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REVIEW ARTICLE

Mechanisms of radioresistance in hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC), one of the most common cancers in the world, is characterized by poor prognosis and recurrence after resection. Its prevalence is highest in developing countries, particularly where there is high incidence of hepatitis B virus infection. Several curative treatments are available for early stage HCC; however, these options are not available for advanced disease. New techniques allowing the specific delivery of high-dose radiotherapy enable their use in the treatment of HCC, which has been avoided in the past due to low hepatic tolerance for radiation. This presents a new challenge—the development of resistance to radiotherapy and subsequent disease recurrence. Recently, the mechanisms controlling radioresistance have begun to be elucidated. Understanding the molecular basis of radioresistance is key to developing new strategies with better treatment response and increased patient survival.

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Introduction

Hepatocellular carcinoma (HCC) is diagnosed in more than half a million people worldwide, is the fifth most common cancer in men and the seventh in women, and the third most frequent cause of cancer-related death in the world [1–3]. It is most prevalent in developing countries, with the highest incidence rates reported in regions where infection with hepatitis B virus (HBV) is endemic, including Southeast Asia and sub-Saharan Africa. Diagnosis rarely occurs before the age of 40 years, and peaks at 70 years [2]. The risk of HCC is increased in those with a family history of the disease, exposure to the aflatoxin, alcohol or tobacco use, and infection with hepatitis C virus (HCV) [2]. HCC is characterized by poor prognosis and recurrence after resection [4].

Depending on the extent of the disease and liver status of the patients, they can be treated with local, locoregional, and/or systemic therapy [3]. Although curative treatments such as surgery and liver transplantation are options for patients with early HCC, many of these are not available for patients with advanced stage disease. In the past, radiation therapy has been avoided as a possible therapy for HCC due to the low radiation tolerance of the liver, as whole liver can only receive doses of approximately 30 Gy using standard fractionation [3]. Recently, however, technological advances have provided the means to deliver high-dose radiotherapy tightly around focal HCC, providing the opportunity to use radiation therapy with curative intent. However, exposing liver cells to radiation causes DNA damage, activating repair mechanisms mediated by cell cycle- and cell survival-related proteins, and leading to radioresistance [3, 5–7]. As we have gained a better understanding of the components of the HCC tumor microenvironment, we have come to understand how these changes promote radioresistance and disease recurrence [8].

Mechanisms of radioresistance

Cancer stem cells (CSCs)

It is well established that HCC, like other primary tumors, is clonally derived after sequential mutations in key genes regulating growth. However, HCC is also known to contain a small subpopulation of cells that, like somatic stem cells, are capable of self-renewal,

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extensive asymmetric division, and multilineage differentiation, and have been proven to proliferate in small cell dysplastic foci and cirrhotic liver tissue [9–11]. Cancer stem cells, which are important for early detection, remain poorly understood, as do the mechanisms behind the highly aggressive nature of HCC. Exploration of the differences between CSCs and normal stem cells, including specific markers, bioenergetic qualities, and molecular mechanisms, is crucial for the development of targeted therapies to eradicate them. Although previous studies have demonstrated that CD133, CD90, CD13, CD24, and epithelial cell adhesion molecule (EpCAM) are CSC markers, the specific markers observed in HCC CSCs remain unclear[9–10, 12].

An important feature of liver stem cells is that despite their large number and rapid rate of cell division during regeneration, they rarely acquire the age-related genetic defects associated with cancer induction or show deterioration in functional competence, suggesting that these cells have protective mechanisms against genetic damage. Among them is the ability of stem cells to selectively sort the old (parental) and new DNA strands when they divide, retaining only parental DNA strands. This ensures that replication-induced errors are excluded from stem cells [12]. Furthermore, random errors introduced into parental strands induce protective responses such as p53-dependent stem cell apoptosis and G1 arrest through transforming growth factor-β (TGF-β) signaling [12]. Cells isolated from a patient with primary and recurrent HCC displayed high expression of oval markers and stem cell markers, and were highly tumorigenic. It was suggested that these tumor-initiating cells could represent a useful target for immunotherapy [13].

The transcriptional profile observed during the self-renewal state of CSCs more closely resembles that of embryonic stem cells (ESCs) than adult stem cells, and key regulators (e.g., octamer-binding transcription factor 4 [Oct4], sex-determining region Y box 2 [Sox2], and Nanog) of ESCs are frequently overexpressed in CSCs from different types of cancer [10]. Expression of Nanog was observed in patients with healthy livers and patients with HCC, suggesting that while Nanog may be a biomarker of CSCs in HCC, it may also play a crucial role in maintaining the self-renewal of liver CSCs, through the insulin-like growth factor 1 receptor (IGF1R) signaling pathway. This could explain why the presence of these cells increases the aggression of the malignancy, with vascular and capsular invasion and resistance to therapy [10].

Radioresistance involves the induction of Wnt/β-catenin, promoting genomic instability and accelerating conversion of nontumorigenic cells to glioma CSCs that can survive radiation. Wnt signaling can promote stem cell renewal and rescue of the hematopoietic stem cell compartment after irradiation, through Wnt-3a and possibly also Wnt-5a signaling [12]. Notch and Hedgehog-Gli1 signaling pathways, involved in human CSC self-renewal and tumorigenicity, also may be responsible for CSC recurrence after radiation therapy [14–15]. The inhibition of checkpoint kinases 1/2 (CHK1/2) disrupts the radioresistance of glioblastoma CSCs, which could make CHK1/2 valuable targets to sensitize CSCs to radiotherapy [14–15]. Successful therapies would target CSCs by inducing their differentiation into nontumorigenic cells, or completely eliminating the cells via inhibition of the self-renewing state [12].

Tumor microenvironment

Hypoxia inducible factor-1 (HIF-1)

Hypoxia can promote tumor progression and induce radiation and chemotherapy resistance, allowing cells to escape from anoxic injury [17]. One of the major mediators of the hypoxic response is HIF-1, a transcription factor that activates hypoxia-responsive genes, and in the HCC microenvironment, a high level of HIF-1 leads to enhanced proliferation and survival of HCC cells. The HIF-1 pathway plays a protective role for the tumor, increasing its capacity to counter oxidative stress after radiation, and inducing the expression of vascular-endothelial growth factor (VEGF) and other proangiogenic factors [14]. HIF-1 sensitizes tumor cells to radiation through induction of ATP metabolism, proliferation, and p53 activation, but also enables endothelial cell survival. It has been noted that CSC-derived tumors are vascular and hemorrhagic after radiation, indicating that hypoxia-mediated endothelial cell survival can contribute to angiogenesis and tumor growth [14]. CSCs may be enriched under hypoxic conditions, and it has been suggested that HIF-mediated radioresistance in tumors may be related to hypoxic CSCs. Inhibition of HIF-1 could enhance the therapeutic efficacy of radiotherapy and chemotherapy by avoiding the development of a vascular niche of CSCs and preventing the supply of oxygen to the bulk tumor [4, 14].

Augmenter of liver regeneration (ALR)

ALR is highly expressed in HCC, but rarely in normal liver cells. It is a member of the ALR/ERV1 protein family, which are sulfhydryl oxidases and other redox proteins with roles in growth regulation, differentiation, changes in mitochondrial and cellular membrane morphology, and formation of the extracellular matrix. These proteins function in several cellular locations, including the nucleus, cytosol, endoplasmic reticulum,

mitochondria, and extracellular space [19–20]. They contain a conserved CXXC motif with an adjacent, noncovalently bound flavin adenine dinucleotide (FAD) cofactor, which is vital to their catalytic activity. Human ALR is a potent growth factor for hepatocytes, and exists as two isoforms of 15 and 23 kDa [19–21]. The smaller 15 kDa isoform (also known as hepatopoeitin) is a hepatotrophic growth factor located in cytoplasm that promotes liver regeneration after partial hepatectomy. The larger 23 kDa isoform localizes to the mitochondrial intermembrane space and, along with MIA40/TIMM40, participates in a disulfide relay system that imports proteins into the intermembrane space [19–20]. In addition, ALR transfers electrons, via FAD, to cytochrome c [19]. There is evidence of increased ALR in hepatocellular and cholangiocellular carcinomas, and its upregulation in HCC cell lines helps them evade radiation-induced apoptosis by protecting the mitochondria and reducing cytochrome c release and caspase 3 activity. The silencing of ALR expression in hepatoma HepG2 cells decreases their viability, making it an attractive target for anticancer therapy and radiosensitization [19]. All the changes caused by radiation are compatible with mitochondrial failure, including reduced ATP production, reactive oxygen species (ROS) generation, and accumulation of rhodamine 123, reflecting changes in the mitochondrial inner membrane. ALR overexpression prevents the deterioration of the bioenergetic state [19].

Cyclooxygenase 2 (COX-2)

COX-2 is induced in inflammatory conditions like rheumatoid arthritis, osteoarthritis, and cancer, and although it is not frequently overexpressed in HCC, recent studies suggest that COX-2 expression correlates with reduced patient survival after radiation therapy. COX-2 protects tumor cells from damage by producing prostaglandins, including prostaglandin E2 (PGE2), which act as tumor survival factors. In addition to neoplastic epithelia, COX-2 is expressed in the microvasculature of tumors, providing further resistance to radiation therapy [22–23].

Overexpression of mitochondrial manganese superoxide dismutase (Mn-SOD)

Low levels of ROS can be beneficial for cells by regulating intracellular signaling and homeostasis, but accumulation can cause damage to proteins, lipids, and DNA, and can lead to carcinogenesis [16]. ROS generated by radiation in the mitochondria damages the mitochondrial DNA and results in cell death, but the accumulation of Mn-SOD can suppress mitochondrial ROS production, lipid peroxidation, and apoptosis in irradiated HCC cells, but does not influence the production of nitric oxide, which can also attack DNA and proteins [17].

Fibrotic processes

Apurinic/apyrimidinic endonuclease (APE1)

Human apurinic/apyrimidinic endonuclease (APE1), an important enzyme in the DNA base excision repair pathway, is correlated with sensitivity to radiotherapy and chemotherapy in cancer cells, and a recent study showed that APE1 depletion enhanced the sensitivity of human HCC cells to radiotherapy. In addition, APE1 maintains a number of transcriptional factors, including p53, in their reduced and active state by both redox-dependent and -independent mechanisms. The tumor suppressor p53 is activated by DNA damage and can induce apoptosis, preventing the propagation of genetically damaged cells. Mutation of p53 leads to evasion of apoptosis and tumorigenesis, and is also correlated with sensitivity to radiotherapy in HCC cells [24].

Signal transducer and activator of transcription 3 (STAT3)-mediated signaling

Efforts to target growth factors involved in the activated networks of the tumor microenvironment has led to the development of suramin, which inhibits platelet-derived growth factor (PDGF), epidermal growth factor (EGF), TGF-β, fibroblast growth factor 2 (FGF2), and insulin-like growth factor (IGF) signaling. Suramin has exhibited anti-proliferative effects against many advanced cancers, and reduces tissue damage and fibrosis in rat model of HCC. Recently, it was shown that suramin inhibits heparanase enzymes, which are involve in extracellular matrix breakdown and regulation of growth factors and cytokines in the tumor microenvironment. The presence of these enzymes has been reported to increase radiation-induced cancer cell invasion [8].

STATs function as signal transduction proteins for cytokine- or hormone-induced pathways that control development, proliferation, and differentiation, as well as the homeostasis of many cell types. Cell surface receptors that utilize STAT effectors are intracellularly associated with members of the Janus family of protein tyrosine kinases (JAKs) that, upon receptor activation by ligand binding, phosphorylate STAT proteins at specific tyrosine residues. Phosphorylated STATs homo- or heterodimerize via their Src homology 2 domains, and subsequently translocate from the cytosol to the nucleus to regulate the transcription of specific target genes [25]. For example, STAT3 is activated by the binding of cytokines and growth factors such as EGF, FGF, and PDGF through tyrosine phosphorylation, and plays a critical role in liver inflammation and tumor progression. It has been reported that CD24 regulates the capacities for self-renewal and tumor initiation in the liver through STAT3-mediated Nanog expression [5, 10]. By downregulating phosphorylation of STAT3,

sorafenib reduces the expression levels of STAT3-related proteins (Mcl-1, survivin, and cyclin D1), increasing the radiosensitivity of HCC [5, 25].

Signaling pathways

The mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway

The MAPK/ERK signal transduction pathway is present in all eukaryotic cells and it's upregulated in approximately 30% of human cancers. This pivotal pathway relays extracellular signals to the nucleus via a cascade of specific phosphorylation events involving Ras, Raf, MAPK/ERK kinases (MEKs), and ERK, and regulates several fundamental cellular processes, including proliferation, differentiation, and survival [26]. Activating missense mutations in Ras and Raf proteins are present in various solid tumors. The downstream Raf serine/threonine kinase, in particular, has been identified as a promising target for anticancer drug design [26–27]. Sorafenib tosylate is the first multi-kinase inhibitor developed that targets Raf [26].

Integrin signaling

Integrins provide a transmembrane link for bidirectional (outside-in and inside-out) signal transduction. During outside-in signaling, the binding of extracellular ligands such as CD147 enhances separation of the cytoplasmic domains, allowing for their interaction with cytoskeletal and signal transduction molecules. During inside-out signaling, separation of the cytoplasmic domains by intracellular ligands, for example, talin, causes conformational changes in the extracellular domains, increasing the affinity of the integrin for extracellular ligands and enhancing outside-in signaling. In a recent study it was observed that calpain contributes to the enhanced malignant properties of HCC cells, an effect that may be due to its cleavage of talin and subsequent activation of inside-out integrin signaling [26]. Focal adhesion kinase (FAK) and PI3K/Akt play important roles downstream of outside-in integrin signaling [28]. FAK signaling contributes to the proliferation and survival of cells and is thus linked to cell adhesion-mediated radioresistance of cancer cells [28]. FAK can inhibit p53 expression, which facilitates radiation-induced apoptosis [28]. PI3K/Akt signaling is well characterized with respect to promoting cell survival and suppressing apoptosis [28]. There is evidence that PI3K pathway inhibition enhances radiation-induced angiogenesis and increases tumor radiosensitivity by normalizing the tumor vasculature [28].

Previous studies have demonstrated that the interaction of CD147 with integrin β1 activates the downstream FAK/PI3K/Akt signaling pathways, enhancing the malignant properties and inhibiting the chemosensitivity of HCC cells, while CD147 inhibition in HCC cells resulted in upregulation of p53, inducing cell cycle arrest or apoptosis upon radiation treatment [28]. CD147 knockout and antibody blockade significantly increased the radiosensitivity of HCC cells and attenuated radiation-induced migration and invasion [28].

The sonic hedgehog (Shh) signaling pathway

Shh is a secreted protein that acts in both autocrine and paracrine fashions, and its signaling pathway is critical to the regulation of both proliferation and differentiation in several types of stem cells. It mediates the activation of transcription factors of the Gli family, which upon activation translocate into the nucleus and activate the transcription of target genes controlling the cell cycle, adhesion, signal transduction, and apoptosis. The dysregulation of Shh signaling contributes to the pathogenesis and progression of HCC [29–30]. Recent studies have reported that antibody-mediated neutralization of Shh reduces radioprotection. Although the mechanisms of action responsible for Shh-mediated radiation resistance in HCC cells are not clear, evidence suggests that inappropriate Shh signaling pathway activation may promote radiation-induced genomic instability and tumorigenesis [29–30].

Cylindromatosis (CYLD)

The tumor suppressor protein cylindromatosis (CYLD) is mutated in Brooke-Spiegler syndrome, an autosomal dominant predisposition to multiple tumors of the skin. CYLD is a deubiquitinating enzyme that negatively regulates the nuclear factor-κB (NF-κB) signaling pathway by removing K63-linked polyubiquitin chains from NF-κB activating proteins [31]. CYLD displays decreased expression in HCC at the protein and mRNA levels compared to surrounding non-malignant tissue; this downregulation makes cells less sensitive to treatment with anti-neoplastic agents, and decreases tumor necrosis factor-α-mediated apoptosis [31].

Radiosensitizing medications

Clinicians continue to face the challenge of recurrent or metastatic HCC, and for this reason, the development of useful inhibitors to target pathways responsible for resistance is a high priority [13]. Combining radiation therapy with a radiosensitizing agent could be a good approach. Conventionally, radiosensitizers target molecules controlling hypoxia, mitotic arrest, DNA damage repair, epigenetic alteration, intracellular redox regulation, and related crosstalk pathways [29].

Recent results support a role for CSC-mediated angiogenesis in the efficacy of radiation. Therefore,

identifying and targeting molecular mechanisms responsible for CSC therapeutic resistance could improve current cancer therapies [14].

Sulfated oligo- and polysaccharide agents can inhibit angiogenesis and induce hypoxia in HCC cells. These include phosphomannopentaose sulfate (PI-88), a mixture of sulfated oligosaccharides that besides inhibiting angiogenesis, also inhibits heparanase activity. A phase II clinical trial demonstrated that treating patients with HCC following surgical resection increased the time before tumor recurrence by 76%. Sulfated polysaccharides from Gekko swinhonis Guenther suppress the secretion of IL-8, an angiogenic factor, and could also benefit patients following surgical resection [18].

Sorafenib inhibits the kinase activity of Raf-1, B-Raf, VEGF receptors 1, 2, and 3, and PDGF receptor β, making HCC cells sensitive to radiation by decreasing STAT3 phosphorylation and reducing the levels of STAT3-induced proteins like Mcl-1, cyclin D1 and survivin[5, 27, 32]. Preclinical data have demonstrated that it acts as a potent radiosentitizer of HCC cell lines, and recent randomized trials have demonstrated that it prolongs overall survival for patients with inoperable HCC, establishing sorafenib as a first-line monotherapy for advanced HCC [3].

Celecoxib is a COX-2-derived PGE2 inhibitor that induces G0/G1 arrest in HepG2 cells. The mechanism may involve inhibition of the repair of sublethal damage, redistribution of the cell cycle, and regulation of apoptosis. The combination of celecoxib with radiation results in a dose-dependent synergistic enhancement in tumor growth inhibition – radiation therapy alone inhibited tumor growth by 56%, but combined with celecoxib resulted in 98% growth inhibition [22].

There are several agents being studied targeting the MAPK/ERK pathway, such as the antisense oligonucleotide ISIS 5132, which depletes Raf-1, decreasing its activity and inhibiting tumor cell growth and metastatic spread. Its development was halted after lack of objective responses in phase II trials of patients with refractory prostate, colorectal and ovarian cancers, but it did induce sustained stabilization of disease, indicating a cytostatic effect [26].

Immunotherapy has not been established in the treatment of HCC, mostly because HCC cells do not seem to be immunogenic, but there is growing evidence that radiotherapy may enhance the antitumor effects of immunotherapeutic agents. Preclinical studies have demonstrated synergy between radiotherapy and agents that target immune checkpoint proteins, like cytotoxic T-lymphocyte associated protein 4 and programmed cell death 1 [3].

Conclusion

Although HCC radiotherapy has evolved to enable the delivery of substantial doses of radiation to a tumor while avoiding radiosensitive healthy organs, tumor recurrence and extrahepatic metastasis are still obstacles requiring further development of irradiation-based treatments, including new therapeutic strategies to overcome radioresistance. Understanding the molecular mechanisms involved in the establishment of radioresistance will help identify new genetic targets for sensitization, improving overall survival while minimizing toxicity.

Many ongoing studies are also attempting to identify targets for HCC treatment in the aim of enhancing chemotherapeutic activity, but many are still in preliminary phases, or have not been adequately studied to determine their synergism with radiotherapy.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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