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p53 and P-glycoprotein influence chemoresistance in hepatocellular carcinoma

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1. ABSTRACT

Chemoresistance is a critical obstacle to the treatment of hepatocellular carcinoma (HCC). The mechanisms underlying resistance to doxorubicin, cisplatin, and 5-fluorouracil involve p53 and P-glycoprotein (P-gp). p53 plays a role in cell growth; therefore, resistance mechanisms involve chemotherapy-induced apoptosis and p53 mutation and inactivation. P-gp is an energy-dependent drug efflux pump regulated by p53. Its role in drug resistance has provided new insights into the mechanisms underlying the involvement of p53 and P-gp in chemoresistance and may alter our traditional understanding of p53 and P-gp function. This review outlines the roles and principal mechanisms of p53 and P-gp mediated chemoresistance in HCC.

2. INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related death worldwide (1,2). Chemotherapy is the best option for patients who are ineligible for surgical treatment. However, HCC is often resistant to chemotherapeutic drugs (3), with only a few drugs eliciting a therapeutic effect in more than 20% of patients with HCC (4). The treatment results obtained with chemotherapeutic agents in advanced HCC have been disappointing. Because the successful long-term use of chemotherapy for HCC is often hampered by resistance to chemotherapeutic agents, the reversal of drug resistance has become a critical issue in HCC therapy.

Drug resistance is a multifactorial phenomenon involving mechanisms such as gene mutation, DNA methylation, alterations in drug metabolism and processing, and changes in the expression or activity of target proteins (5–9). Among these mechanisms, the presence of gene mutations in drug targets is a major cause of acquired resistance in cancer (10). Loss of p53 function, which in a subset of tumors is caused by mutation, is a common feature in human cancers (11). The TP53 mutation is present in almost every type of human cancer, including HCC (11). The multidrug resistance 1 (MDR1) gene product P-glycoprotein (P-gp), an energy-dependent drug efflux pump involved in oncogene activation and tumor aggressiveness, is a predictor of chemoresistance in cancer cells (12–14). P-gp potentially regulates apoptosis, immune cell function, and cellular differentiation, proliferation, and survival (15). The MDR1 gene may be activated during tumor progression in association with mutations in p53 (16). Herein, we discuss the roles of p53 and P-gp in chemoresistance in HCC.

3. p53 GENE IN CHEMORESISTANCE IN HCC

The accumulation of mutant p53 with gain of function can result in drug resistance in cancers via direct suppression of apoptotic pathways

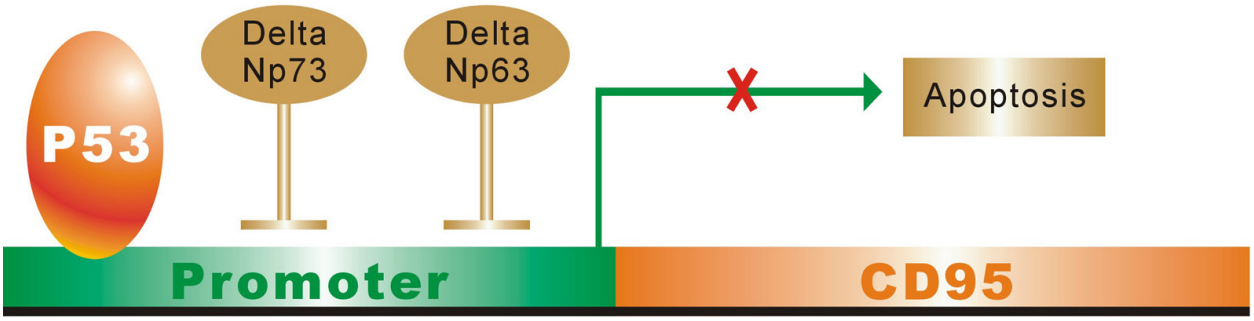

Figure 1. The p53 mediateds chemoresistance in hepatocellular carcinoma (HCC). In HCC, the action of p53 can be inhibited by dominant-negative p73 (Delta Np73), resulting in resistance to chemotherapy. DeltaNp63alpha can directly interfere with the transcriptional activation function of p53 family target genes, resulting in chemoresistance.

(17,18). In HCC, p53 is associated with resistance to several chemotherapeutic drugs. Cisplatin (cis-diamminedichloroplatinum; CDDP) is a fundamental component of standard treatment regimens for cancers of the respiratory, digestive, and genitourinary systems (19). In systemic monotherapy for HCC, the response rate to CDDP is 15% (20), whereas multidrug regimens containing this agent yield higher response rates. The response rates to arterial infusion regimens containing CDDP range from 41% to 61% (21,22) because they achieve higher concentrations of the drug inside the tumor, thereby exerting a more robust antitumor effect. A previous study suggested that CDDP has a synergistic effect with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in most HCC cell lines, regardless of p53 status (23). However, an *in vitro* study of the Bel-7402 (p53 wild type), Huh 7 (p53 mutant), and Hep3B (p53 defective) cell lines demonstrated that CDDP reversal of TRAIL resistance in HCC cells is partially dependent on p53 status (24). Thus, the efficiency of CDDP in apoptosis induction is associated with p53. Defective p53 was later shown to contribute to CDDP resistance (25). Downregulation of p53 expression by long interspersed nuclear element-1 ORF-1 protein (LINE-1 ORF-1p) promotes CDDP and epirubicin resistance in HepG2 cells (26). Therefore, decreased expression of p53 promotes CDDP resistance in HCC cells.

Doxorubicin (Adriamycin, ADA) is the cornerstone of chemotherapy for HCC; however, doxorubicin resistance is an obstacle to successful treatment in these patients. Doxorubicin induces apoptosis in human HCC cells via the p53 pathway (27). Mutant p53 promotes doxorubicin resistance in HCC cell lines (28), whereas wild-type p53 increases doxorubicin chemosensitivity in the drug-resistant human HCC cell line Bel7402/5-FU (29). Inhibition of p53 activation reduces sensitivity to doxorubicin (30). The downstream target of p53, N-myc downstream-regulated gene-1, is also involved in doxorubicin resistance in HCC cells (31). In addition to resistance to doxorubicin, 5-fluorouracil (5-FU) and vincristine resistance in HCC cells is related to the mutation and inactivation of p53 (29,30).

Combination treatment with doxorubicin and sorafenib yields better outcomes than treatment with doxorubicin alone and results in greater median time to progression, overall survival, and progression-free survival in HCC patients (32). These results indicate that sorafenib has a synergistic effect with doxorubicin in the treatment of HCC. The direct target of p53, microRNA-34a, increases the sensitivity of human HCC cells to the antitumor effect of sorafenib, thus potentiating sorafenib-induced apoptosis and toxicity by inhibiting Bcl-2 expression (33).

In HCC cells, p53 mutation and inactivation are key events leading to resistance to CDDP, doxorubicin, 5-FU, and other agents. The p53 mutant p53 (G245D) is associated with resistance to histone deacetylase inhibitors, which decreases the chemosensitivity of HCC cells (34). On the contrary, p53 activity can be inhibited by dominant-negative p73 (Delta Np73), which results in resistance to chemotherapy (35). DeltaNp63alpha directly interferes with the transcriptional activation function of p53 family target genes, which results in chemoresistance (Figure 1) (36). Because chemotherapy-induced apoptosis involving p53 in HCC is mediated by extrinsic and intrinsic pathways (37), the mechanism underlying p53-related chemoresistance may be initiated or regulated by both extrinsic and intrinsic factors.

4. P-GP IN CHEMORESISTANCE IN HCC

Although numerous mechanisms underlying chemoresistance have been described, a large body of evidence strongly supports the involvement of energy-dependent efflux systems (e.g., P-gp) that pump anticancer agents out of cells (38). P-gp, which is encoded by the MDR1 gene, is a 170-kDa protein belonging to the ATP-binding cassette superfamily of membrane transporter proteins (39,40). It reportedly

operates as an ATP-powered drug efflux pump. Several studies have provided functional insight into the role of P-gp in HCC chemotherapy. P-gp is highly expressed in the HCC QGY-TR 50 cell line, which is resistant to actinomycin D, doxorubicin, vinblastine, and vincristine (41). P-gp is also involved in the chemoresistance of human HCC cells to other anticancer drugs such as taxol, 5-FU, and methotrexate (42,43). On the contrary, a P-gp interacting agent has shown anticancer activity in HCC (44).

P-gp overexpression is also associated with doxorubicin resistance in tumor tissues (45–50). In an *in vivo* study, tumor tissues from nude mice implanted with the doxorubicin-resistant HepG2 cell line showed increased P-gp expression (51). Inhibition of P-gp expression increases the cytotoxicity of doxorubicin in the human HCC cell line HepG2 and its drug-resistant subline R-HepG2 (52). Compared with HepG2 cells, R-HepG2 cells show decreased intracellular accumulation of doxorubicin and increased P-gp expression (53). Among the proposed mechanisms of doxorubicin resistance is the mitogen-activated protein kinase-dependent upregulation of P-gp (53). Moreover, the multikinase inhibitor sorafenib tosylate inhibits the expression of P-gp (53). Because the non-steroidal anti-inflammatory drug indomethacin and the cyclooxygenase-2-selective inhibitor SC236 have been found to enhance doxorubicin cytotoxicity in HepG2 and R-HepG2 cells by reversing the upregulation of P-gp expression (52), the COX-2 gene has been proposed to participate in multidrug resistance in HCC by regulating P-gp (54). These studies demonstrate that P-gp promotes doxorubicin resistance in HCC; however, the underlying mechanism remains to be elucidated.

Increased P-gp expression is associated with CDDP resistance in the HepG2 cell line (55), and the CDDP- and doxorubicin-resistant Bel-7402 cell line shows significantly increased P-gp expression (56). However, in the HCC cell line QGY/CDDP, which is established via stepwise increases in CDDP exposure, the mechanism underlying resistance may not be associated with P-gp expression (57). These conflicting findings regarding the resistance of HCC cells to CDDP may be associated with the types of cells studied. Although these *in vitro* findings have not been verified by *in vivo* data, they may provide key contributions to our understanding of the role of P-gp in CDDP resistance in human HCC.

The response to 5-FU treatment can be modulated by CDDP. In 5-FU-resistant BEL-7402/5-FU cells, the inhibition of P-gp function contributes to the reversal of chemoresistance (58,59). However, a recent study has shown that, unlike the roles of multidrug resistance protein 1, Bcl-xl, TS, and E-cad, the role of P-gp in drug resistance may be limited in BEL-7402/5-FU cells (60). These *in vitro* studies used human cell lines, and *in vivo* studies in humans may provide more definite findings.

P-gp appears to play a key role in HCC chemoresistance. The mechanism underlying this resistance in multidrug-resistant overexpressing human HCC cell lines involves P-gp mediation of celecoxib-induced cell-cycle arrest and autophagy via downregulation of the HGF/MET autocrine loop and Bcl-2 expression (Figure 2) (61). Moreover, the CDDP-resistant HCC cell line SK-Hep1 shows increased mitochondrial translocation and functional activation of P-gp (62).

In a study examining the role of P-gp in chemoresistance, Feng *et al.* (63) showed that LINE-1 ORF-1p upregulates P-gp gene expression, which results in increased sensitivity of HepG2 cells to CDDP and epirubicin. A common mechanism involving increased P-gp ATPase activity in doxorubicin, CDDP, and 5-FU resistance has been described (64). Thus, despite the limited role of P-gp in CDDP and 5-FU resistance suggested by *in vitro* studies, the involvement of P-gp in HCC chemotherapy with these drugs warrants further investigation *in vivo*.

5. CONCLUSION

In osteosarcoma and colon carcinoma, mutant p53 activates MDR-1 promoter activity and wild-type p53 represses this activity (65). In HCC, p53 has a similar regulatory effect on P-gp. Although an association between p53 and P-gp expression in advanced HCC was not detected in studies of tumor samples from HCC patients (50), P-gp expression was found to be modulated by downregulation of p53 gene expression (66). Furthermore, transfection of wild-type p53 into Bel-7402 cells resulted in significant downregulation of P-gp expression and increased vincristine chemosensitivity in these cells (67). These findings further demonstrate that p53 mutation, but not p53 protein expression, regulates P-gp expression.

The p53 gene functions in cell cycle control and apoptosis. The involvement of p53 in resistance to CDDP, doxorubicin, and 5-FU among others is mediated by chemotherapy-induced apoptosis and p53 mutation and inactivation. These mechanisms are associated with the role of p53 in cell growth. However, elucidating the role of P-gp, an energy-dependent drug efflux pump regulated by p53, in the resistance to these drugs may provide new insight into chemoresistance mechanisms involving p53 and P-gp and alter our traditional understanding of p53 and P-gp function therein. Therefore, future studies should focus on exploring the mechanisms underlying the regulation of P-gp by p53, which could provide critical information for the development of treatment strategies aimed at

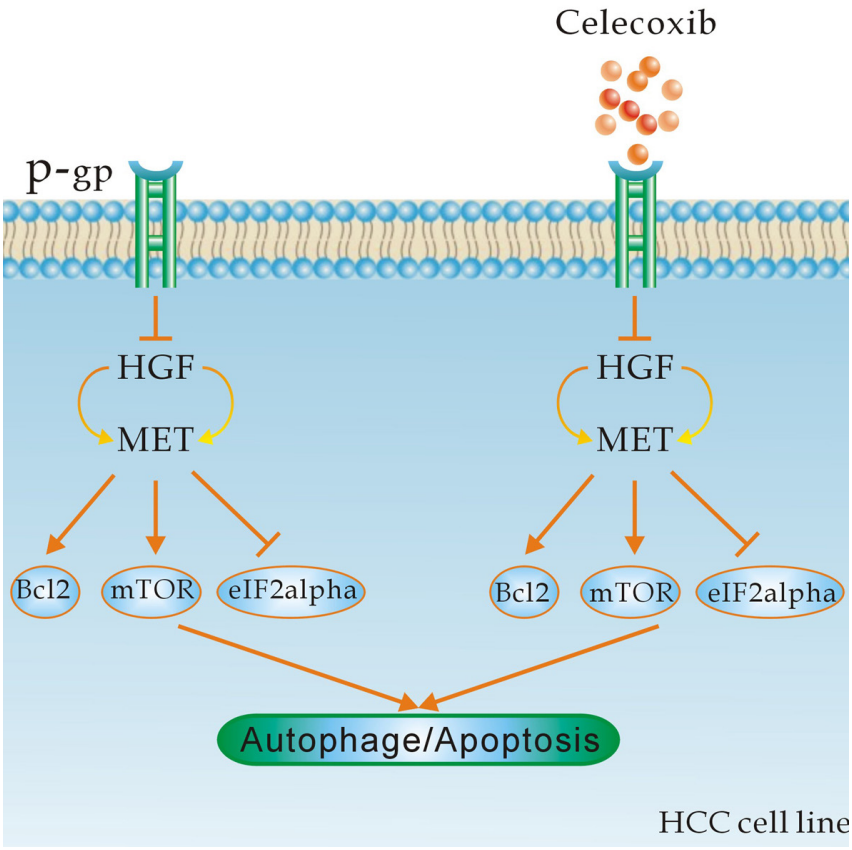

Figure 2. P-glycoprotein (P-gp) can mediate cell-cycle arrest and autophagy in multidrug-resistant hepatocellular carcinoma (HCC). The P-gp can mediate cell-cycle arrest and autophagy induced by celecoxib in human multidrug-resistant overexpressing HCC cell line by down-regulation of the HGF/MET autocrine loop and Bcl-2 expression.

reducing chemoresistance and improving the survival of cancer patients.

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Abbreviations: HCC, Hepatocellular carcinoma; P-gp, P-glycoprotein; MDR1, multidrug resistance 1; TRAIL, TNF-related apoptosis-inducing ligand; 5-FU, 5-fluorouracil; ABC, ATP-binding cassette

Key Words: p53, P-glycoprotein, Chemoresistance, Hepatocellular Carcinoma, Review

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