REVIEW

Unraveling Chemoresistance Mechanisms in Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is an aggressive tumor among liver malignancies, and a predominant cause of cancer related mortalities around the globe. HCC heterogeneity at both the molecular and phenotypic levels complicate disease diagnosis, prognosis, and treatment responses. Despite advancements in standard therapeutic approaches, ranging from surgical resection to systemic therapies, the disease prognosis remains poor in advanced stages. Several available chemotherapies and multikinase inhibitors have been effectively used to target oncogenic pathways. However, the development of chemoresistance continues to limit the effectiveness of inhibitors, as drug resistance involves an interplay of complex mechanisms, including altered drug transport, dysregulation of intracellular signaling, genetic modifications, and epigenetic reprogramming. Furthermore, chronic inflammation within the tumor microenvironment promotes tumor metastasis and reduced drug sensitivity by activating pro-tumorigenic signaling cascades, such as dysregulation of the JAK/STAT pathway mediated by altered expression of suppressors of cytokines. Additionally, epithelial-to-mesenchymal transitions, cancer stemness, autophagy, and immune evasion are factors that reinforce both innate and acquired resistance. Immune checkpoint inhibitors among immunotherapies proposed new hope for treatment of HCC, but interacting resistance mechanisms have made their effectiveness inconsistence. This review summarizes the molecular mechanisms underlying chemoresistance and highlights how understanding these factors can aid the development of advance therapeutic strategies to enhance treatment outcomes.

Key words: *Chemoresistance, Chemotherapy, Hepatocellular Carcinoma, Immunotherapy, Multidrug Resistance, Tumor Microenvironment*

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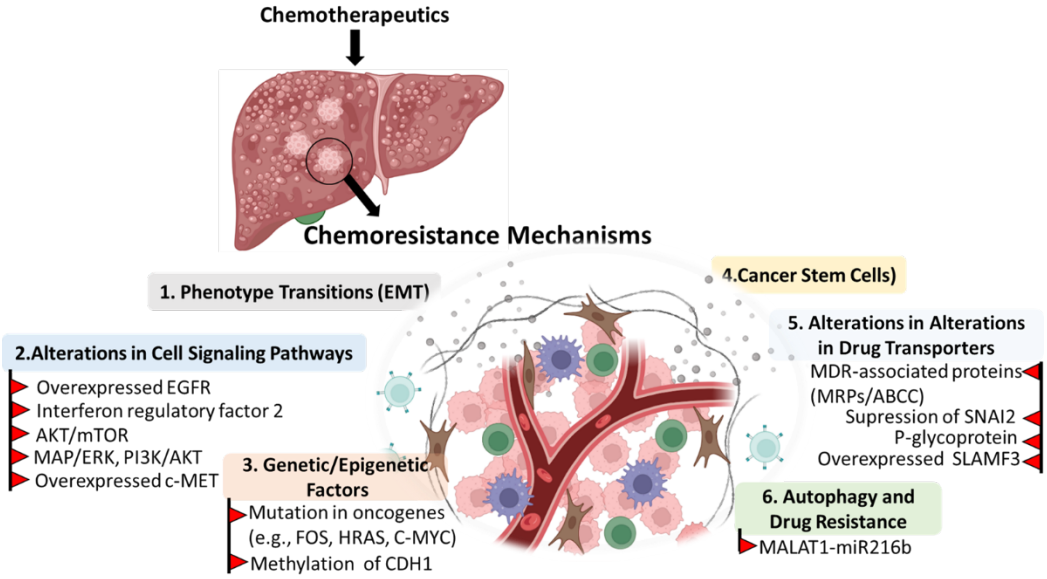
Introduction

HCC is the highly pervasive form of liver cancer, categorized as sixth most common cancer and third major contributor of cancer-related mortalities worldwide (Toh et al., 2023; Koshy, 2024). Due to insufficient healthcare facilities particularly in developing countries HCC incidence is increasing steadily (Singal et al., 2023). HCC prognosis and treatment depend on early detection, liver health, and overall condition of patient. Surgical removal, liver transplant, and ablative methods are curative treatments for early-stage disease, while palliative care is required for advanced stage disease (Dhamija et al., 2019; Rios et al., 2021). Alcoholic liver cirrhosis, NASH, NAFLD, chronic inflammation, and exposure to carcinogens are key risk factors of HCC (Abdelhamed & El-Kassas, 2024). In the beginning chemotherapy showed significant efficacy that declined over time due to high heterogeneity of tumor and development of chemotherapeutic resistance (Ladd et al., 2023; Lei et al., 2024; Marin et al., 2020). Multikinase inhibitors; sorafenib, lenvatinib, cabozantinib, and regorafenib were approved as systemic chemotherapies for advanced HCC since 2007 to 2016 (Teufel et al., 2019; Marin et al., 2020). Although innate drug resistance and development of multidrug resistance (MDR) complicate disease treatment. Despite identification of various resistance-associated genes the exact cause of chemoresistance in HCC still remains elusive (Gao et al., 2018; Lei et al., 2024). This review carried out literature that specifically focused on mechanisms underlying chemoresistance in HCC.

Overview of Chemoresistance in HCC

The ability of tumor cells to grow uncontrollably by evading effects of chemotherapy, either through innate (pre-existing) or acquired (treatment-induced) resistance is known as chemoresistance. Reduced drug influx, MDR, drug inactivation and detoxification by cellular

thiols, inhibition of pro-apoptotic pathways, multiple epigenetic variations, and upregulated DNA- repair mechanisms are various key factors that play a predominant role in resistance (Al - Abdulla et al., 2018; Ladd et al., 2023; Musa et al., 2024). Due to cumulative effects of various molecular and pharmacological factors, it is very challenging to manage chemoresistance in heterogeneous tumors (Marin et al., 2020). To re-sensitize resistant cancerous cells against therapies, it is crucial to identify particular interactions leading to cancer relapse and chemoresistance.



Graphical Representation of Molecular Mechanisms Associated with Chemoresistance in HCC

Molecular Mechanisms of Chemoresistance in HCC

Alterations in Drug Transporters: ABC transporters

The Among 48 ATP-binding transporters present in human genome, ABCB1/MDR1 and BCRP/ABCG2 are essential transmembrane proteins that help tumor cells to develop multidrug resistance (Huang et al., 2013). Downregulation of SNAI2 enable HCC cells to enhance ABCB1 and ABCG2 transcription, leading to MDR development that highlights the involvement of ABCG2 and P-glycoprotein in chemoresistance (Zhao et al., 2016). Diminished expression of MRP1 and MRP2 in Huh-7 cells by overexpressing SLAMF3 (tumor suppressor receptor in HCC) that signifies indispensable role of MDR-associated proteins (MRPs/ABCC) in chemoresistance (Fouquet et al., 2016). Further research is needed to identify additional ABC transporters linked to MDR in malignancies, potentially leading to innovative strategies to enhance effectiveness of chemotherapies for HCC treatment.

Genetic Mutations and Epigenetic Changes

Anticancer therapies work by inducing apoptosis in tumor cells. The significant regulators of apoptosis p53 protein & Bcl-2 family are intricately associated with resistance. Though disruption of these apoptotic signals and cell cycle checkpoints induces MDR in HCC (Zhang et al., 2012). As a result of DNA damage, p53 being a tumor suppressor gene modulates apoptosis and inhibits MDR in HepG2 cells by upregulating Bax and downregulating Bcl-2. PI3K/Akt/MDM2 activation by NgBR promotes p53 degradation and consequently inhibition of apoptosis occurs due to mutations in p53, leading to chemoresistance in HCC (Dong et al., 2016). Dysregulation of tumor cell signaling caused by continuous drug treatment results in anti-apoptotic properties and chemoresistance. Furthermore, impaired microRNAs functioning cause alteration in expression of p53 and oncogenes (FOS, HRAS, C-MYC) contributing to this resistance (Tan et al., 2022). Tumorigenesis is promoted by DNA methylation of promoters of tumor suppressor genes. These epigenetic changes are influenced by external factors. Downregulation of ADAMTSL5 can increase drug uptake and effectiveness (Arechederra et al., 2020). Epigenetic modifications such as methylation status of CDH1 promoter may serve as a marker for MDR. Overexpression of CDH1 by downregulating P-gp improves drug influx, emphasizing that by addressing epigenetic variations we may overcome MDR in HCC (Jiang et al., 2012).

Alterations in Cell Signaling Pathways

The sensitivity of chemotherapeutic drugs is related to multiple tumor-associated proteins and signaling pathways. Wnt/β-catenin, EGFR, c-MET, IGF, PI3K/AKT/mTOR, VEGFR, and PDGFR are key pathways existing in literature that contribute to HCC pathogenesis and ultimately their dysregulation results in angiogenesis, stemness and pro-apoptotic pathway inhibition (El-Khoueiry et al., 2018). IGF2 regulates the expression of β-catenin in HCC promoting tumor proliferation and consequently induces resistance to first-line agents such as sorafenib and lenvatinib (Choi et al., 2022). The activated HGF/c-MET pathway further initiates PI3K/AKT and MAP/ERK signaling promoting epithelial-mesenchymal transition (EMT) (Gao et al., 2021). Overexpressed c-MET decreases the effects of lenvatinib while c-MET inhibition counters lenvatinib resistance by enhancing apoptosis and inhibiting tumor invasion (Sun et al., 2021). Targeted therapies depending on these molecular subtypes could help to overcome drug resistance in HCC [Figure 1].

Autophagy and Drug Resistance

Autophagy plays a dual-role in tumor cells, serving not only as a tumor-suppressor but also as a crucial mechanism for drug resistance. Basal autophagy in normal cells maintains stability of genome while activated autophagy enables cancer cells to

endure stress, facilitating tumor progression (Wang et al., 2017). Inhibiting autophagy can enhance sensitivity of HCC cells to chemotherapy. Studies indicate the reduction in IC_{50} of 5-FU, ADM, and mitomycin C in BEL-7402/5-FU cells by altering MALAT1-specific siRNA and miR-216b, suggesting that MALAT1-miR216b axis modulates autophagy to influence MDR in HCC (Yuan et al., 2016). Role of autophagy in tumor metastasis and treatment effectiveness is still debated, necessitating further research to understand its impact on chemotherapy sensitivity in HCC cells.

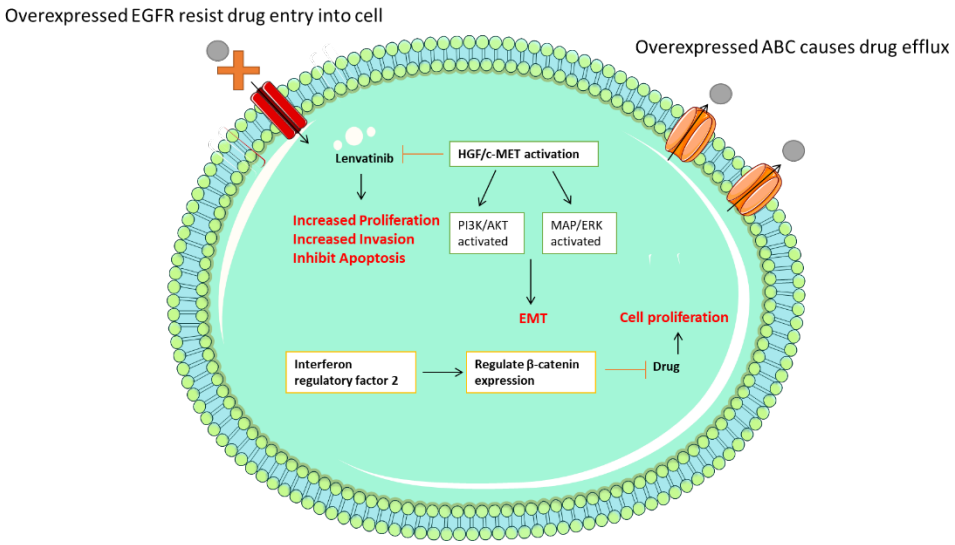


Figure 1: Alterations in key molecular signaling pathways; Overexpressed drug transporters leading to drug efflux and resistance to drug entry. Activated HGF/cMET pathway leads to further activation of P13K/AKT leading to EMT by increasing proliferation along with MAP/ERK pathways. Furthermore, up-regulated IGF2 effects β-catenin resulting in increased drug inhibition and cell proliferation.

Cancer Stem Cells in Chemoresistance

Dormancy during treatment and intrinsic drug resistance of cancer stem cells (CSCs) makes them resilient to multiple targeted agents and chemotherapies (Liang et al., 2020). Previous research suggested that RAB3B with facilitation of enhanced exosome secretions and correlative effect of ABCG2, APOE, and TSPAN13 enable tumor cells to exhibit stem cell-like characteristics, chemoresistance and metastatic capability in HCC (Tsunedomi et al., 2022). Nanog enhances CSCs characteristics and ultimately resulting in resistance to regorafenib and cisplatin. Studies indicate that silencing of Nanog in HepG2 cells via siRNA in conjunction with chemotherapy leads to downregulation of genes associated to stem cells and enhanced apoptosis, implying that stemness may play a functional role in drug resistance (Alemohammad et al., 2022).

Impact of Tumor Microenvironment in Chemoresistance

Microenvironment around tumor is composed of complex cellular facilitates tumor metastasis. TME influences tumor progression and drug resistance by impeding drug delivery to stromal tissues surrounding tumor cells in HCC (Bilotta et al., 2022). Moreover hypoxia, ROS, inflammation, and acidification constrained the efficacy of chemotherapy (Cheng et al., 2024). Resistance to sorafenib is linked to hypoxia-inducible factors (HIFs), and since HCC is significantly hypoxic, it relies on these factors. Activated HIF-1 results in overexpression of ABC proteins, which protect against drug-induced apoptosis and enhance survival through autophagy (Kim et al., 2022). Liver fibrosis is driven by hepatic stellate cells (HSCs) and fibroblasts associated to tumor that secrete tumor growth factors and metastasis promoting cytokines (Tian, 2012). Laminin-332 secreted by HSCs reduces sorafenib-induced apoptosis through interacting tumor cells and restraining the ubiquitination of focal adhesion kinase (FAK) (Scialpi et al., 2023). Lysophosphatidic acid (LPA) is implicated in liver fibrosis and HCC; with elevated expression of collagen 1A1 in HSCs, it contributes to sorafenib resistance (Sokolov et al., 2012).

Phenotype Transitions: EMT overview

EMT is characterized by the loss of differentiation and polarity in epithelial cells, resulting in the acquisition of mesenchymal traits that are enhanced metastasis, invasiveness, migration, and apoptotic resistance. This multistep process is typically associated with tendency of cancer cells to increase aggressiveness and drug resistance (Shibue & Weinberg, 2017). Phosphorylation of YB-1 through EGFR/PI3K/AKT/mTOR pathway promotes EMT resulting in sorafenib resistance which indicates an intricate correlation between genes related to chemoresistance and EMT (Lv et al., 2020; Liao et al., 2020). This highlights the interlinking poorer disease prognosis and treatment inefficacy in HCC.

Inflammation-associated Pro-survival Pathways Contributing to Chemoresistance

Chronic inflammation promotes tumor survival and proliferation in advanced stage diseases. Intrinsic activation pro-survival pathways enable malignant cells in HCC to evade apoptosis and initiation of inflammation associated signaling pathways which further complicates therapeutic effect of anticancer drugs (Qu et al., 2014; Fang et al., 2012). Downregulation of SOCS2 initiates STAT3 activation, a driver of chemoresistance (Lai et al., 2019). Restoration of SOCS2 expression in HCC could help overcome inflammation (Ashfaq et al., 2022). Moreover, it is suggested that overexpression of SOCS2 in HepG2 cells results in constraint STAT3 activation and ultimately reduction in expression of pro-inflammatory cytokines. Therefore, effective impairing of proliferative and

migratory potential of HCC cells contributes to suppress tumor progression (Ahmad et al., 2025). Mutant PTEN along with SNAI1 halt sorafenib-induced apoptosis through hyperactivated PI3K/AKT pathway and promotes resistance to chemotherapy (Li et al., 2018).

Table 1: Summary of the studies included in current review.

Mechanism of chemoresistance	Sample used in studies	References
Alterations in Drug Transporters: ABC transporters	Hep3B and HepG2 HCC cell lines	(Huang et al., 2013)
	15 pairs peritumoral (pT) samples of HCC patients undergoing surgical resection & Huh-7 and HepG2 cell lines	(Fouquet et al., 2016)
	HL-7702 (human immortal hepatic cells) and HCC cell line MHCCLM3	(Zhao et al., 2016)
Genetic Mutations and Epigenetic Changes	HepG2, R-HepG2 (doxorubicin-induced MDR sub-lineage cell line)	(Jiang et al., 2012)
	HCC tissue microarray comprising 89 primary HCC samples with their corresponded surrounding liver tissues along with Human HCC cell lines Bel7402 and 5-fluorouracil-selected drug-resistant Bel7402/5FU	(Dong et al., 2016)
	The study categorized 74 HCC patients into three groups: 41 untreated individuals, 28 who underwent nivolumab therapy, and 5 who received pembrolizumab	(Tan et al., 2022)
	43 R26stopMet mice "(international nomenclature Gt(ROSA)26Sortm1(Actb-Met)Fmai)" with HCC and having a conditional mouse-human chimeric Met transgene into the Rosa26 locus	(Arechederra et al., 2020)
Alterations in Cell Signaling Pathways	Individuals aged 18 years and older having metastatic and unresectable HCC	(El-Khoueiry et al., 2018)
	376 eligible patients treated with sorafenib or lenvatinib between Jan 2018 to April 2020	(Choi et al., 2022)
	HEK-293T, SNU398, HT1080 cell lines	(R. Gao et al., 2021)
	151 individuals underwent curative liver resection at Zhongshan Hospital from January 2009 to January 2010, with an additional cohort of 199 HCC patients, of which 136 were in the control group that did not undergo adjuvant therapy of sorafenib from January 2009 to January 2013	(Sun et al., 2021)
Autophagy and Drug Resistance	BEL-7402 along with its multidrug-resistant sub-line BEL-7402/5-fluorouracil	(Yuan et al., 2016)
Cancer Stem Cells	SK-HEP-1 and HuH-7 cell lines	(Tsunedomi et al., 2022)
	HepG2 cell line	(Alemohammad et al., 2022)
Impact of Tumor Microenvironment	Patients who underwent curative surgical resection and performed ^{18}F-FDG scans for preoperative staging, along with HepG2, SK-Hep1, and Huh7 cell lines	(Kim et al., 2022)
	H22 hepatoma cells lines & Male KM mice having 6-12 week age and 18-22g weight	(Tian, 2012)
	HLE and HLF cell lines	(Scialpi et al., 2023)
	Paraffin-embedded samples were obtained from 22 patients undergoing hepatic resection for HCC, & HepG2 and HuH-7 cell lines	(Sokolov et al., 2012)
Phenotype Transitions	50 paired fresh HCC tissues were acquired from patients who underwent tumor resection at "First Affiliated Hospital of Zhengzhou University (Zhengzhou, China)" between May 2016 and November 2018. HepG2 and Huh7 cell lines were also used	(Lv et al., 2020)
	HEK293T, sorafenib-resistant HCC cell lines: HuH-7R, Hep3BR, PLC-5R, and Sk-Hep-1R were used along with non-resistant HCC cell lines: Sk-Hep-1, HuH-7, Hep3B, PLC-5	(Liao et al., 2020)
Pro-survival Pathways Contributing to Chemoresistance	HCC cell lines: Huh-7, PLC5, Sk-Hep1 , and Hep3B were used	(Chen et al., 2010)
	HepG2 cell line	(Qu et al., 2014)
	HCC cell line, QGY-7703 , Male athymic nude mice	(Fang et al., 2012)
	MHCC-97H, HepG2, Huh7, Hep-3B, SMMC-7721), LO2 immortalized human liver cell line and activated LX2 HSCs	(Li et al., 2018)
	Huh7 and Huh7R	(Ma et al., 2021)

To enhance sorafenib sensitivity in HCC, this pathway targeting may act as promising strategy to overcome chemoresistance. Hyperactivation of JAK/STAT3 and MAPK/ERK pathway due to overexpression of FGF19 & JAK1 accelerates tumor progression and resistance to sorafenib- induced apoptosis (Ma et al., 2021). Additionally, resensitization of TRAIL-induced apoptosis-resistant HCC cells through inhibiting STAT3 by sorafenib, further signifies function of dysregulated JAK/STAT pathway in chemoresistance (Chen et al., 2010). Due to the multifactorial nature of MDR in HCC, investigation of alternative mechanisms by which cancer cells can evade treatment is crucial rather than targeting of a single pathway.

Biomarkers of Chemoresistance in HCC

circRNAs are dysregulated in various cancers and significantly contribute to tumor development, as well as modulating tumor sensitivity to chemotherapy. Exosomes, rich in circRNAs, facilitate intercellular communication by utilizing a distinct mechanism for sorting RNA cargo. These exosomes transport circRNAs that increase the outflow of chemotherapeutic agents, leading to reduced intracellular drug concentrations in recipient cells, which alters pivotal cellular mechanisms, including cell cycle progression, angiogenesis, apoptosis, invasion, autophagy, and migration (Liu et al., 2021). Key regulators of gene expression, miRNAs can act as tumor suppressors or as oncogenes by silencing mRNAs associated to carcinogenesis. Occasionally, changes in gene expression are involved in carcinogenesis, invasion, and metastasis. miR-199a-3p is down-regulated in HCC and targets CD44+ HCC cells (Q. Li et al., 2024). The observed downregulation leads to diminished invasive capacity and increased sensitivity to doxorubicin treatment. Likewise, miR-221, recognized as an oncogenic miRNA involved in the pathogenesis of HCC, has been shown to reduce in vitro proliferation by arresting cell cycle and elevating apoptotic markers in orthotopic HCC models (Fan et al., 2020). miR-221 regulates CD44 via the PI3K/AKT/mTOR signaling pathway, which is intricately linked to augmented tumor metastasis, invasiveness, and therapeutic resistance (Fan et al., 2020; Lei et al., 2024). Advancements in machine learning and cutting-edge technologies, including immunosensors, multimolecular analytical systems, circRNA-based platforms, and exosome-derived vaccines, are revolutionizing precision cancer therapy (Ladd et al., 2023; Cheng et al., 2024). These innovations offer new avenues for personalized and targeted treatment strategies, improving drug efficacy while reducing adverse effects.

Current Strategies to Overcome Chemoresistance in HCC

Reversal of MDR in HCC is crucial for improving chemotherapy effectiveness. Commercially available chemotherapies comprising of a single anticancer agent have limited efficacy for HCC, emphasizing to utilization of combination therapies that target distinct molecular pathways. In the recent years to overcome MDR in HCC, plant-based natural products in combination with chemotherapeutic agents are being used with minimal side effects and significant anti-cancer activity (Wang et al., 2023). Now a days, immunotherapies particularly ICIs have been used for their tendency to eliminate cancer cells by interacting immune system. Anti-PD-L1 antibody (atezolizumab) in conjunction with anti-VEGF antibody (bevacizumab) improved survival rates in HCC patients compared to sorafenib monotherapy (Daud et al., 2016; Vogel & Saborowski, 2019). Despite advancements in immunotherapies, targeted therapies remain a significant treatment approach for HCC by targeting various molecular signaling pathways activated in tumor growth and angiogenesis. Sorafenib-induced inhibition of KIT, VEGFR, PDGFR, RAF, MEK, ERK pathways along with blockage of 1-3 VEGF, 1-4 FGF, and α-PDGF receptors by lenvatinib contributes to suppression of tumor proliferation and angiogenesis (Panneerselvam et al., 2023). Similarly multi-kinase inhibitor, regorafenib targets VEGFR 1- 3, TIE 2 angiogenesis receptors, PDGFR-β, FGFR stromal receptors, and KIT, RET, RAF oncogenic receptor tyrosine kinases. Regorafenib shares structural similarities with sorafenib but demonstrates enhanced and broader activity against VEGFR kinases, providing a potential alternative following resistance to other therapies (Lei et al., 2024). Although combination therapies offer significant clinical benefits, they also introduce potential adverse effects. Further research is needed to optimize combination strategies to overcome MDR in HCC by reducing side effects.

Conclusion and Future Perspectives

This review highlights the extensive knowledge gained from ongoing research in liver cancer pharmacology. Thorough comprehension of complex and dynamic processes of chemoresistance is critical for developing highly selective and sensitive novel biomarkers, which enable early prediction of treatment failure before administering drugs to patients with HCC. Identifying vulnerabilities in HCC's defenses against existing therapies is equally important for advancing strategies to sensitize tumor cells to restorative treatments. The most effective approaches to overcoming resistance to therapy include: (i) development of advanced immunotherapeutic agents that specifically target HCC cells while sparing normal hepatic cells, (ii) development of the next generation TKIs having enhanced pharmacokinetics and reduced cytotoxicity, and (iii) Strategic application of sensitization tools utilizing pharmacological and molecular approaches. These innovations are expected to pave the way for novel curative options to enhance outcomes in advanced HCC significantly over the next decade. Additionally, future research may investigate the involvement of miRNAs and the influence of the tumor microenvironment on the effectiveness of immunotherapies, offering new avenues for optimizing treatment. By focusing on these areas, this study provides hope for improved and personalized therapies.

Abbreviations

AKT/mTOR, Ak strain transforming/mammalian target of rapamycin; anti-PD-L1, Anti-programmed death-1-ligand-1; ABCG2, ATP binding cassette subfamily G member 2; ADAMTSL5, A disintegrin and metalloproteinase with thrombospondin motifs like-5; CDH1, Cadherin 1; c-MET, Mesenchymal-epithelial transition factor; CTNNB1, β-catenin; ERK, Extracellular signal-regulated kinase; FAK, Focal adhesion kinase ; 5-Fu, 5-fluorouracil; JAK/ STAT3, Janus kinase-signal transducer and activator of transcription 3; MALAT1, Metastasis-associated lung adenocarcinoma transcript 1; MAP, mitogen-activated protein; MEK, Mitogen-activated protein kinase; NgBR, Nogo-B receptor; PI3K, Phosphatidylinositol-3-kinase; SLAMF3, Signaling lymphocyte activation molecule family member 3; SNAI2, Snail family transcriptional repressor 2;TP53, Tumor Protein p53; TKI,

Tyrosine kinase inhibitor; Wnt/β-catenin, Wingless-related integration site/ beta catenin; YB-1, Y-box binding protein-1

Author contributions

Conceptualization & Supervision: AT; Methodology and review structure: IA; Writing – original draft: SJ, IA, MS; Writing – review & editing: SJ, IA; Revision of manuscript: SJ, MS; Visualization (figures and tables): IA, MS, SJ. All authors have read and approved the final manuscript.

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