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Review Article

A Review On the Sources and Mechanisms of Chemoresistance in Hepatocellular Carcinoma

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Abstract

Degenerative Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths worldwide, with surgical resection followed by chemotherapy being the primary treatment method. However, the complex nature and high metastatic potential of HCC often render treatment plans ineffective, and acquired drug resistance frequently results in disease relapse in patients. In this review, we conducted an extensive literaturesearch of different databases, including Medline, Scopus, and Cochrane, to identify studies that have addressed chemoresistance in HCC. This article provides a comprehensive knowledge of molecular mechanisms of chemoresistance in HCC, including genetic polymorphism, apoptosis, DNA methylation, tumor suppressor genes, DNA repair, topoisomerases, drug efflux, and epithelial-mesenchymal transition. Understanding these mechanisms is crucial for developing personalized combination therapies, identifying chemosensitive populations, and evaluating the effectiveness of chemotherapeutic agents through cell culture and orthotopic models. Therapies that can counter these resistance mechanisms need to be developed to better manage and control the disease. This would increase the patient survival rate and help decrease the use of multiple chemotherapeutic agents that greatly increase the risk of toxicities encountered by patients. Further studies are needed, so a combined effort by healthcare professionals and pharmaceutical companies can be the key to combatting the ever-rising rate of chemoresistance in HCC.

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Keywords: Hepatocellular carcinoma, resistance, genetic polymorphism, DNA repair, tumor suppressors

1. Introduction

Cancer constitutes a significant portion of global public health issues, with demographic characteristics projecting a rise in its incidence in the next few decades; over 20 million new cases annually are anticipated by 2025(Zugazagoitia et al. 2016). Liver cancer is among the most commonly diagnosed cancers and a leading cause of cancer-related mortality worldwide(Sung et al. 2021). Hepatocellular carcinoma (HCC) represents over 80% of liver cancer cases. It is a global challenge due to its high malignancy, recurrence, progression, and drug resistance (van Malenstein et al. 2013). The management of HCC has undergone a significant transformation in recent decades due to modern curative treatments such as hepatic resection, liver transplantation, targeted chemotherapy via the hepatic artery, and systemic therapies(Liao et al. 2015).

Chemotherapy remains a major treatment route for cancer patients. While tumors generally exhibit a satisfactory response when initially exposed to chemotherapeutic drugs, drug resistance may develop later, with most patients developing advanced disease (Liu 2009). Chemotherapy resistance may occur before drug treatment (inherent resistance) or emerge during treatment (acquired resistance) (Mellor and Callaghan 2008). The causes of cancer-specific drug resistance are believed to be linked to random drug-induced mutational incidents (genetic hypothesis), drug-induced non-mutational adaptations of gene function (epigenetic hypothesis), and drug-induced karyotypic alterations (karyotypic hypothesis)(Duesberg et al. 2007) (Roberti, Sala, and Cinti 2006). The most commonly analyzed cytogenetic events include microsatellite instability, and chromosomal instability, while the most studied epigenetic mechanisms are DNA methylation, modifications in histone proteins, and microRNAs (Zoratto et al. 2014) (Ng and Yu 2015),(Colussi et al. 2013). It is generally accepted that DNA constitutes the molecular earmark for these chemotherapies, leading to inhibited transcription (Fischel et al. 2002). Understanding various resistance mechanisms for different chemotherapeutic agents is necessary to develop improved treatment strategies, ideally leading to personalized drug regimens, better treatment response, and the prevention of ineffective treatment.

2. Mechanism of Resistance to Traditional Chemotherapy

Chemotherapeutic resistance, either intrinsic or acquired, is caused and sustained by reduced drug accumulation and increased drug export, alterations in drug targets and signaling transduction molecules, rapid repairing of drug-induced DNA damage, and evasion of apoptosis (Sun et al. 2016) (Shi et al. 2020). The main factors contributing to the development of drug resistance include pharmacological and physiological factors such as drug metabolism and excretion, inadequate access of the drug to the tumor, inadequate infusion rate, and inadequate delivery route. These are extremely important issues in clinical practice and fundamental in drug development (Garattini 2007). The activation of drug resistance mechanisms can occur at the genetic level through gene amplification, transcriptional level through epigenetic modifications, or proteomic level after mutation or aberrant expression. Additionally, the faulty processing of microRNA (miRNA) results in the altered function of a targeted gene (Kozinn et al. 2013). Many anticancer drugs, such as platinum compounds, alkylating agents, and nitrosoureas, cause direct damage to the structural integrity of the DNA, and resistance to these compounds results from the activation of DNA repair systems.

3. Role of Genetic Polymorphisms in Chemoresistance

Sorafenib is currently regarded as the first-line systemic treatment for advanced HCC worldwide (Llovet et al. 2008). Sorafenib is a molecule-targeting agent that specifically targets the vascular endothelial growth factor receptors (VEGFR1, 2, 3), platelet-derived growth factor receptor (PDGFR), and Raf family kinases (primarily C-Raf, rather than B-Raf) (Liu et al. 2006). A sustained capacity of cancer cells to perform DNA repair, despite the disruptive actions of chemotherapeutic drugs, promotes cell survival and growth, leading to resistance(Cox and Weinman 2016). In HCC, the

Table 1: List of drugs and their targets used against HCC.

Name of the drug	Target molecule	Mechanism	Limitation	Year and references
Tamoxifen	Estrogen receptor	Inhibit of P-glycoprotein	Minimum effect	**(Tan et al. 2000)**
5-Fluoracil	Thymidylate synthase	Incorporation into RNA and DNA	Co-treatment with other drugs required	**(Longley, Harkin, and Johnston 2003)**
Thalidomide	VEGF, TNF-α, Ikβ	Anti-angiogenic. and immunomodulatory	Fatigue, somnolence, constipation	**(Hsu et al. 2003, Dimopoulos and Eleutherakis-Papaiakovou 2004)**
Octreotide	Somatostatin receptors	Anti-tumor effect.	Somatostatin receptor type 2 (SSTR2) was found in some but not all patients with HCC	**(Bläker et al. 2004, Nguyen-Khac et al. 2009)**
Sorafenib	Raf, VEGFR2, VEGFR3, DGFRs	Anti-angiogenetic	Hypertension, diarrhea, proteinuria, skin- related toxicities, an increased risk for thromboembolism, and bleeding events	**(Roodhart et al. 2008)**
Sunitinib	PDGFRs, KIT, RET, and FLT3	Anti-angiogenetic	Modest clinical efficacy	**(Zhu et al. 2009)**
Bevacizumab	VEGF	Blocks VEGF binding to its receptor	Low rate of response, gastrointestinal bleeding, including variceal bleeding	**(Finn and Zhu 2009)**
Erlotinib, gefitinib, cetuximab	EGFR	EGFR inhibitor	Minimum effect	**(Llovet and Bruix 2009)**
Doxorubicin	DNA topoisomerase II	Induce histone eviction	The use of single agents in therapy is practically nonexistent currently because of its erratic and low response	**(Pang et al. 2013)**
Cisplatin	DNA	Cross-link DNA, induces apoptosis	Allergic reactions, gastrointestinal disorders, decrease immunity to infections, kidney problems, hemorrhage	**(Dasari and Tchounwou 2014)**
Oxaliplatin	**DNA**	**Cross-link DNA, induces apoptosis**	**Increase autophagy results in tumor resistance. Reduction of DYRK2 promotes cell proliferation and resistance.**	**(Zhang, Xu, et al. 2016)**

APE1/Ref-1 protein is over-expressed in both tissue and serum, and cytoplasmic localization is associated with a low degree of cancer differentiation and short survival time, indicating a prognostic function in multidrug resistance (MDR) phenotype (Lian, Yuan, and Gao 2020, Di Maso et al. 2007). In addition to its DNA repair function, the molecular basis of transcriptional regulation of APE1 is associated with drug resistance. APE1, preferably in the acetylated form, stably interacts with Y-box-binding protein 1, enhances its binding to the Y-box element that leads to the activation of the multi-drug resistance 1(*MDR1*) gene (Chattopadhyay et al. 2008). Loss of APE1's acetylation impairs *MDR1* activation and sensitizes cells to cisplatin or etoposide(Sengupta et al. 2011). *APE1* D148E is one of the most extensively studied variants, and it, together with the *XRCC1* R194W polymorphism, plays a role in the cisplatin resistance of HCC cells (Yang and Zhao 2015)

Various genetic variations have been identified in the DNA sequences of *ABC* transporter genes. A recent human genetic study using next-generation sequencing (NGS), on 138,000 individuals from seven major populations revealed an extension of population-specificity in *ABC* variants (Xiao, Zhou, and Lauschke 2020). Results found clinically relevant variants for drug-transporter members of the *ABCB* family, *ABCC* family, and *ABCG2*, which have been associated with chemotherapy resistance in the past. The functional significance of single nucleotide polymorphisms (SNPs) in *ABCB1* (PGP/MDR1), *ABCC1* (MRP1), *ABCC2* (MRP2), and *ABCG2* (BCRP) has been proved by *in-vitro*, *in-vivo*, drug disposition, and clinical outcome studies (Lepper et al. 2005, Cascorbi 2006). *ABCG2* (BCRP) was found to mediate the efflux of sorafenib, so co-treatment of sorafenib with an *ABCG2* inhibitor greatly augmented the cytotoxicity in HCC cells (Huang et al. 2013). This sorafenib resistance might be attributed to the genetic polymorphism in *ABCG2 (Tandia et al. 2017, Boudou-Rouquette et al. 2012)*. Many studies have shown the impact of these SNPs by using different *ABCC2* SNPs generated through site-directed mutagenesis targeting C24T-, G1249A-, G3542T-, T3563A-, C3972Tand G4544A-MRP2. Genetic variability in the *ABCC2* gene also influenced the *in- vitro* (Schaller and Lauschke 2019) expression, tracking, and transport activity of MRP2(Wen, Joy, and Aleksunes 2017) . Additionally, the solute carrier *(SLC)* superfamily of transporters, consisting of 400 membrane-bound proteins, has been shown to play important roles in physiological processes, including the cellular uptake of nutrients (Lin et al. 2015) (Schaller and Lauschke 2019). Several studies indicated the importance of member 22 of the *SLC* family (organic cation/anion transporter) in sorafenib resistance. *SLC22A1* encoding OCT1 has been reported to be involved in the uptake of sorafenib in animal models and human cells (Marin, Herraez, et al. 2013). Down-regulation of OCT1 and OCT3 (*SLC22A3*) was observed in HCC (Geier et al. 2017, Martinez-Becerra et al. 2012, Zhang et al. 2014) which was further associated with poor survival rate in patients treated with sorafenib, independently from the clinical staging of the associated liver disease (Grimm et al. 2016). Furthermore, DNA methylation of OCT1 has been reported to be associated with OCT1 downregulation (Schaeffeler et al. 2011)

4. P53 Mutant: A Major Obstacle to Chemosensitivity

The accumulation of inactivating p53

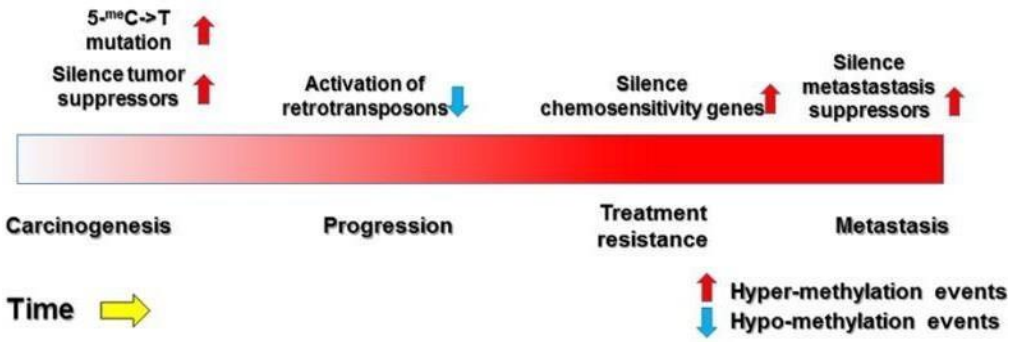

Figure 1. Hypo-methylation and hyper-methylation role in treatment resistance and tumor metastasis.

mutations can result in drug resistance in cancers by directly suppressing apoptotic pathways (Lowe et al. 1993, Kamesaki et al. 1993). This is particularly seen in HCC, where p53 is linked to resistance against several chemotherapeutic drugs (Go and Adjei 1999). Doxorubicin (Adriamycin or ADA) is the cornerstone of chemotherapy for HCC; however, resistance to doxorubicin is a major challenge in the successful treatment of HCC. The p53 pathway plays a crucial role in doxorubicin-induced apoptosis in HCC cells (Zheng et al. 2010), and mutant p53 promotes resistance to doxorubicin in HCC cell lines.(Li, Lin, and Tan 2004). Inhibition of p53 activation reduces sensitivity to doxorubicin (Fang et al. 2012). Mutations and inactivation of p53 are key factors that lead to resistance to various agents, including Cisplatin (CDDP), doxorubicin, and 5-FU inHCC cells.

5. Role of Epigenetic Modification in Chemoresistance

One of the crucial epigenetic processes contributing to tumorigenesis is the aberrant DNA methylation pattern, which usually affects promoter sequences of genes responsible for cell cycleregulation, apoptosis, DNA repair, metabolism of carcinogens, and angiogenesis (Esteller 2007). Among various epigenetic mechanisms, DNA methylation is the most extensively studied and promising molecular indicator for cancer diagnosis and prognostic assessment. It refers to DNA sequence-independent mechanisms underlying the cross-cell generational transmission of gene expression memory (Bonnette et al. 2009). Studies have shown that dynamic patterns of DNA methylation play a crucial role in liver cancer development, clinical diagnosis, and treatment (Laugsand et al. 2015) (McPherson, McMullin, and Mills 2017). Aberrant DNA methylation patterns can disrupt the expression of critical genes, encoding tumor suppressors, such as multiple tumor suppressor 1 (*p16*), Ras association domain family 1A (*RASSF1A*), suppressor of cytokine signaling 1 (*SOCS-1*), human runt-related transcription factor 3 (*RUNX3*), and frequently deleted in liver cancer (*DLC-1*) resulting in HCC (Khan et al. 2017). Moreover, the silencing of DNA methylation-regulated Bcl-2-like protein 10 (*BCLB*) gene expression can also contribute to the development of HCC ,and may carry potential therapeutic implications for HCC treatment (Liu et al. 2017). Furthermore, DNA methylation induces abnormal histone modifications, such as acetylation on Lys-27 (HH3K27ac) and methylationat Lys-5 (H3K4me3)

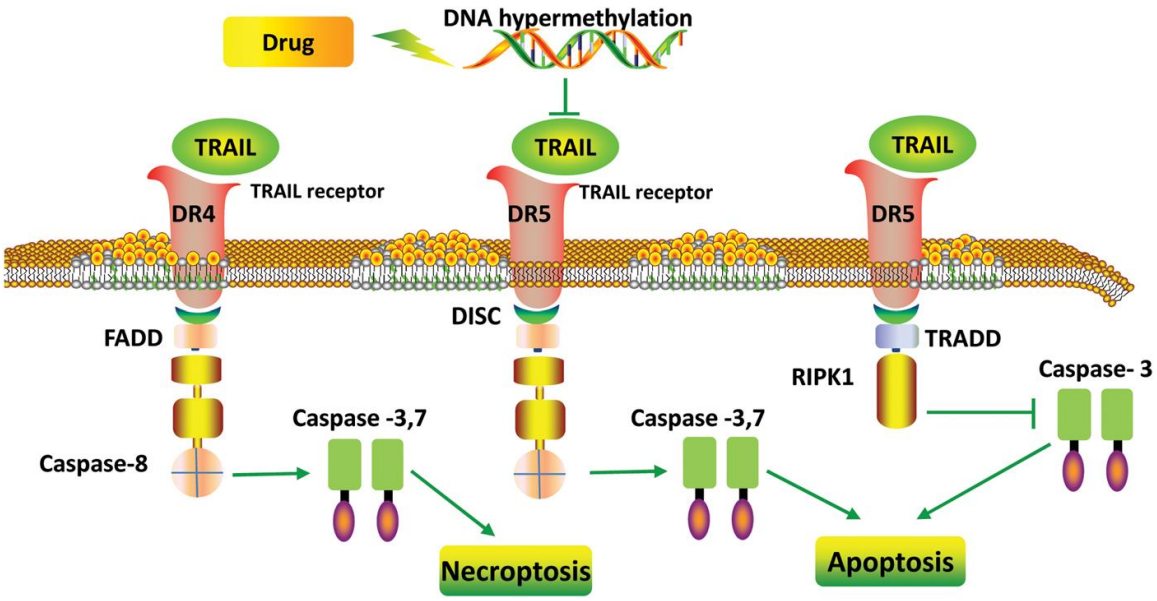

Figure 2. Tumor cell resistance by the methylation of apoptosis genes.

(He et al. 2012). The expression of microRNAs (miRNAs), such as miR-129-2, can also exacerbate liver cancer (Liu et al. 2016). Genomic profiling at DNA methylation and miRNA levels has illustrated a novel mechanism for how DNA methylation-regulated miR-193a-3p regulates the 5-FU resistance of HCC cells by repressing serine/arginine-rich splicing factor 2 (SRSF2) expression. SRSF2 up-regulates the proapoptotic splicing form of caspase 2 (CASP2L) and sensitizes HCC cells to 5- FU. Forced changes in miR-193a-3p levels can reverse all of the phenotypic features examined, including cell proliferation, cell cycle progression, and 5-FU sensitivity, in cell culture and nude mice. This newly identified miR-193a-3p-SRSF2 axis highlights a new set of companion diagnostics required for optimal 5-FU therapy of HCC, which involve assaying both the DNA methylation state of the miR-193a gene, the expression of miR-193a-3p, and SRSF2 as well as the relative level of the proapoptotic versus antiapoptotic splicing forms of caspase 2 in clinical samples (Ma et al. 2012). Human organic cation transporter-1 (hOCT1, gene *SLC22A1*) has been observed to enhance sorafenib uptake in hepatoma cells, but not regorafenib, through overexpression (Prado- Martinez et al. 2013). In rodent HCC, OCT1 is down-regulated, which leads to impaired sorafenib uptake. Deficient hOCT1 expression is suggested to be a common trait in the MDR phenotype shared by the three major types of liver cancer: HCC, cholangiocarcinoma, and hepatoblastoma. In mice with subcutaneously implanted HCC, sorafenib inhibited the growth of hOCT1 overexpressing tumors. The expression of hOCT1 was inversely correlatedwith *SLC22A1* promoter methylation in human HCC, and demethylation with decitabine enhanced hOCT1 expression in hepatoma cells. Additionally, an increased proportion of aberrant hOCT1 mRNA variant was found in HCC samples (Al-Abdulla et al. 2019).

6. Long Non-Coding RNAs (lncRNAs)

Mounting evidence indicates that long non-coding RNAs (lncRNAs) play crucial roles in

regulating chemoresistance in HCC (Ding et al. 2018). Many research findings suggest that the 'lncRNA colorectal neoplasia differentially expressed' (lncRNA CRNDE) affects drug resistance in HCC through down-regulation of p27KIP1, large tumor suppressor 2 (LATS2), and CUGBP Elav-like family member 2 (CELF2), all of which have been demonstrated to be involved in the chemosensitivity of cancer cells (Daniel et al. 1999, Wang, Hsu, and Lee 2015) (Kawahara et al. 2008). Specifically, studies demonstrated that CRNDE regulates the chemosensitivity of an HCC cell line by modulating the LATS2 and Hippo signaling pathways, which may represent a potential mechanism through which CRNDEmediates chemoresistance in HCC (Xie et al. 2020).

7. Apoptosis Gene Methylation-Mediated Tumor Cell Resistance

Apoptosis is a vital biological process for eliminating damaged, harmful, excessive cells. Anticancer drugs induce apoptosis by inducing cytotoxicity. Studies have found that anticancer drugs decrease the expression of DNA-methyltransferase1(DNMT1) and the methylation of CpGs in the acetylcholinesterase (AChE) promoter in HCC cells undergoing apoptosis. Conversely, inhibiting the expression of DNMT1 by Azacitidine (5-AZA) or RNA interference (RNAi) can restore the production of AChE, and the decreased expression of AChE by RNAi can preventthe apoptosis of HCC cells induced by anticancer drugs (Venturelli et al. 2011).

DNA methylation may play an important role during the development, maintenance, and resistance of cancer cells. Molecular evidence suggests that decitabine can effectively treat apoptosis tumors as it not only reverses the epigenetic phenotype of malignant tumors but also effectively resensitizes antiapoptotic tumor entities to apoptosis-inducing mediators such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (Shen et al. 2013)

8. Role of De-novo Synthesis in Chemoresistance

In addition to being the basic building blocks of RNA and DNA, nucleotides are also involved in all major aspects of cell proliferation and metabolism(DeBerardinis et al. 2008) (Cairns, Harris, and Mak 2011). There are two major pathways for nucleotide synthesis in cells: 'the de-novo synthesis pathway' and 'the salvage pathway' (Sakkas et al. 2002, Dervieux et al. 2002) (Panwar et al. 2020). The salvage synthetic pathway uses either exogenous nucleic acid raw materials or endogenous nucleic acid intermediates as substrates. The de-novo synthesis of purines uses amino acids, carbon dioxide, and formyl as raw materials; the de-novo synthesis of pyrimidines uses glutamine, carbon dioxide, one carbon unit, and aspartic acid as raw materials. Maintenance of intracellular levels of nucleotides is critical for cell survival and fate, thus de-novo synthesis of nucleotides is strictly regulated at multiple levels, such as the regulation of precursors, and the regulation of enzymes at transcriptional and post-translational levels(Flicek et al. 2014, Ben-Sahra et al. 2013) (Kim, Lee, and Na 2017). Some previous studies showed that enzymes in nucleotide de novo synthesis were activated by post-translational modification in HCC. For example, CAD was phosphorylated by β-catenin/AKT2 axis to potentiate nucleotide synthesis in HCC (Liu et al. 2022).

However, the transcription regulation of the nucleotide synthetic genes in HCC hasn't been fully understood. *FOXK2* belongs to the forkhead box *(FOX*) transcription factor

superfamily, which plays important roles in cell proliferation, differentiation, autophagy, and aerobic glycolysis (Cortazar et al. 2014, Sukonina et al. 2019). *FOXK2* shuttles between the nucleus and cytoplasm, which is controlled by DNA damage-induced phosphorylation or nutrition starvation(He et al. 2018, Wu et al. 2020). For example, DNA damage induces CHK2-mediated FOXK2 phosphorylation at Ser61 and traps FOXK2 in the cytoplasm through binding with 14–3–3γ, to regulate the expression of autophagy-related genes (Wu et al. 2020). Upon insulin stimulation, *FOXK2* translocates to the nucleus dependent on the Akt-mTOR pathway. Knock-down of *FOXK2* in liver cells resulted in the up-regulation of apoptosis-associated genes and down-regulation of cell cycle and lipid metabolism-associated genes, resulting in decreased cell proliferation (Kamada et al. 2019). Other studies also showed that FOXK2 acts as an independent prognostic factor and exerts an oncogenic role via activation of the PI3K/AKT signaling pathway in HCC (Lin, Chen, and Lin 2017).. Another finding suggests that PIAS4-mediated *FOXK2* SUMOylation also promotes nuclear translocation and activation, which DNA damage suppresses. DNA damage signals to control *FOXK2* cellular localization and functions. Thus, these findings will bring new insights into the dissection of nucleotide de novo synthesis pathway components. Furthermore, because up-regulation of *FOXK2* is closely linked to HCC predisposition and poor prognosis, and elevated *FOXK2* SUMOylation causes resistance to 5-FU in HCC, these findings might also have important implications for cancer etiology and response to chemotherapy (Li et al. 2023).

9. Topoisomerases and HCC Chemoresistance

Topoisomerases are crucial enzymes central to preserving the DNA double helix structure. In various types of cancer, the expression of topoisomerase2A (TOP2A) has been observed to be abnormal and is recognized as a significant prognostic indicator for the progression and recurrence of tumors, as well as a predictor of unfavorable survival outcomes (Engstrøm et al. 2014, Almeida et al. 2014). In addition, an increased protein score of TOP2A has been linked to a lack of response to chemotherapy *in-vitro* models of doxorubicin-resistant HCC (Pang et al. 2005). Remarkably, the cell lines that were transfected with topoisomerase demonstrated resistance to cisplatin and other alkylating drugs that were roughly five to ten times higher. Accordingly, combining Tirapazamine, a new anticancer drug, with Topoisomerase I inhibitors produced a synergistic cytotoxic effect, inducing significant apoptosis in various HCC cell types, as anticipated (Cai et al. 2014). Consequently, focusing on topoisomerases could be a suitable approach for patients with HCC who are unresponsive to conventional cytotoxic treatment.

10. Role of Signaling Pathways in Chemoresistance

The process of epithelial-to-mesenchymal cell transition (EMT) is crucial in the progression of malignant tumors. It allows for increased cellular motility and acquisition of drug resistance, invasiveness, and metastatic properties (van Malenstein et al. 2013). The PI3K/Akt signaling pathway plays an important role in hepatocarcinogenesis, with its activation inducing chemoresistance in HCC cells. (Kunter et al. 2014, Dong et al. 2017, Zhang et al. 2016). Studies have shown that down-regulating thePI3K pathway affects extracellular signal-regulated kinase (ERK), suppressing the initiation of EMT, suggesting

a crosstalk between the PI3K/Akt and ERK1/2 signaling pathways and that EMT may directly or indirectly regulate transcription factors associated with these pathways (Zhang et al. 2018). *TRIM37* enhances sorafenib resistance by up-regulating AKT activity and phosphorylated AKT levels, subsequently activating canonical AKT signaling. These findings identify TRIM37/AKT axis as a potential target for overcoming sorafenib resistance in patients with HCC (Tan et al. 2021). Glycochenodeoxycholic acid (GCDC) promoted chemoresistance of HCC cells *in-vitro* by down-regulating apoptotic gene expression and up-regulating anti-apoptotic gene expression. GCDC promotes chemoresistance in HCC cells via EMT and activation of the *STAT3* signaling pathway. These results proved that GCDC contributes to the chemoresistance of HCC and could be a potential target in HCC therapy (Shi et al. 2020).

Silencing Aurora-A significantly increases chemosensitivity, while overexpression decreases chemosensitivity and reduces chemotherapy-induced apoptosis by promoting NF-κB-mediated transcription of miR-21. This novel Aurora-A/NF-κB/miR-21/PTEN axis sheds light on HCC chemoresistance mechanisms (Zhang et al. 2014). Calcium (Ca^{2+}) plays a key role in tumor cell proliferation, apoptosis, autophagy, and drug resistance. Voltage-gated calcium channels have been found to mediate Ca^{2+} influx. Acid-sensing ion channel 1a also mediates calcium influx and drug resistance in HCC cells(Zhang et al. 2017). Notably, Ca^{2+} regulates the PI3K/AKT signaling pathway (Divolis et al. 2016, Zheng et al. 2008), which induces drug resistance by mediating tumor cells to escape apoptosis. Extracellular acidosis contributes to drug resistance, including reduced apoptoticpotential, genetic alterations, and elevated activity of the multidrug transporter, p-glycoprotein (Zhang et al. 2017)

11. Conclusions

Clinicians, patients, and pharmaceutical companies are facing a formidable challenge due to increasing cases of resistance in patients with HCC. The chemotherapeutic drugs currently being utilized against HCC have demonstrated strong chemoresistance, causing a setback in treatment regimens aimed at it. Additionally, liver cancer patients have a low tolerance for chemotherapy due to liver dysfunction. Identifying appropriate targets for sensitizing resistant cells is crucial, but designing effective strategies is challenging. Development of targeted drugs has not improved outcomes significantly, possibly due to factors like apoptosis evasion, stem cell activation, enhanced DNA repair, a lack of suitable immunotherapy targets, dynamic changes in EMT, and others. These factors, individually or in concert, contribute to refractoriness to drug therapy in HCC. Moreover, therapeutic effectiveness may vary depending on patient-specific factors and tumor development stage. Therefore, formulating a unified molecular targeted therapeutic strategy for all HCC patients is unlikely to succeed. Hence, future HCC therapies should be based on a combination of context and stage-dependent molecular targeted drugs against resistance, with or without conventional drugs, to treat HCC successfully. Recent studies have suggested that combining a small molecule inhibitor with anticancer treatments may prevent drug resistance development and tumor growth more effectively.

Conflict of Interest

The authors declare that they have no competing

interests.

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Study Approval
NA.

Consent Forms
NA.

Data Availability
All the raw data related to this study is available with the authors.

Author's Contribution:
The study was conceptualized by QTA, literature was searched by MA & MA, graphics were made BR& AI, Initial draft was written by FB, final draft was written by QUA.

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