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Latest Research Progress on the Mechanisms of Lenvatinib Resistance

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Abstract

Hepatocellular carcinoma (HCC) poses a formidable obstacle to global health. Modern medicine has made tremendous efforts to address the threat posed by HCC, but most current treatment methods are only effective for early-stage HCC, whereas the majority of HCC cases are diagnosed at an advanced stage. Targeted therapy has revolutionized the treatment strategy for HCC, offering survival hope to advanced-stage patients. Targeted therapy can not only extend the survival of patients with advanced disease when used alone, but also achieves satisfactory therapeutic effects when combined with other treatments. Sorafenib and lenvatinib are the sole two approved first-line targeted therapeutic drugs. Lenvatinib was officially approved by the FDA in 2019 as a first-line targeted drug, exhibiting superior overall survival efficacy compared to sorafenib. Consequently, lenvatinib, as the preferred first-line targeted therapy at present, occupies an indispensable position in prolonging the survival of advanced HCC patients. Unfortunately, the increasing prevalence of lenvatinib resistance has significantly hindered its clinical application, preventing a substantial proportion of patients from fully benefiting from this frontline medication. Therefore, elucidating the underlying mechanisms of resistance is crucial to tackle lenvatinib resistance and facilitate research aimed at reversing resistance. This review summarizes the lenvatinib resistance mechanisms focusing on HCC cell plasticity, abnormal transport processes, abnormal cell proliferation signaling pathways, escaped programmed cell death, and enhanced cancer cell metabolism.

Keywords

Hepatocellular Carcinoma, Lenvatinib, Drug Resistance

1. Introduction

1.1. Current Situation and Treatment of HCC

Primary liver cancer is one of the most common malignancies, characterized by high incidence and mortality rates. According to the latest statistics, in 2022, the number of new liver cancer cases globally reached 865,269, with over 750,000 deaths. It is projected that by 2025, the global number of liver cancer cases will exceed one million, making it the sixth most common malignancy and the third leading cause of cancer-related deaths worldwide. The five-year survival rate for patients with advanced liver cancer is less than 20%. The pathological classification of primary liver cancer mainly includes three types: hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, and mixed hepatocellular-cholangiocarcinoma, among which approximately 80% are HCC. There are regional differences in the incidence of HCC, with East Asia, Southeast Asia, Central Africa, and West Africa having the highest incidence rates [1] [2]. Unlike the decreasing mortality rates observed in other common cancers such as breast cancer, lung cancer, and prostate cancer, the mortality rate associated with HCC continues to rise at a rate of 2% - 3% per year [3]. It is evident that the danger posed by HCC to all of humanity has reached a significantly high level.

1.2. Targeted Therapy

At initial diagnosis, fewer than 30% of patients with HCC are eligible for radical treatment. Targeted therapy has emerged as a beacon of hope for those in the middle and advanced stages of the disease [4]. Sorafenib, which has been approved for over a decade as the first targeted therapy for HCC, has demonstrated limited clinical efficacy, with drug resistance posing as the foremost challenge. In light of this pressing issue, the need for innovative targeted therapies is both urgent and critical. Lenvatinib, recently approved as the second first-line targeted therapy, demonstrates comparable clinical efficacy to sorafenib [5] [6]. Nevertheless, lenvatinib, an oral small-molecule inhibitor of multiple receptor tyrosine kinases, confronts the same resistance issue as sorafenib. This shared challenge poses a significant impediment to the survival prospects of patients with advanced HCC. In the absence of alternative targeted drugs to lenvatinib, it is imperative to unravel the mechanisms underlying drug resistance and devise strategies to counteract resistance against specific targets. In this review, we comprehensively consolidate the mechanisms of lenvatinib resistance reported in recent years (as shown in **Table 1**). These insights are pivotal for ongoing drug research endeavors aimed at reversing resistance and paving the way for more effective treatment options for patients with HCC.

2. Mechanisms of Lenvatinib Resistance

2.1. HCC cell Plasticity

Tumor cell plasticity plays a pivotal role in cancer stemness and eventual emergence of drug resistance. Cellular plasticity ensures that cancer cells with a single

genotype can switch their phenotypic states (or cellular identities) in response to external stimuli, driving tumors to survive and thrive under harsh microenvironments and anticancer drug treatments. A typical characteristic of this phenotypic switching is reversibility, manifested as the loss of resistance when tumor cells are cultured in the absence of drugs. Indeed, subpopulations of cancer cells that adapt to treatment can serve as a reservoir for proliferation and the acquisition of random genetic mutations. Consequently, those cancer cells with genetic mutations develop better resistance to treatment, and they will survive and be transmitted generation after generation as the most fit clones under drug selection. Key mechanisms of cancer cell phenotypic switching include the migration of epithelial-to-mesenchymal transition (EMT) and the colony formation of mesenchymal-to-epithelial transition (MET). Additionally, in the context of the cancer stem cell (CSC) theory, cancer cell plasticity can also be interpreted as the ability of differentiated cancer cells to revert to a stem-like state [7] [8].

2.1.1. CSCs Expansion

The concept CSC was proposed four decades ago, suggesting that tumor growth resembles the renewal of healthy tissue, being driven by a small number of stem cells. These stem cells, when other tumor cells are decimated, awaken from dormancy and reconstitute the entire tumor, which then demonstrates greater resistance to external adverse conditions [9].

Wang *et al*. utilized RNA sequencing to confirm the elevated expression of Frizzled10 (FZD10) in CSCs. Their investigation unveiled that FZD10 fosters self-renewal, tumorigenicity, and metastasis of liver CSCs by activating the β-catenin/YAP1 axis, and this augmentation contributes to lenvatinib resistance [10]. Additionally, TM4SF1, a vital member of the transmembrane 4 superfamily, plays a crucial role in tumorigenesis and development. Yang *et al*. confirmed that the expression of TM4SF-1 positively correlates with the tumor stemness of HCC. MYH9, a downstream protein of TM4SF1, bolsters the resistance of HCC cells to lenvatinib by regulating the classic NOTCH pathway to promote HCC cancer stemness [11]. Cao *et al*. observed that among 30 HCC patients who underwent surgery and received adjuvant lenvatinib therapy, those with higher NOVA2 expression levels exhibited shorter overall survival. Therefore, the correlation between NOVA2 expression in HCC tumors and drug resistance should be taken into account. Mechanistically, NOVA2 augments the self-renewal and oncogenic potential of liver CSCs by activating the Wnt pathway, significantly diminishing the sensitivity of HCC cells to lenvatinib. Furthermore, the notable upregulation of NOVA2 is regulated by RNA methylation [12].

2.1.2. EMT Process

EMT serves as a pivotal process in the normal progression of embryonic development and tissue regeneration. Nonetheless, the aberrant reactivation of EMT is intimately linked to the malignant characteristics of tumor cells during cancer progression and metastasis, fostering migration and invasion, augmenting cancer

stemness, and bolstering resistance to therapeutic interventions. EMT entails a highly dynamic and plastic transformation of epithelial cells between their epithelial and mesenchymal states. When viewed through the lens of cancer cell dynamics, EMT emerges as a continuous and dynamic spectrum, spanning a continuum from an epithelial to a mesenchymal state. Tumor cells that occupy intermediate states within this epithelial-mesenchymal spectrum exhibit both epithelial and mesenchymal traits, allowing them to survive and metastasize more effectively. The introduction of the CSC concept furnishes a foundational framework for comprehending tumor cell plasticity. The identification of EMT programs as crucial regulators of CSC phenotypes further enriches this framework and presents a fresh perspective for exploring the interplay between tumor cell plasticity and drug resistance [13] [14].

Zheng *et al*. observed that Chromobox Homolog 1 (CBX1) is frequently upregulated in cancer and is associated with adverse clinical outcomes in HCC. They unveiled a mechanism underlying intrinsic resistance to lenvatinib, involving CBX1 initiating the EMT process through the downstream signaling axis of IGF-1R/AKT/SNAIL. Notably, overexpression of CBX1 results in elevated levels of p-AKT and Snail, while reducing the expression of E-cadherin, a process that can be reversed by the AKT antagonist MK-2206. This discovery offers a novel clinical strategy to reverse lenvatinib resistance [15]. Furthermore, Feng *et al*. used qRT-PCR to identify that the expression of circ_0007386 is elevated in HCC tissues and found a correlation with poorer prognosis. Mechanistic investigations revealed that circ_0007386 functions as a competitive endogenous RNA for miR-507, thereby preventing the downregulation of cyclin T2 (CCNT2). Importantly, the circ_0007386/miR-507/CCNT2 axis also promotes the EMT process, reducing the sensitivity of HCC cells to lenvatinib [16].

2.2. Abnormal Transport Process

HCC enhances lenvatinib resistance by regulating drug transport or exosome secretion. Classical drug transporter proteins include the ATP-binding cassette (ABC) transporter family, and overexpression of ABC transporters confers resistance to targeted therapy by reducing the accumulation of targeted drugs within tumor cells [17]. Additionally, exosomes are also involved in targeted drug resistance to a certain extent. Exosomes are vesicles ranging in size from 40 to 100 nm that are released into the extracellular space from many cell types. These vesicles are widely distributed in various bodily fluids. In recent years, non-coding RNAs have been discovered in exosomes, which can be absorbed by neighboring or distant cells, thereby regulating the drug sensitivity of recipient cells [18].

ABC transporter: Abnormal drug transport is a vital mechanism of resistance to chemotherapeutic drugs in various solid tumor cells. When membrane transporter proteins are overexpressed, they can decrease the amount of anticancer drugs inside the cells by exporting them or blocking their entry. Most of these proteins belong to the ABC transporter family, which are energy-dependent

transmembrane proteins known as efflux pumps. They play a significant role in both drug resistance, by increasing drug efflux, and cancer development, through their regulation of downstream pathways and intercellular signaling molecules [19]. HCC cells enhance the exocytosis of tumor cells to lenvatinib by activating EGFR and stimulating the EGFR-STAT 3-ABCB 1 axis to reduce intracellular drug concentration, which depends on abnormal cholesterol metabolism and lipid raft activation [20].

Exosomes: Zhang *et al.* observed a significant elevation of circMED27 in the serum of patients with HCC, which predicts a shorter overall survival and is associated with lenvatinib resistance. HCC cells secrete circMED27 into the serum via exosomes. As a competitive endogenous RNA (ceRNA) for miR-655-3p, circMED27 upregulates USP28-related pathways, promoting lenvatinib resistance in HCC cells [21]. In another study, Hao *et al.* conducted high-throughput sequencing on HCC and matched normal tissues, and utilized qRT-PCR to detect the overexpression of circPAK1 in HCC. CircPAK1 enhances HCC progression by inactivating the Hippo signaling pathway. This inactivation occurs through circPAK1's competitive binding with 14-3-3ζ for YAP, which weakens the recruitment and cytoplasmic fixation of 14-3-3ζ to YAP, thereby promoting the nuclear localization of YAP. More importantly, CircPAK1 mediates the transmission of lenvatinib resistance via exosomes, providing a potential therapeutic target for HCC patients [22].

2.3. Abnormal Cell Proliferation Signaling Pathway

Lenvatinib is a multitarget tyrosine kinase inhibitor (TKI) that inhibits vascular endothelial growth factor receptor (VEGFR) 1 - 3, fibroblast growth factor receptor (FGFR) 1 - 4, platelet-derived growth factor receptor (PDGFR) α, as well as the proto-oncogenes RET and KIT. Among these anticancer drugs, lenvatinib stands out as the most important due to its potent antiangiogenic activity. It exerts tumor toxicity primarily by inhibiting VEGF and FGF signaling pathways, as well as their downstream PLCγ, Ras-Raf-MEK-ERK, and PI3K-AKT pathways [23]. Unfortunately, with prolonged lenvatinib treatment, HCC cells evolve unique mechanisms to evade the cytotoxic effects on cellular proliferation pathways. These mechanisms either involve reducing the expression of lenvatinib's drug targets or enhancing downstream signaling pathways within the cells, ultimately leading to the lenvatinib resistance.

PI3K/AKT/mTOR pathway: The PI3K/AKT/mTOR signaling pathway is a highly conserved signal transduction network in eukaryotic cells, promoting cell survival, cell growth, and cell cycle progression. The transmission of growth factor signals to transcription factors within the PI3K/AKT/mTOR pathway is highly regulated through multiple cross-interactions with several other signaling pathways. Disruptions in signal transduction can facilitate the onset and progression of cancer. Notably, distortions in the PI3K/AKT/mTOR pathway occur in approximately 50% of tumors and are closely associated with cancer drug resistance. For

instance, hyperactivation of PI3K, loss of PTEN function, and activation of AKT are prominent driving factors for therapeutic resistance and disease progression in cancer [24].

Cancer-associated fibroblasts (CAFs) are the primary stromal cell type composing the tumor microenvironment (TME), capable of stimulating tumor cell proliferation, invasiveness, and metastatic potential across various cancer types, including HCC. Studies investigating the correlation between CAFs and sensitivity to lenvatinib have revealed that CAF-derived secreted phosphoprotein 1 (SPP1) plays a crucial role in inducing tyrosine kinase inhibitor (TKI) resistance in HCC. The specific mechanism involves SPP1 secreted by CAFs binding to the extracellular domains of integrin complexes (integrins $\alpha V\beta 5$, $\alpha 5\beta 1$, and $\alpha V\beta 1$) on HCC cells, subsequently phosphorylating PKCα in the cytoplasmic domain. This process subsequently activates the PI3K/AKT/mTOR pathways, resulting in resistance to lenvatinib. More significantly, treatment with SPP1 inhibitors (such as SPP1-BP or SPP1-APT) has been found to reverse CAF-induced lenvatinib resistance [25]. Long noncoding RNA, nuclear paraspeckle assembly transcript 1 (NEAT1) variant 1 (NEAT1v1), transforms HCC cells from MEK/ERK-dependent growth to AKT-dependent growth through superoxide dismutase 2 (SOD2). The transition modulates the responsiveness of HCC cells to molecular targeted drugs independently of endoplasmic reticulum (ER) stress, manifesting as NEAT1v1-induced AKT addiction, which contributes to lenvatinib resistance. It is noteworthy that this mechanism has thus far been exclusively confirmed in hepatoma cell lines, and in vivo studies are eagerly anticipated to refine and expand our understanding of this process [26].

Ras-Raf-MEK-ERK pathways: The RAS/RAF/MEK/ERK (MAPK) signaling cascade is essential for intercellular and intracellular communication, regulating fundamental cellular functions such as growth, survival, and differentiation. It also serves as a hub for integrating signals from intricate intracellular networks to orchestrate cellular functions. Alterations in the RAS-RAF-MEK-ERK-MAPK pathway are frequently reported in human cancers, typically stemming from deregulated receptor tyrosine kinases or gain-of-function mutations primarily targeting the RAS or RAF genes. Notably, tumors often develop drug resistance by modulating targets within this pathway, which is a crucial mechanism for tumor survival [27] [28]. GTPase-activating protein (GAP) catalyzes the conversion of GTP to GDP, thereby inactivating RAS, and its loss-of-function mutations often promote tumor progression. KLHL7 is a component of the BCR (BTB-CUL3-RBX1) E3 ubiquitin ligase system, primarily involved in K-48-linked polyubiquitination, playing a crucial role in the proteasome-mediated degradation of target proteins. Compared to normal tissues, the expression of KLHL7 is significantly increased in HCC tissues and promotes lenvatinib resistance by degrading RASA2 (a RAS GAP), This degradation leads to constitutive activation and regulation of the RAS-MAPK signaling pathway. Intriguingly, MG-132, a proteasome inhibitor, has the capacity to reverse this inhibitory effect [29].

2.4. Escaped Programmed Cell Death

The pathways leading to tumor cell death encompass both accidental cell death and programmed cell death (PCD). Accidental cell death is a passive uncontrolled process triggered by external stimuli, whereas PCD is a form of controlled cell death governed by an intricate gene network [30]. Recent advancements have significantly deepened our understanding of how epigenetic alterations contribute to lenvatinib resistance by inducing abnormal PCD. PCD in tumor cells involves several critical escape mechanisms that contribute to lenvatinib resistance, such as ferroptosis and autophagy [31].

2.4.1. Ferroptosis

Ferroptosis is an iron-dependent form of regulated cell death triggered by the toxic accumulation of lipid peroxides on the cell membrane. It differs in mechanism and morphology from other forms of cell death, such as apoptosis, and thus holds significant research value. Since its inception in 2012, research on ferroptosis has expanded exponentially over the past few years. Generally, cancer cells are highly sensitive to ferroptosis due to their elevated metabolism, particularly those in a mesenchymal state and prone to metastasis. Intriguingly, cancer cells can weaken their sensitivity to ferroptosis by self-regulating to supress the accumulation of reactive oxygen species, which undoubtedly accelerates the process of drug resistance in cancer cells [32] [33].

The pathway of ferroptosis is a pivotal mechanism by which lenvatinib exerts its lethal effects. Nuclear factor erythroid-derived 2-like 2 (Nrf2) functions as an antioxidant by modulating the activity of lipid peroxidation-associated proteins and several proteins involved in ferroptosis. HCC cells overexpressing Nrf2 often exhibit resistance to lenvatinib due to inadequate reactive oxygen species (ROS) accumulation [34]. Beta-lactamase-like protein (LACTB), a serine protease with an active site, drives ferroptosis by stabilizing the p53 protein and inhibiting the transcription of HSPA8. As a potential inducer of ferroptosis, lenvatinib relies on LACTB as a crucial mediator protein. However, LACTB acts as a tumor suppressor in HCC, and its significant downregulation often results in insufficient ferroptosis, thereby contributing to lenvatinib resistance [35]. Ferritin heavy chain (FTH1), a crucial subunit of ferritin, inhibits the accumulation of intracellular Fe^{2+} and reduces the sensitivity of cancer cells to ferroptosis. Elevated expression of CircPIAS1 in HCC tissues and cells upregulates Nuclear Protein 1 (NUPR1) through competitive binding with miR-455-3p. NUPR1 plays a central role in the interplay between oxidative stress and ferroptosis by promoting FTH1 expression, thereby decreasing intracellular Fe^{2+} and lipid ROS levels while increasing glutathione (GSH) content. This suggests that NUPR1 may serve as a master regulator of iron metabolism in cancer cells and confer lenvatinib resistance in HCC. Additionally, the NUPR1 inhibitor ZZW-115 reverses the oncogenic effects of circPIAS1 and sensitizes HCC cells to lenvatinib [36].

2.4.2. Autophagy

Autophagy plays a housekeeping role in removing misfolded or aggregated proteins and clearing damaged organelles such as mitochondria, endoplasmic reticulum, and peroxisomes. While autophagy is generally regarded as a survival mechanism, its dysregulation is associated with non-apoptotic cell death. Autophagy is a double-edged sword in tumor drug resistance: it contributes to the development of resistance and protects cancer cells from the effects of drugs, but it can also kill cancer cells with inactive apoptotic pathways. Anticancer drugs can induce autophagy, which may activate apoptotic signaling pathways in resistant cells, promoting the reversal of drug resistance. Increasing evidence about how autophagy and related processes influence cancer development and progression helps guide efforts to design anticancer therapies based on inhibiting or promoting autophagy [37] [38].

The expression of LncRNA HOTAIRM 1 in drug-resistant cells was significantly different from that in parent cells. Overexpression of HOTAIRM 1 significantly increased Beclin-1 protein levels and promoted lenvatinib resistance. It is worth noting that down-regulation of HOTAIRM1 combined with autophagy inhibitors can significantly improve the efficacy of lenvatinib in the treatment of lenvatinib-resistant HCC [39]. Pan *et al*. discovered that LAPTM5 promotes lenvatinib resistance in HCC through an unbiased whole-genome CRISPR-Cas9 screen coupled with database analysis. LAPTM5, located on the lysosomal membrane, controls the formation of autophagolysosomes. Hypomethylation of the LAPTM gene and TP53 mutations drive high expression of LAPTM5 in HCC, which maintains the malignant potential of HCC cells in nutrient-deprived environments by promoting intrinsic macroautophagy/autophagic flux, thereby driving resistance to lenvatinib. Hydroxychloroquine (HCQ) or LAPTM depletion synergistically inhibits tumor growth when combined with lenvatinib. Importantly, inhibiting LAPTM5 or combining HCQ, an autophagy inhibitor that blocks autophagosome-lysosome fusion, with lenvatinib represents a promising strategy to overcome lenvatinib resistance in HCC [40]. NRP1 is a transmembrane glycoprotein that promotes tumor progression by interacting with the targets of TKI inhibitors. Lenvatinib reduces the expression of Neuropilin-1 (NRP1) in HCC through autophagic degradation. However, under hypoxic conditions, hypoxia-inducible factor 1α (HIF-1α) and 2α (HIF-2α) rescue the autophagy-dependent degradation of NRP1 by inhibiting the autophagic process, which has been identified as a key mechanism underlying the loss of lenvatinib efficacy. Therefore, NRP1 may be considered an intriguing molecular target in human HCC to prevent autophagy-related lenvatinib resistance [41].

2.5. Enhanced Cancer Cell Metabolism

A defining characteristic of malignant tumors is their uncontrolled proliferation, leading to a disparity where the body's standard metabolic processes are inadequate to meet their growth demands. In response to this challenge and to adapt to

the harsh environments induced by lenvatinib, HCC cells reorganize their metabolic processes to sustain their survival, proliferation, and dissemination. In contrast to normal cells, which predominantly depend on glucose metabolism for energy, most malignant tumors exploit glucose metabolism alongside a variety of other substances, such as fats and cholesterol, to generate the energy required for their unrestrained growth. To optimize the use of these additional substances, cancer cells regulate the expression of proteins related to metabolic functions, significantly reducing their sensitivity to lenvatinib and promoting drug resistance [42].

Table 1. Mechanisms of lenvatinib resistance.

Molecules	Expression	Target	**Mechanism**	**Ref.**
		HCC cell plasticity		
FZD10	Up	β-catenin/YAP1 axis	Activating β-catenin/YAP1 axis	[10]
TM4SF1	Up	MYH9	Regulating the classic NOTCH pathway	[11]
NOVA2	Up	Wnt	activating the Wnt pathway	[12]
CBX1	Up	IGF-1R	Activating the IGF-1R/AKT/SNAIL axis	[15]
Circ0007386	Up	MiR-507	Preventing the downregulation of cyclin T2	[16]
		Transport process		
EGFR	Up	Stat 3-ABCB 1	Enhancing the exocytosis of tumor cells to lenvatinib	[20]
CircMED27	Up	miR-655-3p	Upregulating USP28-related pathways	[21]
CircPAK1	Up	YAP-14-3-3ζ	Promoting the nuclear localization of YAP.	[22]
		Cell proliferation signaling pathway		
SPP1	Up	Integrins $\alpha V\beta 5$, $\alpha 5\beta 1$, and $\alpha V\beta 1$	Phosphorylating PKCα in the cytoplasmic domain.	[25]
LncNEAT1v1	Up	SOD2	Transforming HCC cells from MEK/ERK-dependent growth to AKT-dependent growth	[26]
KLHL7	Up	RASA2	Constitutively activating the RAS-MAPK signaling pathway.	[29]
		Programmed cell death		
Nrf2	Up		Inadequate ROS accumulation	[34]
LACTB	Down	P53 protein and HSPA8	insufficient ferroptosis,	[35]
Cirpias1	Up	MiR-455-3p/NUPR1	Promoting FTH1 expression, thereby decreasing intracellular Fe2+ and lipid ROS levels	[36]
LncRNA HOTAIRM 1	Up	Beclin-1	Promoting protective autophagy	[39]
LAPTM5	Up	Autophagolysosomes	Promoting intrinsic macroautophagy/autophagic flux	[40]
HIF-1α/HIF-2α	Up	NRP1	Rescue the autophagy-dependent degradation of NRP1	[41]

Continued

Metabolism				
BNIP3	Up	Amp-ENO2	Shifting energy production from mitochondrial oxidative phosphorylation to glycolysis	[43]
NAT10	Up	HSP90AA1	Enhancing ERS	[44]
SREBP2	Up	MTOR	activating the mTOR/IL-1β pathway	[45]

Resistant cells demonstrate a significant advantage in energy competition against sensitive cells. Mechanistically, within a subset of HCC cells, hyperactivation of BNIP3 (BCL2 Interacting Protein 3)-mediated mitophagy shifts energy production from mitochondrial oxidative phosphorylation to glycolysis by modulating the (AMP-Activated Protein Kinase)-ENO2 (Enolase 2) signaling pathway. This process results in the sacrifice of sensitive cells under energy competition conditions and promotes the development and maintenance of lenvatinib resistance [43]. N4-acetylcytidine (ac 4C) represents a relatively rare acetylation modification of mRNA, with NAT10 acting as a lysine acetyltransferase involved in this modification process. Endoplasmic reticulum stress (ERS), a subcellular pathological state triggered by diverse intracellular and extracellular physicochemical factors, manifests primarily as calcium homeostasis disruption and excessive protein synthesis. This phenomenon is accentuated in HCC cells abundant in endoplasmic reticulum, contributing to decreased lenvatinib sensitivity. NAT10 enhances ERS to participate in the process of lenvatinib resistance by regulating the downstream HSP90AA1 mRNA ac 4C modification. Remodelin, a specific small-molecule NAT10 inhibitor, has been identified to inhibit the proliferation of HCC cells and induce their apoptosis, revealing the potential value of Remodelin in reversing lenvatinib resistance by reducing NAT10 activity [44]. Previous studies have demonstrated that abnormal accumulation of cholesterol often leads to poor therapeutic efficacy of TKIs. Mammalian target of rapamycin (mTOR) serves as a key regulator of cell growth, proliferation, and survival. An increase in intracellular cholesterol levels correlates with elevated mTOR phosphorylation. Moreover, elevated cholesterol levels promote the release of a series of inflammatory cytokines, further diminishing the efficacy of TKIs. Fan *et al.* discovered that high expression of sterol regulatory element-binding protein 2 (SREBP2) is associated with poor prognosis in patients with HCC, partly due to SREBP2 reducing lenvatinib efficacy by activating the mTOR/IL-1β pathway. However, betulin, an SREBP2 inhibitor, significantly reduces cellular cholesterol content in HCC cells. Combination treatment with lenvatinib and betulin restores the sensitivity of HCC cells to lenvatinib [45].

3. Summary and Prospect

Lenvatinib, as the second-in-line targeted therapeutic drug for first-line treatment of hepatocellular carcinoma (HCC), demonstrates comparable extended overall

survival (OS) to sorafenib. However, compared to sorafenib, lenvatinib exhibits significantly higher objective response rates, longer progression-free survival, and delayed time to disease progression across all secondary endpoints. Currently, lenvatinib is clinically preferred for the treatment of patients with intermediate to advanced stages of the disease. Although this emerging drug brings new hope to patients with intermediate to advanced stages of the disease, the long-term outlook for lenvatinib is not optimistic, with drug resistance posing a key challenge. In order to solve the dilemma of lenvatinib resistance, it is important to explore the different mechanisms of lenvatinib resistance. In this review, we comprehensively have summarized the recently reported mechanisms of lenvatinib resistance, categorizing them into five primary domains: HCC cell plasticity, abnormal transport processes, abnormal cell proliferation signaling pathways, escaped programmed cell death, and enhanced cancer cell metabolism. By clarifying how drug resistance occurs, we uncover a multitude of viable intervention targets, this extensive range of targets serves as a basis for developing strategies to either block or enhance the activity of these targets, ultimately allowing us to overcome drug resistance.

It is noteworthy that this article highlights drugs capable of alleviating lenvatinib resistance, referred to as lenvatinib sensitizers. An emerging research area focuses on the targeted delivery of active drugs combined with nanoparticles to tumor tissues, aiming to achieve a synergistic therapeutic effect. Looking ahead, the treatment approach of transporting lenvatinib and sensitizers to tumor tissues through advanced nanoscale delivery systems is expected to reverse lenvatinib resistance. Undoubtedly, this approach will offer broader clinical options for the treatment of advanced HCC, ushering in a promising new chapter in the therapeutic landscape of this disease.

Conflicts of Interest

The authors declare no competing interests.

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