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REVIEW

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Mechanisms of drug resistance in hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer, associated with high morbidity and mortality worldwide. Despite advancements in diagnostic methods and systemic treatments, including tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), the development of drug resistance remains a significant challenge in HCC management. Traditional treatments such as surgical resection and transarterial chemoembolization offer limited efficacy, especially in advanced stages. Although novel therapies like lenvatinib, sorafenib, regorafenib, and ICIs have shown promise, their effectiveness is often hindered by primary and acquired resistance, leading to poor long-term survival outcomes. This review focuses on the molecular mechanisms underlying resistance to targeted therapies and immunotherapies in HCC. Key factors contributing to resistance include alterations in the tumor microenvironment (TME), immune evasion, hypoxia, changes in cellular metabolism, and genetic mutations. Additionally, molecular players such as ferroptosis, autophagy, apoptosis, endoplasmic reticulum stress, ABC transporters, and non-coding RNAs(ncRNAs) are discussed as contributors to drug resistance. Understanding these mechanisms is critical for the development of novel therapeutic strategies aimed at overcoming resistance, improving patient outcomes, and ultimately enhancing survival rates in HCC patients.

Keywords Hepatocellular carcinoma, Drug resistance, Targeted therapy, Immune checkpoint inhibitors, Tumor microenvironment

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. ranking as the sixth most prevalent cancer worldwide and the fourth leading cause of cancer-related deaths [1]. According to 2023 data from the American Cancer Society, the incidence of liver cancer (including intrahepatic bile duct cancer) in the United States exhibits marked sex- and age-specific disparities, with an estimated 41,210 new cases projected for 2023. Globally, persistent disparities are particularly pronounced in regions endemic for viral hepatitis. In East Asia, hepatitis B virus (HBV) infection remains the leading driver of hepatocellular carcinoma (HCC), while sub-Saharan Africa faces the dual burden of HBV and hepatitis C virus (HCV) infections. Epidemiological analyses indicate that 75% of the global liver

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cancer burden can be attributed to modifiable risk factors: chronic HBV/HCV infections (54%), alcohol abuse (18%), and metabolic syndrome-associated obesity (13%) [2, 3]. Despite advancements in diagnostic technologies, HCC is often diagnosed at an advanced stage, severely limiting the effectiveness of curative treatments such as surgical resection and liver transplantation [4]. Even when detected early, the recurrence rate post-surgery remains high, contributing to poor long-term survival outcomes. While traditional locoregional therapies such as transarterial chemoembolization (TACE) provide palliative benefits, they lack curative potential [5]. Compounding these limitations, conventional chemotherapy and radiotherapy demonstrate limited efficacy in HCC management and are often contraindicated in cirrhotic patients [6].

Recent advancements in systemic treatment of HCC have introduced targeted therapies and immunotherapies, providing new hope for patients with advanced disease [7]. TKIs such as sorafenib and lenvatinib have become standard first-line treatments [8, 9]. Several clinical studies have evaluated other systemic treatments and found that a small number of drugs showed survival benefits in Phase III clinical trials, including second-line drugs like regorafenib, cabozantinib, and ramucirumab [10–12]. However, their effectiveness often extends survival by only a few months, as they are limited by the development of drug resistance and adverse effects [13, 14].

The emergence of ICIs has revolutionized the treatment of HCC, with ICIs gradually becoming the cornerstone of systemic therapy for advanced HCC [15, 16]. For instance, the combination of atezolizumab (an anti-PD-L1 antibody) and bevacizumab (an anti-VEGFA antibody) provided a better prognosis for patients with advanced HCC compared to the targeted drug sorafenib [17]. Additionally, the combination of the anti-PD-1 antibody sintilimab and the biosimilar bevacizumab (IBI 305) has shown improved overall survival (OS) in Chinese patients with advanced HBV-related HCC compared to sorafenib [18]. Despite these recent advances in immunotherapy, only 15–20% of HCC patients respond to ICI therapy, achieving an objective response and extending survival. HCC remains a highly lethal disease due to the development of acquired drug resistance and the resulting increase in morbidity and mortality.

The intricate molecular pathogenesis of HCC frequently contributes to drug resistance, posing a significant challenge for therapeutic interventions [19]. For example, in a Phase III non-inferiority trial comparing lenvatinib and sorafenib as first-line treatments for unresectable HCC, the objective response rate was 24% for lenvatinib, with sorafenib showing a lower response rate [9]. A randomized, placebo-controlled, Phase III clinical trial assessing the efficacy of regorafenib in advanced HCC patients who progressed on sorafenib treatment reported an objective response rate of 11% [10]. These findings underscore the critical need to delay and mitigate the development of resistance, which remains a focal point for future therapeutic strategies [20]. Numerous clinical trials investigating combination therapies are seeking to address the challenge of overcoming drug resistance; however, the underlying molecular mechanisms driving primary resistance remain to be fully elucidated.

This review aims to elucidate the various mechanisms underlying resistance to targeted therapies and acquired immunotherapies, providing valuable insights that will guide the development of novel therapeutic strategies to improve patient outcomes.

Targeted therapy resistance mechanisms

During targeted therapy, overcoming drug resistance remains a significant challenge, with genetic heterogeneity within tumors and the existence of drug-resistant clones being key underlying mechanisms [21, 22]. While daughter cancer cells are cleared during treatment, cancer stem cells (CSCs) often survive due to their enhanced ability to withstand stressors such as DNA damage. CSCs mediate tumor growth by generating new daughter cancer cells, which eventually produce resistant clones that promote tumor progression and recurrence [23].Targeted therapy has made substantial progress in recent years by selectively targeting key signaling pathways in tumor cells, which reduces damage to normal cells, offering better safety and specificity [24] (Table 1).Although Sorafenib, the first multi-target tyrosine kinase inhibitor (TKI) for advanced HCC, extends median overall survival from 8 to 11 months [25], its clinical utility is substantially constrained by rapid development of resistance. Key mechanisms include acquired genetic mutations (e.g., EGFR amplification) and compensatory activation of bypass signaling pathways (e.g., PI3 K/AKT and Wnt/β-catenin), which collectively sustain tumor cell survival under therapeutic pressure. Notably, hepatic CSCs are enriched after long-term sorafenib exposure, contributing to resistance by maintaining stemness and enabling tumor recurrence. Recent studies suggest that inhibiting these CSCs or targeting CSC-specific pathways could enhance the sensitivity of HCC to sorafenib, potentially overcoming this resistance [26]. Despite showing efficacy in clinical trials, sorafenib's survival extension is limited to only a few months, prompting the exploration of alternative therapies such as lenvatinib. Lenvatinib, a multi-target TKI, has

Table 1 Targeted therapy drug resistance pathways

Targeted Therapy Drug Resistance Pathways			
Drug Name	**Major Effect**	**Target**	**Refs**
Lenvatinib	**Angiogenic pathway activation**	VEGF/VEGFR2 (Promotes tumor angiogenesis, activates downstream RAS/MEK/ERK signaling) ETS-1(Transcription factor enhancing VEGFR2 expression)	[28, 32–34]
	EMT	c-Met(Activation of HGF/c-Met pathway promotes EMT and drug resistance) CD73 (Induces EMT via AKT phosphorylation, enhances cancer stem cell traits)	[35, 36]
	Dysregulation of HGF/c-Met pathway	c-Met (Activates PI3 K/AKT and MAPK/ERK pathways, bypassing VEGFR inhibition)	[37]
	Hypoxic microenvironment	HIF-1α/HIF-2α (Induces VEGF expression, promotes angiogenesis and EMT)	[38, 39]
	Compensatory signaling pathway activation	MAPK/ERK, PI3 K/AKT (Cross-activation of pathways bypassing drug target inhibition)	[29, 40]
	Immune evasion & microenvironmental regulation	CD73 (Inhibits immune response, promotes AKT signaling and EMT)	[41]
Sorafenib	**Epigenetic Regulation**	Maintains stemness and resistance via Hippo signaling inhibition (DNA methylation) Alters DNA methylome and gene expression in response to sorafenib	[42–44]
	Drug Transport and Efflux	Reduces intracellular sorafenib via upregulated ABC transporters (MRP1, MRP2)	[45, 46]
	Dysregulated Cell Death Pathways	Switches autophagy from protective to pro-death mechanism via Akt inhibition Inhibits ferroptosis and promotes survival via MT-1G-mediated redox balance	[47–49]
	TME Impact	Induces HIF-1α and HIF-2α activation to promote angiogenesis and metabolic adaptation Recruits immunosuppressive cells (TAMs, TANs) to inhibit antitumor immunity	[50–52]
	stemness and tumorigenicity	Enhances stemness and tumorigenicity via Wnt/β-catenin signaling activation	[53]
Regorafenib	**CSC Signaling**	Short-term drug exposure activates Wnt signaling, leading to nuclear enrichment of β-catenin and induction of hepatic stem/progenitor markers	[54]
	Stemness Maintenance	Overexpressed RhoA activates the Hippo pathway, inhibiting Kibra/NF2 complex formation and promoting nuclear translocation of YAP and CD44 expression	[55]
	EMT-Mediated Signaling	Long-term resistant cells exhibit activated TGF-β signaling, increased SMAD phosphorylation, and upregulation of mesenchymal genes (Vimentin, SNAI1) and stem cell markers (CD24, CD133)	[54]
	RTK-RAS-MAPK Canonical Pathway	Overexpressed EGFR activates downstream RAS/RAF/ERK signaling, bypassing drug-targeted kinase inhibition to sustain proliferation	[56]

been approved as a first-line treatment for unresectable HCC [27]. In a randomized Phase 3 non-inferiority trial, lenvatinib demonstrated non-inferiority to sorafenib in terms of overall survival, with median survival times of 13.6 months for lenvatinib and 12.3 months for sorafenib [28].Though resistance to lenvatinib can develop, studies suggest that combining lenvatinib with other treatments, such as immunotherapy, could delay resistance onset [29]. Lenvatinib's broader targeting of VEGF and FGF signaling pathways compared to sorafenib may also help reduce resistance caused by compensatory activation of alternative pathways, making it a viable alternative to sorafenib as a first-line treatment [28]. Resistance mechanisms to sorafenib include epithelial-mesenchymal transition (EMT), cancer stem cell properties, and changes in the TME. Studies have shown that in sorafenib-resistant HCC organoids, stemness-related and EMT-related

gene sets are significantly upregulated, further exacerbating tumor aggressiveness and drug resistance [30]. For example, genes related to CSCs like Myc and EGFR, as well as EMT-related genes like TGFβ1 and E2 F, are significantly enriched in sorafenib-resistant HCC organoids [31]. Additionally, the upregulation of the mTOR signaling pathway is closely related to sorafenib resistance, indicating the importance of these pathways in regulating HCC cell growth and survival.

The signaling cascade of epidermal growth factor receptor (EGFR), VEGF receptor, Wnt/β-catenin, insulin-like growth factor (IGF) and platelet-derived growth factor receptor (PDGFR) are critical drivers in the development and progression of HCC [57]. Sorafenib and lenvatinib, both multi-target TKIs, inhibit EGFR, VEGF receptors, and PDGFR, among others. Existing or acquired genetic variants in these signaling pathways can lead to resistance to molecular therapies targeting these pathways.

EGFR is a transmembrane receptor involved in cell proliferation, differentiation, and survival. EGFR overexpression is associated with liver cirrhosis and HCC recurrence [13]. A study of six human HCC cell lines revealed that activated EGFR promotes sorafenib resistance in HCC cells. The efficacy of sorafenib was enhanced when EGFR was inhibited using two chemical inhibitors (erlotinib or gefitinib), a monoclonal antibody (cetuximab), and RNA interference against EGFR [58]. FGFR signaling is involved in liver embryogenesis and plays a key role in wound healing and angiogenesis in adults [59]. In HCC, up to 8% of patientsexhibit high levels of DNA amplification at the FGF19/FGF4 locus. Previous studies have shown that mesenchymal-epithelial transition factor (MET) and FGFR activation contribute to resistance to EGFR inhibition, while MET and ERBB2 receptor tyrosine kinase (ERBB2/3) activation confer resistance to FGFR inhibition [60]. In a Phase 1 clinical study of BLU-554 (fisogatinib), a potent, selective, and irreversible FGFR4 inhibitor, initial results showed its efficacy as a second-line treatment for patients with FGF19 overexpression in HCC, with an overall response rate (ORR) of 17% [61]. Subsequent studies demonstrated that EGFR activation is a key factor in resistance to FGFR4 inhibition.

The Wnt/β-catenin pathway is a critical driver in liver development and can be abnormally activated in various ways. The most common mutations in HCC are β-catenin (CTNNB1) mutations in about 30% of cases, and AXIN1/2 mutations in 5–10% of cases [62]. This pathway is also regulated by mesenchymal epithelial transformation factor (c-MET) [63, 64]. Abnormal activation of c-MET, a receptor for hepatocyte growth factor (HGF), promotes HCC initiation and metastasis, playing a key role in therapeutic resistance [65].

Chemotherapy Resistance in Hepatocellular Carcinoma Treatment

Chemotherapy is widely used in the treatment of HCC, but its effectiveness is often significantly limited by multidrug resistance (MDR) (Table 2).HCC cells generally exhibit intrinsic or acquired resistance to chemotherapy drugs, primarily due to the overexpression of drug efflux pumps, EMT, activation of hypoxia-inducible factor 1-alpha (HIF1-α), and enhanced DNA damage repair mechanisms [66, 67]. These resistance mechanisms undermine the efficacy of chemotherapy drugs, often leading to recurrence after treatment and posing substantial challenges for clinical therapy.In recent years, significant advancements have been made in drug delivery systems targeting CSCs. Research summarized by Duan et al. highlights the potential of specifically targeting CSCs to improve therapeutic outcomes. CSCs are considered key factors in tumor invasion, metastasis, drug resistance, and recurrence after treatment [68]. These drug delivery systems, particularly those targeting CSC niches and specific signaling pathways, represent a promising strategy to overcome the limitations of conventional treatments.Traditional chemotherapy drugs often fail to completely eliminate CSCs within tumors, and these CSCs can drive tumor recurrence and the development of resistance through self-renewal and differentiation. Targeting CSCs not only improves treatment efficacy but also enhances long-term survival rates [23].

For instance, common chemotherapy agents like 5-fluorouracil (5-FU) and cisplatin often lead to resistance through the mechanisms described above [77, 86]. Studies have shown that HCC cells develop resistance to 5-FU by activating the PI3 K/PDK1/ROCK1 and ERK signaling pathways [87]. This resistance involves not only the activation of drug efflux pumps but also alterations in intracellular signaling pathways, further enhancing the tumor cells'resistance to treatment. Similarly, the efficacy of doxorubicin (ADM) is limited.Although increasing the dose may provide some short-term therapeutic benefit, it does not significantly improve long-term outcomes and instead increases the risk of severe side effects, such as cardiotoxicity and immune suppression [24].

Tumor Microenvironment and Immune Resistance Mechanisms

Immunotherapy has achieved significant progress in HCC treatment by activating the patient's immune system to attack tumor cells. ICIs are another major advancement in liver cancer treatment, with PD-1/PD-L1 inhibitors showing good efficacy in some patients.

Table 2 Chemotherapy drug resistance pathways

Chemotherapy Drug Resistance Pathways			
Drug Name	**Major Effect**	**Target**	**Refs**
5-Fluorouracil (5-FU)	**Signaling Pathway Activation**	a.High Nrf2 expression activates the HIF-1α/HSP70 signaling pathway, enhancing antioxidant stress response and cell survival to mediate 5-FU resistance b.Activation of the PI3 K/AKT/GSK-3β pathway upregulates glycolytic enzymes (HK2, PFK1, PKM2), increases glucose uptake and lactate production, thereby leading to drug resistance	[69, 70]
	Cell Cycle Regulation	High CDK1 expression promotes cell cycle progression and enhances 5-FU resistance	[71]
	Protein Modification & Stability	USP39 stabilizes SMC4 protein via deubiquitination, promoting tumor cell proliferation and 5-FU resistance	[72]
	Transcription Factor & Nuclear Translocation Regulation	UBE2 N inhibits p53 nuclear translocation, leading to decreased p53 transcriptional activity and increased expression of anti-apoptotic genes, promoting resistance	[73]
Doxorubicin	**Signaling Pathway Activation**	Activating the Notch1/Hes1 signaling pathway, downregulating PTEN expression, and promoting Akt phosphorylation, thereby enhancing Doxorubicin resistance in HCC cells	[74]
	EMT	EMT activation (E-cadherin↓/Vimentin↑) drives Doxorubicin resistance in HCC cells	[75]
	Post-Transcriptional Regulation (mRNA Stability)	AUF1 binds to the 3′-UTR region of alpha-fetoprotein (AFP) mRNA, enhancing its stability and upregulating AFP expression, which promotes HCC cell proliferation and induces Doxorubicin resistance	[76]
Cisplatin	**Reduced drug influx and increased efflux**	a.Downregulated copper transporter CTR1 reduces cisplatin uptake b.Upregulated efflux transporters (ATP7 A, ATP7B, MRP2) enhance drug extrusion	[77]
	PI3 K/AKT Pathway	Low expression of STEAP4 directly promotes AKT phosphorylation and activation, enhancing cell survival and inhibiting apoptosis to confer cisplatin resistance	[78, 79]
	Wnt/β-Catenin Pathway	Upregulated miR-130a suppresses the tumor suppressor RUNX3, promoting nuclear accumulation of β-catenin and increased expression of Axin2 to activate transcription of resistance-related genes	
	Hippo Pathway	YAP overexpression upregulates GLUT3 (a glucose transporter) and Bcl-2 (an anti-apoptotic protein), enhancing glycolysis and anti-apoptotic capacity to reduce cisplatin sensitivity	
	Nrf2 Antioxidant Pathway	Downregulated miR-340/5p relieves inhibition of Nrf2, activating antioxidant genes such as NQO1 and HO-1 to reduce cisplatin-induced DNA damage and apoptosis	
	Inhibition of apoptosis signaling	p53 mutation/inactivation; upregulated anti-apoptotic proteins (Bcl-2, XIAP) Blockade of caspase-3/−7 activation and apoptotic execution	[80, 81]
Oxaliplatin	**Abnormal Signaling Pathways**	a. Activates the Akt/GSK3β Signaling Pathway:SphK1 is highly expressed in HCC tissues,It promotes oxaliplatin resistance in HCC cells b. Activates the Akt Pathway:regulating mitochondrial apoptosis-related proteins (Bcl-2, Bax, Caspase-9) and Akt/GSK3β phosphorylation to mediate resistance	[82, 83]
	EMT	Snail-mediated MET BMP4-MEK/ERK/ELK1-induced EMT	[84, 85]

However, the majority of HCC patients have low response rates to ICIs, with only 15–20% benefitting [88]. This low response rate is mainly due to the complexity of the TME and immune escape mechanisms [66, 89]. This low response rate is largely attributed to the complex nature of the TME, which plays a critical role in immune resistance. The TME is composed of a variety of immune and stromal cells, as well as extracellular components, which create a supportive niche for tumor cells and contribute to immune escape. Studies suggest that immune resistance involves multiple mechanisms, primarily the dynamic interactions within the TME, including immune evasion mechanisms, such as the upregulation of immune checkpoints like PD-L1, and the establishment of tumor immune tolerance through suppressive immune cells like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). These interactions hinder the immune system's ability to effectively target and eliminate tumor cells, resulting in immune resistance and tumor recurrence [90].

Hypoxia and drug resistance

The hypoxic tumor microenvironment (oxygen tension < 5 mmHg) drives therapeutic resistance through hypoxia-inducible factor 1α/2α (HIF-1α/2α)-mediated adaptive responses [91]. Under hypoxic stress, tumor cells adapt through HIF-mediated metabolic reprogramming: HIF-1α drives the transcriptional upregulation of glucose transporters (GLUT1/3, encoded by SLC2 A1/SLC2 A3) and glycolytic enzymes (HK2, PFKL, LDHA), forcing a metabolic switch from oxidative phosphorylation to aerobic glycolysis (Warburg effect) that accelerates pyruvate-to-lactate conversion, while HIF-1α/2α upregulates monocarboxylate transporter MCT4 (SLC16 A3) to extrude lactate into the TME, creating an acidic microenvironment (pH 6.0–6.5) with lactate concentrations reaching 10–30 mM—5–10 times higher than physiological levels (1.5–3 mM) [92].This lactate-enriched milieu fuels immunosuppression through three interconnected mechanisms—competitive glucose depletion and microenvironment acidification impair $CD8^+$ T/NK cell glycolysis, suppressing IFN-γ production and cytotoxicity [93]; lactate-activated GPR81/GPR132 signaling promotes M2 macrophage polarization and Treg/MDSC expansion [94]; and HIF-1α-lactate crosstalk upregulates PD-L1 while activating the CD39/CD73-adenosine-A2 AR axis to paralyze T cell responses [95]. The temporal dynamics of HIF isoforms critically influence therapeutic outcomes, with HIF-1α governing acute hypoxia responses and HIF-2α dominating chronic adaptation [92, 96]. Notably, sorafenib—a first-line HCC therapy—paradoxically induces resistance by suppressing HIF-1α while triggering compensatory HIF-2α overexpression via TGF-α/EGFR signaling, enhancing tumor cell survival [97, 98], thereby positioning HIF-2α inhibition as a strategy to augment sorafenib efficacy and induce hypoxic HCC apoptosis. Emerging combination therapies targeting this hypoxia-lactate-immune axis show promise: preclinical evidence demonstrates that HIF-2α inhibitor PT-2385 restores NK cell function and reverses sorafenib resistance, while MCT4 blocker AZD3965 traps intracellular lactate to boost $CD8^+$ T cell infiltration, synergizing with PD-1 inhibitors to achieve 40% higher tumor regression rates [99]. Future research must unravel isoform-specific HIF regulatory networks in tumor heterogeneity and develop spatial metabolomics strategies to dismantle the hypoxia-driven immunosuppression-chemorefractory coupling.

Role of immune cells in the TME

In HCC, treatment efficacy remains limited by various factors within the TME [100] (Fig. 1). Immune cells, as a significant component of the TME, influence the response to immunotherapy and the development of drug resistance through complex interactions. Tregs and MDSCs inhibit anti-tumor immune responses through multiple mechanisms, promoting tumor immune escape [101]. Tregs secrete inhibitory cytokines (such as IL-10 and TGF-β) and upregulate immune checkpoint molecules (such as CTLA-4 and PD-1), suppressing effector T cell activity [102]. MDSCs release metabolic enzymes that inhibit T cell expansion and promote the conversion of naive T cells into Tregs. High levels of MDSCs in HCC are associated with poor response to ICIs and poor prognosis [103]. Tumor-associated macrophages (TAMs), primarily of the pro-tumor M2 type, secrete various cytokines (such as IL-10 and TGF-β) and chemokines, suppressing anti-tumor immune responses and promoting tumor growth and metastasis [104]. For instance, TAMs secrete IL-6 to activate the STAT3 signaling pathway, promoting tumor cell survival and growth [105, 106]. Moreover, TAMs can secrete CXCL1 and CXCL2 to enhance stem cell-like properties of tumor cells, contributing to sorafenib resistance [107]. $CD8^+$ T cells are crucial for anti-tumor immune responses. However, prolonged antigen exposure in the TME leads to $CD8^+$ T cell exhaustion, characterized by reduced cytotoxicity and high expression of inhibitory receptors (such as PD-1, CTLA-4, TIGIT, and LAG-3) [108]. These exhausted $CD8^+$ T cells are common in advanced HCC and correlate with poor patient prognosis [109]. Enhancing the function of these cells could significantly impact cancer progression, making them a key target for immunotherapy.

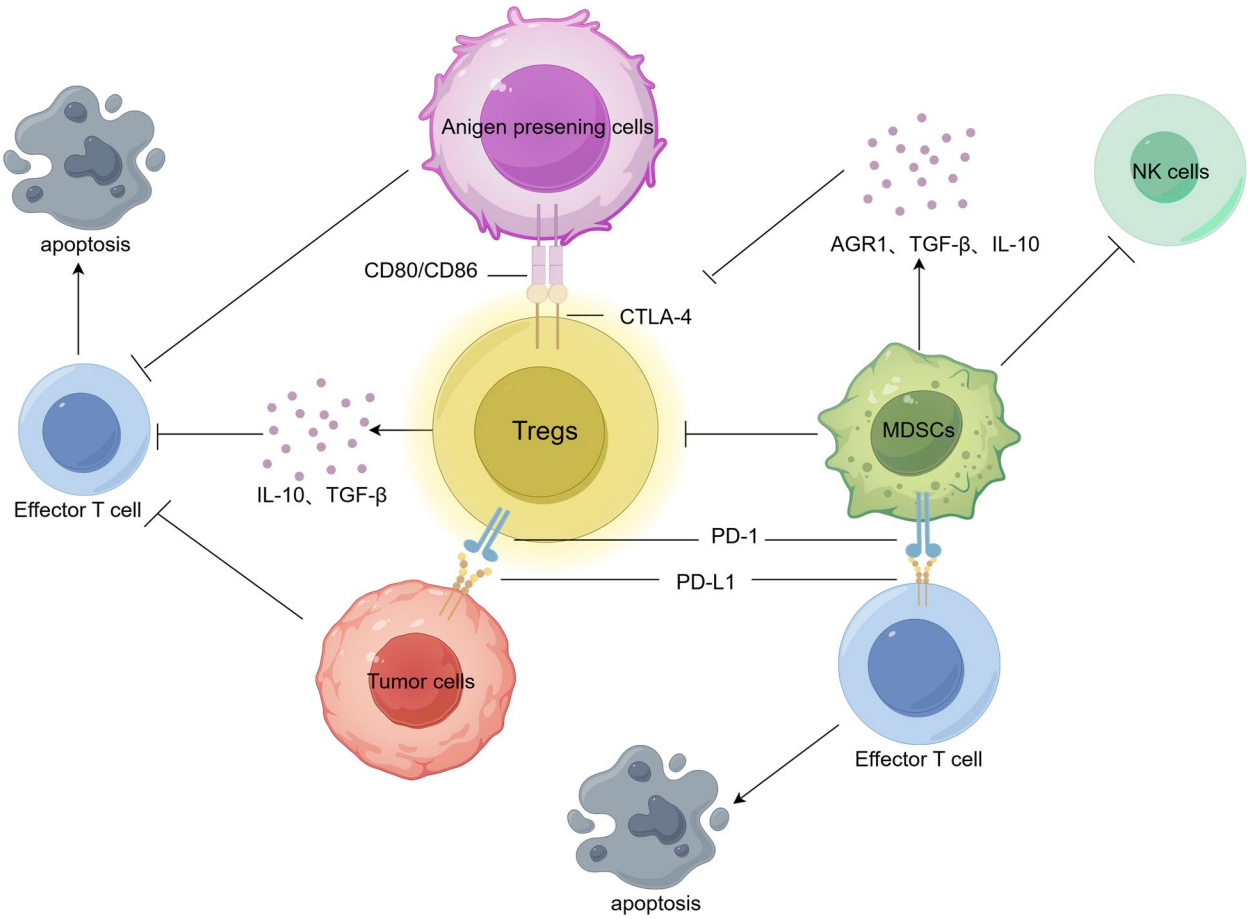

Fig. 1 Mechanisms of immune evasion promoted by Tregs and MDSCs via immune checkpoints and inhibitory cytokines This figure illustrates how Tregs and MDSCs promote immune evasion by inhibiting effector T cell activity through multiple pathways in the TME. Tregs interact with antigen-presenting cells via CTLA-4 and secrete IL-10 and TGF-β to suppress effector T cells. MDSCs further inhibit effector T cells through the PD-1/PD-L1 pathway, enhancing tumor immune evasion. The function of NK cells is also suppressed, reducing the clearance of tumor cells

Cytokines and Chemokines in the TME

Cytokines and chemokines in the TME regulate tumor growth, inflammation, immune escape, and response to therapy. Pro-inflammatory cytokines like IL-6 and IL-1 play dual roles in HCC, promoting tumor growth and participating in the formation of drug resistance. Studies on immune regulation within the TME of HCC have underscored the pivotal roles these cytokines play in influencing tumor behavior and therapy response [110]. IL-6 activates the STAT3 signaling pathway, promoting the proliferation and survival of liver cancer cells [105]. Additionally, IL-6 induces the expansion of MDSCs, which suppress effector T cell function, thus promoting tumor immune escape [111]. Chemokines are crucial for tumor cell migration and invasion. For example, the CXCR4 chemokine receptor highly expressed in HCC cells is closely associated with enhanced tumor migration and invasion. This mechanism involves promoting tumor cell survival and metastasis through the AKT/ERK signaling pathway [112] (Fig. 2).

Tumor-associated fibroblasts and extracellular matrix

Tumor-associated fibroblasts (CAFs) and the extracellular matrix (ECM) play significant roles in HCC resistance [113]. CAFs secrete various growth factors and ECM components creating an environment that supports tumor growth and invasion. For example, CAFs secrete TGF-β and other growth factors that promote tumor cell proliferation and migration,further emphasizing the role of TGF-β signaling in modulating the immune microenvironment and contributing to therapeutic resistance in HCC [114]. The TROY gene is upregulated by CAF-secreted TGF-β1, which promotes tumor stemness and resistance through the PI3 K/AKT/TBX3 signaling pathway [115]. The ECM not only

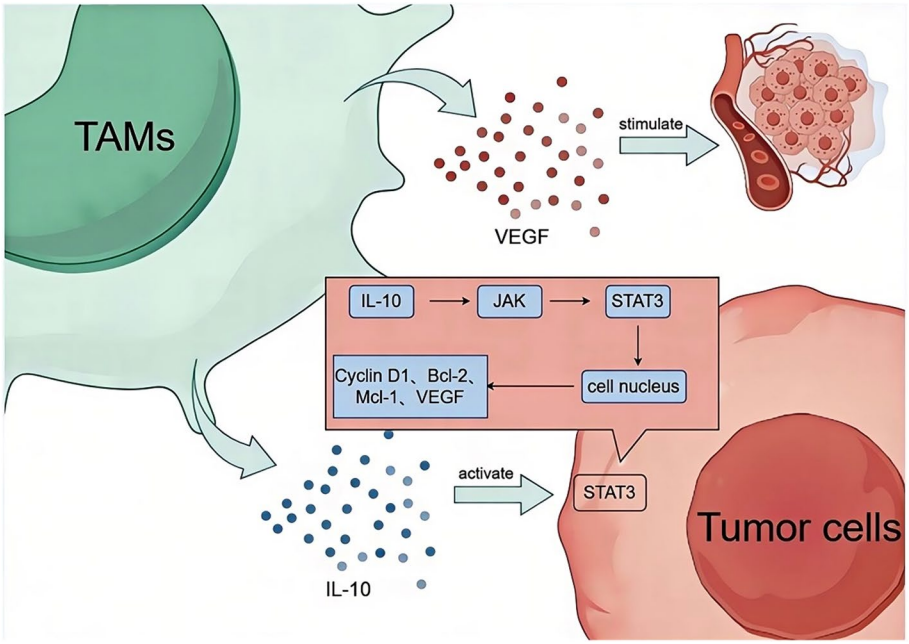

Fig. 2 TAMs promote tumor immune evasion and drug resistance via the JAK/STAT3 signaling pathway. This figure illustrates how tumor-associated macrophages (TAMs) promote immune evasion and drug resistance by secreting IL-10 and VEGF, which activate the JAK/STAT3 signaling pathway in tumor cells. IL-10 activates the JAK/STAT3 pathway, inducing the expression of survival and angiogenesis-promoting genes such as Cyclin D1, Bcl-2, Mcl-1, and VEGF, thereby enhancing tumor cell survival, proliferation, and immune evasion. VEGF secretion further promotes tumor angiogenesis, supporting tumor growth

provides structural support for tumor cells but also influences cell signaling pathways regulating tumor cell response to treatment. For instance, matrix metalloproteinases (MMPs) secreted by CAFs degrade the ECM, releasing trapped growth factors and cytokines, further promoting tumor progression and resistance [116]. The stiffness and composition of the ECM also significantly impact tumor cell behavior. A rigid ECM can enhance tumor cell survival and resistance to chemotherapy through integrin signaling pathways [117]. Studies have shown that CAFs can increase tumor cell resistance by secreting inducible nitric oxide synthase (iNOS). Nitric oxide (NO) produced by iNOS enhances tumor cell survival through various mechanisms, including DNA damage repair and anti-apoptotic pathways, thus contributing to resistance [118, 119].

HCC exhibits significant heterogeneity, primarily due to the presence of hepatic CSCs [26]. Although these cells constitute only a small portion of the tumor, their ability to self-renew and differentiate significantly contributes to both primary and acquired drug resistance, particularly in the case of lenvatinib treatment. Targeting these CSCs could be a promising strategy to overcome resistance mechanisms, specifically lenvatinib resistance, thereby improving therapeutic outcomes and patient prognosis [120].

The drug resistance of HCC fundamentally stems from an adaptive network formed by dynamic interactions among multiple components within the TME. The hypoxic microenvironment directly drives targeted therapy resistance through HIF-α isoforms, while simultaneously inducing lactate metabolic reprogramming, suppressing $CD8^+$ T cell function, and upregulating PD-L1, creating a vicious cycle of drug resistance and immune evasion. Additionally, immunosuppressive cells in the TME (Tregs, MDSCs, and M2-TAMs) secrete inhibitory factors (e.g., IL-10, TGF-β) and metabolic enzymes to establish an"immune desert,"while exhausted $CD8^+$ T cells lose cytotoxic activity due to persistent antigen exposure, further impairing immunotherapy efficacy. Cytokines (e.g., IL-6/STAT3) and chemokines (e.g., CXCR4/AKT-ERK) act as"double agents,"promoting tumor proliferation while recruiting immunosuppressive cells, thereby forming a multidimensional resistance network. Furthermore, CAFs enhance tumor stemness and create physical drug barriers by secreting TGF-β, iNOS, and remodeling the ECM. Finally, CSCs serve as the core hub of resistance, functioning as a persistent"reservoir"of resistant clones through self-renewal, metabolic plasticity, and interactions with the TME.

Current research limitations include fragmented focus on isolated pathways, failing to address the

interconnected hypoxia-immune-metabolism axis. Traditional therapies falter in MDSC-dominated"immune deserts"necessitating innovative strategies: multimodal therapies targeting compensatory networks, microenvironment-responsive nanomedicine, and CSC-specific eradication. Overcoming HCC resistance requires dismantling its ecological complexity through systems-level interventions.

Ferroptosis-Related Mechanisms

Ferroptosis is a novel iron-dependent form of cell death distinct from traditional apoptosis and necrosis [121]. Recent studies have shown that ferroptosis plays a crucial role in HCC proliferation, invasion, and resistance [122]. Sorafenib exerts ferroptosis-inducing effects through system Xc^- inhibition, depleting cystine uptake and consequently reducing glutathione synthesis. However, compensatory activation of YAP/TAZ signaling in resistant cells transcriptionally upregulates SLC7 A11 (xCT), restoring glutathione production and establishing redox homeostasis. This adaptive mechanism highlights YAP/TAZ-SLC7 A11 axis as a critical therapeutic vulnerability [123]. Furthermore, studies have found that regulating the expression of ferroptosis-related markers, such as FTL and FTH1, enhances the sensitivity of HCC to ferroptosis inducers like sorafenib, revealing the connection between ferroptosis and drug resistance [124]. This suggests that modulating ferroptosis pathways could be a new strategy to overcome sorafenib resistance [125, 126]. The core mechanism of ferroptosis-related drug resistance lies in tumor cells maintaining redox homeostasis through the YAP/TAZ-SLC7 A11 axis to counteract sorafenib-induced ferroptotic stress. Current research remains overly focused on single targets (e.g., SLC7 A11), while future studies should explore other ferroptosis-related targets (e.g., iron metabolism regulators like FTL/FTH1 or lipid peroxidation pathways) to uncover novel vulnerabilities. This multi-target approach could offer new avenues to overcome resistance by disrupting the adaptive crosstalk between ferroptosis and compensatory survival pathways.

Autophagy, apoptosis and Endoplasmic Reticulum Stress

Autophagy, apoptosis, and endoplasmic reticulum (ER) stress play key roles in the drug resistance of HCC. Autophagy has a dual function in cancer cells. Basal autophagy acts as a tumor suppressor by maintaining genomic stability in normal cells. However, once cancer develops, activated autophagy helps cancer cells survive under various stress conditions, thus promoting tumor progression. Yuan et al. found that MALAT1-specific siRNA and miR-216b mimics significantly reduced the IC50 values of 5-FU, ADM, and mitomycin C (MMC) in BEL-7402/5-FU cells while inhibiting intracellular autophagy activity. This suggests that the MALAT1-miR-216b axis regulates autophagy and affects MDR in HCC cells [127]. Apoptosis is a form of cell death that involves a series of intracellular signaling pathways. Resistance to apoptosis induction is a major cause of chemotherapy failure, and dysregulation of apoptotic signals is a key factor in the development of MDR [128]. Experimental studies have identified several apoptosis-related signaling molecules that are closely associated with MDR in liver cancer, including p53 and the Bcl-2 family of proteins. Zhang et al. [129] reported that p53 suppressed the growth of MDR HepG2 cells by increasing Bax expression and decreasing Bcl-2 expression.Moreover, the Nogo-B receptor (NgBR) activates the PI3 K/Akt/MDM2 pathway, leading to p53 protein degradation via the ubiquitin–proteasome system and resulting in chemotherapy resistance in HCC cells [130]. Overexpression of p53 mutants can inhibit apoptosis and reverse the anticancer effects of chemotherapeutic agents, including ADM and cisplatin, causing MDR in cancer cells [131]. Bcl-2 overexpression also contributes to resistance to anticancer drugs [132]. For example, the overexpression of Bcl-xL protein is associated with tumor growth and sorafenib resistance [133, 134]. Bcl-2 protein is one of the most important members associated with acquired resistance (not primarily against sorafenib), as it can inhibit caspase activation by preventing the release of cytochrome C or the entry of glutathione into the nucleus of HCC cells [135]. Chen et al. [136] found that the overexpression of Mcl-1 in HCC contributes to the development of a malignant phenotype, he high expression of the anti-apoptotic protein Mcl-1 in HCC is considered one of the key factors contributing to resistance to apoptosis and certain chemotherapeutic agents.and the activation of proliferative pathways is linked to chemotherapeutic resistance [137]. Regarding cell death, previous studies have focused on the ER as a third subcellular compartment involved in apoptosis execution. The accumulation of misfolded proteins and changes in calcium homeostasis in the ER lead to ER stress, ultimately triggering apoptotic cell death. This aligns with findings that ER stress, particularly through the unfolded protein response (UPR), contributes to chemotherapy resistance in HCC via multiple pathways, including autophagy and the PERK/ATF4 axis [138]. In summary, autophagy, apoptosis, and ER stress interact to play crucial roles in HCC drug resistance.A key limitation of current research lies in its narrow focus on isolated mechanisms, while drug resistance arises from the synergistic interplay of autophagy, apoptosis, and endoplasmic reticulum stress (ERS). For instance, ERS may activate autophagy via the UPR to clear damaged organelles while suppressing apoptotic signaling,

ultimately reinforcing resistance. Future studies should prioritize developing multi-target intervention strategies that concurrently modulate these interconnected pathways to disrupt the adaptive survival-death balance in HCC cells.

ABC transporter protein

ABC transporters are ATP-dependent transmembrane proteins with highly conserved sequences [66]. The protein family consists of numerous members capable of recognizing a wide range of substrates, which ultimately leads to MDR in tumors. ABC transporters are often overexpressed in tumor cells, acting as drug efflux pumps and inducing MDR by reducing the intracellular concentration of anticancer drugs [139, 140]. For example, in sorafenib-resistant cells, the expression levels of ABC transporter genes are upregulated [141]. Studies have shown that HMOX1 is upregulated in sorafenib-resistant HCC cells and promotes resistance by regulating the expression of ABC transporters [142]. ABC transporters mediate MDR in HCC through drug efflux pump activity, yet their resistance mechanisms likely extend beyond the isolated function of individual proteins. Current research overlooks functional redundancy and synergy among ABC family members (e.g., compensatory co-expression of ABC subtypes). Future studies should focus on developing broad-spectrum ABC inhibitors or targeting regulatory hubs (e.g., HMOX1/NF-κB axis) to block the initiation and progression of MDR.

Gene mutations

Gene mutations play a crucial role in HCC resistance. Numerous molecular alterations in HCC cells involve changes in the Wnt/β-catenin pathway, oxidative stress pathway, mTOR, and MAP kinase pathways [143, 144]. These mutations lead to uncontrolled cell proliferation, angiogenesis, cell cycle dysregulation, and inhibition of apoptosis, promoting resistance. For instance, activation of the FGFR4 signaling pathway has been linked to sorafenib resistance [145]. The drug resistance driven by gene mutations in HCC is inherently a networked mechanism involving multi-pathway crosstalk. Current studies overly focus on isolated mutations, while future research should systematically dissect pathway interactions and develop combinatorial targeting strategies.

Epigenetic Changes in HCC

Epigenetic changes, including DNA methylation, histone modifications, and ncRNAs, play significant roles in HCC development and resistance. Abnormal DNA methylation patterns, such as hypermethylation of tumor suppressor genes and hypomethylation of oncogenes like ADAMTSL5, contribute to HCC progression and drug resistance [146, 147]. For example, hypermethylation of the RASSF1 A gene has been linked to poor prognosis and resistance to chemotherapy in HCC patients [148, 149]. Histone modifications, such as acetylation and methylation, also regulate gene expression involved in cell cycle control, apoptosis, and DNA repair, influencing HCC resistance [150, 151]. Additionally, NcRNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play crucial roles as regulators of gene expression in HCC. Recent studies have demonstrated that these ncRNAs are not only involved in the occurrence and progression of HCC, but they also significantly contribute to the development of drug resistance by modulating key signaling pathways that affect cell survival and drug response [152]. Dysregulation of these ncRNAs can enhance the resistance of cancer cells to therapeutic agents, making them important candidates for therapeutic targeting. For instance, the lncRNA HOTAIR has been shown to enhance doxorubicin resistance in HCC by modulating the PTEN-PI3k/Akt pathway [153]. Similarly, miR-122 and miR-223 have been identified as key players in mediating drug resistance through their effects on MDR-related genes and signaling pathways [154]. Current research often isolates single epigenetic mechanisms, while HCC drug resistance is driven by a synergistic network of DNA methylation, histone modifications, and ncRNAs. Future strategies should focus on developing multi-target epigenetic drugs to disrupt this coordinated resistance framework.

Non-coding RNAs in cancer drug resistance

Non-coding RNAs (ncRNAs) refer to RNA molecules that do not encode proteins. Over 90% of the RNA in the human body consists of non-coding RNA. Similar to proteins, ncRNAs play essential roles in various biological processes, such as cell proliferation, migration, apoptosis, angiogenesis, and immune responses [155]. Additionally, ncRNAs are involved in drug resistance in multiple cancer types. Among the ncRNAs associated with drug resistance, miRNAs and lncRNAs are the most commonly observed [156]. MicroRNAs are single-stranded non-coding RNA molecules approximately 22 nucleotides in length and have been shown to be associated with drug resistance in HCC [157, 158]. Emerging evidence highlights the oncogenic role of miR-221 in HCC pathogenesis. Mechanistic studies demonstrate that antisense oligonucleotides specifically targeting miR-221 effectively suppress HCC cell proliferation in vitro and significantly attenuate tumor growth in vivo. Notably, in an orthotopic HCC xenograft model, administration of these oligonucleotides induces marked tumor cell apoptosis accompanied by upregulation of cell cycle arrest biomarkers [159]. LncRNAs, typically longer than 200 nucleotides, exert

their effects through interactions with DNA, RNA, and proteins, influencing various physiological and pathological processes [160], and play a crucial role in drug resistance [161, 162]. For instance, LINC01134, as a lncRNA, plays a key role in oxaliplatin (OXA) resistance by regulating the LINC01134/SP1/p62 axis, altering cell viability, apoptosis, and mitochondrial homeostasis, thus affecting OXA resistance [163]. In addition, circular RNAs (circRNAs) are also an important type of non-coding RNA. It has been found that circRNA-SORE is upregulated in sorafenib-resistant HCC cells, where it enhances drug resistance by binding to YBX1 and preventing its degradation [164]. YTHDF1, an m6 A reader, is also closely associated with drug resistance in HCC, particularly in resistance to lenvatinib and sorafenib. YTHDF1 enhances the stability and translation of NOTCH1 mRNA through m6 A modification, thus promoting HCC stemness and drug resistance [165]. Modifications of ncRNAs not only directly influence drug resistance but also indirectly affect drug resistance through other mechanisms. For example, NEAT1 regulates miR-362-3p and MIOX to promote ferroptosis, playing a significant role in the drug resistance of tumor cells. These studies highlight the critical role of ncRNAs and their modifications in cancer drug resistance and provide potential targets for anticancer therapies [166]. Current research predominantly focuses on single non-coding RNA types, yet HCC drug resistance is driven by a synergistic network of miRNAs, lncRNAs, and circRNAs. Future strategies should prioritize combinatorial targeting of multiple ncRNA types to disrupt core resistance signaling hubs.

Prospects and challenges

The drug resistance mechanisms in HCC are highly complex, involving both tumor cell-intrinsic adaptive regulation—such as metabolic-immune axis interactions (HIF-2α inhibition, MCT4 blockade), ferroptosis pathways (multi-layered targeting of iron homeostasis and lipid peroxidation), crosstalk between cell death pathways (autophagy-apoptosis-ERS), upstream regulatory master switches of ABC transporters (HMOX1/NF-κB axis), non-coding RNA networks, and epigenetic-genetic synergies—and dynamic interplay with the TME, including cancer stem cell (CSC) resilience, stromal reprogramming, and immune microenvironment modulation. Addressing HCC drug resistance is an urgent priority. Future breakthroughs in overcoming this challenge lie in precisely targeting tumor vulnerabilities and advancing novel technologies. For instance, CRISPR screening can rapidly identify resistance-associated genes such as FGFR4 mutations or YAP signaling activation, enabling the design of tailored combination therapies—like pairing FGFR4 inhibitors with YAP pathway blockers—to prevent tumor recurrence. To counter ferroptosis evasion, dual-target agents that simultaneously inhibit antioxidant defenses and enhance lipid peroxidation pressure could disrupt tumor redox balance, thereby reversing resistance. Innovations in drug delivery, such as"smart nanoparticles"capable of precise spatiotemporal drug release, allow coordinated delivery of chemotherapeutic and epigenetic drugs to eliminate bulk tumor cells while resetting CSC malignant memory. Crucially, overcoming resistance requires moving beyond single-pathway approaches to adopt multidimensional strategies. Clinically, emerging 3D organoid-based drug sensitivity testing can screen optimal drug combinations within a week, offering personalized therapeutic options and contributing significantly to combating drug resistance.

Conclusion

Despite significant progress in understanding the mechanisms of drug resistance in HCC, several key challenges remain. First, the complexity of the TME continues to be a major issue, as the interactions between different cell types within the TME are not yet fully understood, complicating the development of treatment strategies. Second, the high genetic and epigenetic heterogeneity of HCC leads to significant differences in drug responses among patients, making it difficult for current treatments to produce consistent effects across all subtypes. Finally, despite growing interest in the discovery of biomarkers, no widely accepted biomarkers have been identified to reliably predict the efficacy of targeted or immune therapies, limiting the widespread application of personalized treatments. Therefore, future research needs to address these challenges by gaining a more thorough understanding of the interactions between the cells and molecular mechanisms responsible for drug resistance. This will facilitate the discovery of new therapeutic approaches, provide feedback to clinical practice, and ultimately improve the survival rates of HCC patients.

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Authors' contributions

Yongchun Zou and Xinliang Wan drafted this review and designed the figures; Qichun Zhou and Gangxing Zhu completed the data collection and provided editorial assistance; Shanshan Lin gave some valuable suggestions; Qing Tang, Xiaobing Yang and Sumei Wang reviewed and modifed the manuscript. All authors made substantial, direct and intellectual contribution to the review. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interest
The authors declare no competing interests.

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