, protein phosphorylation and histone acetylation can allow tumor cells to obtain MDR (160). In addition, in HCC cells, STAT3 is activated by calcium, and the cdk5-STAT3 pathway is associated with oncogenesis in DNA repair (*Figure 1*) (161). Therefore, STAT3 is responsible for calcium-induced resistance of HCC cells to multiple drugs. These data were summarized to highlight the abnormal activation of signaling pathways. Regulation of signal transduction is much more likely to lead to a need to change drugs or to lead to a lack of irradiation efficacy in HCC.

Abnormal expression of apoptotic proteins

It has been demonstrated that XIAP expressed highly in approximately 90% advanced liver cancer cells. XIAP decreased cell apoptosis and led to drug-resistance by inhibiting caspase activation. The apoptotic suppressor survivin had oncogenic specificity and expressed remarkably in HCC cells and tissues. It directly affected on caspase

to suppress cells death and acted an important role in proliferation and differentiation of tumors as well as invasion and metastasis. The FAS and its receptor indicated the possibility of HCC recurrence. cFLIP, as an intracellular inhibitor of caspase8, expressed in all of the human HCC cell lines and the HCC tissues and non-oncogenic liver tissues, leading to drug-resistance.

BRE, which is an antiapoptotic protein that is highly expressed in HCC, can cause resistance to chemical drugs in HCC by combining with the TNF and FAS (162).

Most gene mutations can lead to an imbalance in the expression of BCL-2 family and induce resistance to radiotherapy and chemotherapy. Low expression of the antiapoptotic proteins BAX or BCL-XS in HCC cells with P53 mutation suggest that the BCL-2 family and the anti-oncogene TP53 are so important that they may be new targets for HCC therapy.

Conclusions

In summary, HCC resistance to radiotherapy and chemotherapy is an intricate process with comprehensive interaction of multiple factors, various genes and diverse pathways. The related factors, mechanisms and the reversal of tolerance should be further studied to improve the effects of treatment for HCC.

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Footnote

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