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LETTER TO THE EDITOR

Hepatocellular carcinoma resistance to tyrosine kinase inhibitors: Current status and perspectives

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Abstract

The study conducted by Wang *et al*, focuses on the role of Rho GTPase activating protein 12 (ARHGAP12), in hepatocellular carcinoma (HCC). This research reveals that ARHGAP12 expression, markedly elevated in malignant cells of HCC, correlates strongly with adverse outcomes for patients. Furthermore, the study illustrates that ARHGAP12 enhances the ability of HCC cells to invade and contributes to their resistance to tyrosine kinase inhibitors (TKIs) through modulation of the focal adhesion pathway. To comprehensively investigate the relationship between ARHGAP12 and TKI resistance, this study integrates single-cell and bulk RNA sequencing methodologies along with data from tumor immune single-cell hub 2, Gene Expression Omnibus, The Cancer Genome Atlas, CellMiner, Genomics of Drug Sensitivity in Cancer 2, as well as immunohistochemical staining and proteomic analyses. Statistical analyses, including the Wilcoxon rank-sum test and receiver operating characteristic curve analysis, were employed to evaluate the correlation between ARHGAP12 expression levels and clinical parameters, as well as drug sensitivity. It is evident that a more profound exploration of the molecular dynamics of HCC, especially those related to resistance against TKIs, is essential.

Key Words: Tyrosine kinase inhibitor; Hepatocellular carcinoma; Resistance; Cancer therapy; Rho GTPase activating protein 12

Core Tip: This study reveals the potential clinical value of Rho GTPase activating protein 12 (ARHGAP12) and provided the target direction for clinical tyrosine kinase inhibitor resistance and highlights the potential role of ARHGAP12 in drug resistance by revealing its involvement in the focal adhesion pathway. Through gene enrichment and protein-protein interaction network analyses, it was found that ARHGAP12 might regulate integrin beta 1, impacting cell attachment, migration, and cytoskeleton interactions.

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TO THE EDITOR

The recent publication by Wang *et al*[1], in the *World Journal of Gastrointestinal Oncology* presents a significant advancement in understanding the mechanisms underlying resistance to tyrosine kinase inhibitors (TKIs). This seminal research meticulously investigates the elevated levels of Rho GTPase activating protein 12 (ARHGAP12) in malignantly transformed cells of hepatocellular carcinoma (HCC), aiming to unveil its capabilities as a strategic target for mitigating drug resistance. The comprehensive study utilizes an extensive array of data, drawing from diverse databases including specific liver cancer and TKI usage datasets. It intricately details variations in ARHGAP12 expression, scrutinized at the RNA and protein levels through sophisticated techniques such as Bulk-seq and SCNA-SEQ. The research delves into the connections between ARHGAP12 expression and critical clinical outcomes such as tumor progression stages and immune evasion mechanisms. By elucidating these relationships, the study pioneers new pathways for targeted therapeutic interventions in the treatment of drug-resistant HCC, solidifying the position of ARHGAP12 as a pivotal factor in clinical treatment strategies against TKI resistance.

Globally, primary liver cancer ranks as the sixth most prevalent malignancy and is the fourth leading cause of cancer-related deaths. HCC accounts for 75%-80% of all primary liver cancer cases. It is observed that approximately 50%-60% of patients with advanced HCC undergo systemic treatments during their disease management[2-4]. The development of HCC is typically associated with risk factors such as hepatitis virus infections, liver cirrhosis, and genetic predispositions that initiate abnormal signaling leading to increased cellular proliferation. TKIs serve as the first-line treatment for advanced HCC. Although TKI-based systemic therapies have demonstrated certain efficacy in clinical management, the persistent problem of drug resistance remains a significant barrier to improving treatment outcomes. Against this backdrop, the search for novel therapeutic targets has become a key research focus. ARHGAP12, known for its role in regulating cytoskeletal dynamics and cell motility, may be associated with both tumor progression and drug resistance, offering new prospects for HCC treatment[5-8]. Consequently, a thorough investigation into the expression of ARHGAP12 in HCC, its underlying mechanisms, and its relationship to TKI resistance is crucial for the development of more effective therapeutic strategies.

CURRENT SITUATION AND CHALLENGES OF TKI RESISTANCE

In the last decade, Sorafenib has been the initial TKI available for the treatment of advanced HCC. The SHARP study, however, reported an objective response rate for Sorafenib of only 2%[4], highlighting the widespread intrinsic resistance to this treatment in most HCC cases. Recent studies have identified that factors such as epigenetic influences, transport mechanisms, regulated cell death, and the tumor microenvironment play significant roles in the development of resistance to Sorafenib in HCC (Figure 1)[9]. Furthermore, Sorafenib is known to induce ferroptosis, an iron-dependent cell death characterized by intense lipid oxidation and metabolic irregularities, in various cancer cell types, including HCC. Approaches that increase cellular susceptibility to ferroptosis might therefore enhance the effectiveness of TKIs[10].

Currently, systemic treatments based on TKIs, such as Sorafenib, Regorafenib, Lenvatinib, and Donafenib, are prevalently prescribed for patients diagnosed with HCC at Barcelona Clinic Liver Cancer stages B and C. Despite their widespread use, these TKI treatments achieve only a moderate increase in survival rates when administered as single-agent therapies. One of the formidable challenges faced by TKI therapy is the onset of resistance, particularly after prolonged treatment duration. This resistance arises from a complex interplay of factors. For instance, tumor cells might develop resistance by reactivating previously suppressed signaling pathways through genetic mutations or alterations in gene expression, effectively bypassing the inhibitory effects of TKIs. Additionally, the tumor microenvironment plays a crucial role in fostering resistance, with endothelial and stromal cells within it potentially initiating alternative signaling pathways that aid tumor cell survival and proliferation. The diverse nature of HCC further complicates the effectiveness of TKI therapies, leading to variability in treatment responses due to differing levels of sensitivity among individual tumor cells[11].

Despite their notable efficacy in HCC clinical management, TKIs persist in the obstinate issue of resistance, an issue that still requires inquisitiveness and clever approaches to reconcile. We highlight directions for future research that should focus on the development of combination therapies including molecularly targeted drugs, immunotherapies, and

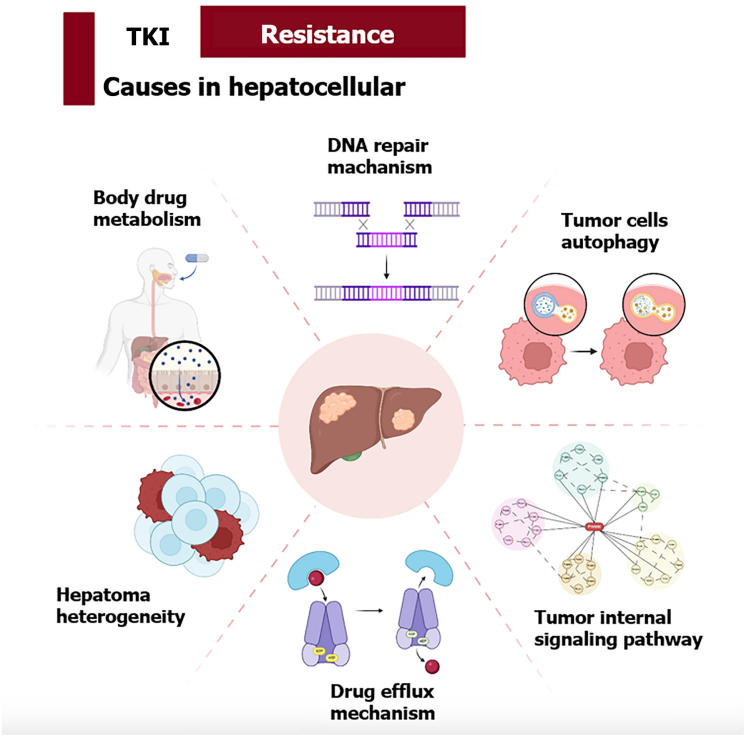

Figure 1 Mechanism of drug resistance in tyrosine kinase inhibitor treatment of hepatocellular carcinoma.

traditional Chinese medicinal approaches that will lead us to tailor treatments and identify breakthrough TKI resistance targets. We anticipate that this approach will lead to better therapeutic outcomes and to an improved quality of life for people with HCC.

A number of recent studies have shown the promising potential of these integrated treatment strategies (Table 1). Combination therapies are increasingly investigated to enhance the treatment of HCC by targeting multiple molecular pathways synergistically. Molecular-targeted drugs such as PKI-587 and Sorafenib play a crucial role in inhibiting phosphorylation within the Ras/Raf/mitogen activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin signaling pathways, thereby curtailing the progression of HCC [12]. The combination of Sorafenib and Dasatinib targets phosphorylation within the Src/FAK pathway and reduces the release of vascular endothelial growth factor, effectively inhibiting HCC progression[13]. Immunotherapy combinations, such as Atezolizumab and Bevacizumab, leverage Bevacizumab's anti-angiogenic properties to disrupt the vascular support of tumors, enhancing therapeutic efficacy[14]. When used in conjunction with programmed death-ligand 1 (PD-L1) inhibitors, this approach further enhances therapeutic efficacy by inhibiting angiogenesis, depriving tumor tissues of essential blood supply, and bolstering the immune system's response against tumors. This dual mechanism effectively impedes the development of HCC[15]. Pembrolizumab and Lenvatinib, through synergistic use of combined therapies, significantly enhance T-cell-mediated anti-tumor responses, modify the tumor microenvironment, and increase T-cell infiltration into tumors, effectively halting the progression of HCC[16]. In the Cabozantinib and Nivolumab combination, Cabozantinib, a small-molecule multi-target TKI[17], when administered alone, notably enhances neutrophil infiltration while reducing the ratio of CD8 + programmed death-1 (PD-1) + T cells within tumors. When combined with PD-1 inhibitors, Cabozantinib amplifies these effects, aiding in the suppression of HCC tumor growth[18]. In conjunction with PD-L1 inhibitors, this therapy enhances outcomes by blocking angiogenesis, which reduces blood supply to tumor cells and strengthens the immune system's ability to combat cancer, thereby effectively hindering HCC progression[15]. The combination of natural medicines, such as the concurrent use of Celastrol and Sorafenib, significantly enhances their synergistic therapeutic effects on HCC. This enhancement is achieved through the strategic inhibition of both the AKT signaling pathway and the vascular endothelial growth factor's autocrine loop. Such dual inhibition substantially enhances Sorafenib's inherent anti-tumor capabilities, leading to more pronounced suppression of HCC progression[19]. The synergistic application of these two drugs notably increases the expression levels of B-cell lymphoma 2-associated X protein, caspase 7, and poly adenosine diphosphate ribose polymerase within HCC cells. This enhancement facilitates the apoptosis of cancer cells in malignant HCC, effectively curtailing tumor progression[20]. Bufalin synergistically enhances Sorafenib's anti-tumor efficacy, primarily through inhibition of the AKT signaling pathway and promotion of apoptotic processes. By suppressing Sorafenib-induced AKT activation, Bufalin effectively reverses Sorafenib resistance in HCC cells[21]. Moreover, optimal therapy combinations and the development of novel biomarkers are required to boost the clinical benefit from TKI-based treatments in HCC management[22].

Table 1 Advances in hepatocellular carcinoma drug combinations

Drug combination	Drugs
Combinations of molecular-targeted drugs	PKI-587 + Sorafenib
	Sorafenib + Dasatinib
Combinations of immunotherapy drugs	Atezolizumab + Bevacizumab
	Pembrolizumab + Lenvatinib
	Cabozantinib + Nivolumab
Combinations of natural medicines	Celastrol + Sorafenib
	Bufalin + Sorafenib

ARHGAP12: A POTENTIAL DRUG TARGET

ARHGAP12, classified as a Rho GTPase-activating protein, is instrumental in the regulation of GTP hydrolysis by Rho GTPases through its specific Rho GAP domain, impacting cellular dynamics related to the cytoskeleton and migration [23]. This protein's elevated expression in HCC is strongly associated with both tumor progression and a diminished response to conventional therapies. By activating key signaling pathways such as PI3K/Akt and MAPK/extracellular signal-regulated kinase, ARHGAP12 drives cellular proliferation and fosters mechanisms that resist apoptotic cell death, thereby undermining the therapeutic efficacy of TKIs. Moreover, ARHGAP12 potentially boosts resistance by upregulating drug efflux mechanisms, notably P-gp, which leads to reduced intracellular levels of TKIs and strengthens the cancer cells' defensive responses against these drugs. The role of ARHGAP12 extends to modifying the tumor microenvironment in ways that support tumor growth and enhance invasive capabilities. Given its pivotal role in conferring TKI resistance, targeting ARHGAP12 offers a promising strategy for counteracting resistance in HCC and devising innovative treatment modalities[24-26].

To build upon the premise that ARHGAP12 may serve as a potential therapeutic target, Wang *et al*[1] conducted a comprehensive assessment of its expression in relation to tumor progression and drug resistance. Specifically, they utilized single-cell sequencing to measure ARHGAP12 mRNA levels across various cell types, supplemented by tumor immune single-cell hub 2 database analyses to delineate expression differences in distinct cellular populations. Bulk RNA-seq data, combined with information from the Gene Expression Omnibus database, provided further insights into ARHGAP12 expression profiles in diverse populations and HCC tissues, with DAVID enrichment analysis shedding light on its underlying molecular mechanisms. Additionally, the protein-level expression of ARHGAP12 was confirmed through immunohistochemical staining of 816 tissue samples, integrated with proteomic data from the Proteomics Data Commons. To evaluate the clinical relevance of ARHGAP12 and its impact on drug sensitivity, Wang *et al*[1] employed datasets from The Cancer Genome Atlas, CellMiner, and Genomics of Drug Sensitivity in Cancer 2, applying statistical methods such as the Wilcoxon rank-sum test and receiver operating characteristic curve analyses. These findings collectively underscore ARHGAP12's potential role in HCC progression and TKI resistance, highlighting its promise as both a diagnostic biomarker and a therapeutic target. Nevertheless, to solidify these findings, the integration of clinical sample analyses using qRT-PCR and Western Blot is recommended to enhance the reliability of the data and provide a more detailed correlation with patient clinical outcomes.

Clarifying the connection between the mechanistic alterations of ARHGAP12 and its role in drug resistance is essential for understanding therapeutic challenges in HCC. Analyzing the intersections between the mechanisms of ARHGAP12 and pharmacological responses could provide valuable insights into resistance mechanisms. A detailed study[1] incorporated gene enrichment analyses centered on ARHGAP12, alongside PPI network assessments and evaluations of gene expression variations linked to TKI resistance. This research pinpointed the focal adhesion (FA) pathway as crucially involved due to ARHGAP12's influence. ARHGAP12 is thought to regulate this pathway by controlling integrin beta1, which in turn affects cellular adherence, migration, and cytoskeletal interactions. In particular, ARHGAP12's ability to modulate Rho GTPase activity and influence the interactions of integrins with their ligands could substantially impact cellular behaviors crucial for migration, tissue repair, and the metastatic spread of tumors.

CONCLUSION

In HCC, ARHGAP12 is markedly upregulated, particularly in tumors that exhibit TKI resistance. This elevated expression suggests a central role for ARHGAP12 in driving or sustaining resistance, likely through its influence on the FA pathway. To fully validate ARHGAP12 as a therapeutic target, further investigations—encompassing preclinical functional assays, *in vivo* studies, and clinical trials—are needed. Elucidating the precise mechanisms by which ARHGAP12 contributes to TKI resistance may pave the way for novel treatment strategies aimed at improving patient outcomes and overcoming current therapeutic limitations.

FOOTNOTES

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