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Hepatocellular carcinoma resistance to Tyrosine Kinase Inhibitors: Current status and perspectives

Miao YR *et al*. Drug resistance and treatment of HCC

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Abstract

The study conducted by Wang *et al*. and published in the World Journal of Gastrointestinal Oncology, focuses on the role of ARHGAP12, a Rho GTPase activating protein, 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 (FA) pathway. It is evident that a more profound exploration of the molecular dynamics of hepatocellular carcinoma, 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 ARHGAP12 and provided the target direction for clinical TKI resistance and highlights the potential role of ARHGAP12 in drug resistance by revealing its involvement in the Fanconi anemia (FA) pathway. Through gene enrichment and protein-protein interaction network analyses, it was found that ARHGAP12 might regulate ITGB1, impacting cell attachment, migration, and cytoskeleton interactions.

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 behind resistance to TKIs. This seminal research meticulously investigates the elevated levels of ARHGAP12 in malignantly transformed cells of 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.

INTRODUCTION

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, including sorafenib and lenvatinib, are particularly effective in targeting VEGFR and other critical kinases such as PDGFR and c-KIT. These inhibitors work by disrupting the tumor's vascular support and cell growth mechanisms, curtailing angiogenesis, and substantially slowing the progression of the disease, thereby enhancing patient survival rates. [5-8]

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 BCLC 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 durations. 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, PIs there persists 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 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 (see Table 1). Combination therapies are increasingly investigated to enhance the treatment of hepatocellular carcinoma

(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/MAPK and PI3K/AKT/mTOR 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]. The combination of Tremelimumab and Nivolumab, where Tremelimumab targets CTLA-4 on T cell surfaces, significantly enhances T cell activity when used with anti-PD-1 antibodies. This synergy not only strengthens anti-tumor immune responses but also aids in suppressing HCC progression [14, 15]. Immunotherapy combinations, such as Atezolizumab and Bevacizumab, leverage Bevacizumab's anti-angiogenic properties to disrupt the vascular support of tumors, enhancing therapeutic efficacy [16]. When used in conjunction with 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 hepatocellular carcinoma [17]. Durvalumab and Tremelimumab combination, where Tremelimumab targets CTLA-4 to suppress its activity, significantly enhances T cell functionality and strengthens the body's anti-tumor immune response. In the HIMALAYA trial, patients with advanced hepatocellular carcinoma showed improved overall survival when treated with this combination therapy, known as the STRIDE regimen, demonstrating superior efficacy compared to those treated with Sorafenib [18]. The therapeutic strategy combining Nivolumab and Ipilimumab, anti-CTLA-4 antibodies with anti-PD-1 antibodies, significantly boosts T-cell activity and enhances immune responses against tumors. Administered in the CheckMate 040 trial to patients with advanced hepatocellular carcinoma, this approach showed notable efficacy [19]. 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 hepatocellular carcinoma

[20]. Cabozantinib and Nivolumab combination, where Cabozantinib, a small-molecule multi-target TKI [14], when administered alone, notably enhances neutrophil infiltration while reducing the ratio of CD8+PD1+ T cells within tumors. When combined with PD-1 inhibitors, Cabozantinib amplifies these effects, aiding in the suppression of hepatocellular carcinoma tumor growth [21]. Bevacizumab and Atezolizumab, leveraging Bevacizumab's recognized anti-angiogenic properties, disrupt the vascular supply to tumors [16]. 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 hepatocellular carcinoma progression [17]. The combination therapy of Ramucirumab and Durvalumab suppresses tumor angiogenesis and amplifies immune checkpoint inhibition, effectively halting the proliferation of hepatocellular carcinoma cells [14]. Combinations of natural medicines, such as Sorafenib and cucurbitacin B (CuB), a natural tetracyclic triterpenoid from the Cucurbitaceae family, demonstrate a synergistic effect in treating hepatocellular carcinoma. This combination effectively inhibits STAT3 phosphorylation, thereby curtailing the advancement of hepatocellular carcinoma [22]. Utilizing Celastrol in conjunction with Sorafenib significantly enhances their combined therapeutic impact on hepatocellular carcinoma. This enhancement occurs through a strategic blockade of both the AKT signaling pathway and the VEGF autocrine loop. Such dual inhibition substantially enhances Sorafenib's inherent anti-tumor capabilities, leading to more pronounced suppression of hepatocellular carcinoma progression [23]. The synergistic application of these two drugs notably increases the expression levels of B-cell lymphoma 2-associated X protein (Bax), caspase 7, and poly ADP ribose polymerase (PARP) within hepatocellular carcinoma cells. This enhancement facilitates the apoptosis of cancer cells in malignant hepatocellular carcinoma, effectively curtailing tumor progression [24]. Curcumin targets and inhibits thrombin, which reduces P300-mediated histone acetylation within the promoter region of TGF-β1. Concurrently, anti-PD-1 therapy blocks the interaction between PD-1 and PD-L1, preventing their binding.

Together, these agents synergistically refine the tumor immune microenvironment, significantly halting the advancement of hepatocellular carcinoma [25]. Moreover, optimal therapy combinations and development of novel biomarkers are required to boost the clinical benefit from TKI-based treatments in HCC management[26].

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[27]. 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/ERK, 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[28-30].

To assess ARHGAP12 as a potential therapeutic target, a comprehensive evaluation of its expression relative to tumor characteristics is imperative. According to Wang's study[1], ARHGAP12 demonstrates elevated expression in malignant hepatocellular carcinoma cells, as substantiated by single-cell and Bulk-seq sequencing analyses, with further validation at the protein level *via* immunohistochemistry[1]. Nevertheless, to solidify this finding, 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. Wang's research highlights the

significant association between increased ARHGAP12 expression and the advancement of clinical pathological features, underscoring its potential role in tumorigenesis.

Clarifying the connection between the mechanistic alterations of ARHGAP12 and its role in drug resistance is essential for understanding therapeutic challenges in hepatocellular carcinoma. 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 FA pathway as crucially involved due to ARHGAP12's influence. ARHGAP12 is thought to regulate this pathway by controlling ITGB1, 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, there is a notable increase in the expression of ARHGAP12, especially in cases that are resistant to TKIs. This elevation points to a potentially pivotal role for ARHGAP12 in fostering resistance within HCC. The influence of ARHGAP12 on the FA pathway might be crucial for maintaining the TKI-resistant phenotype. Nonetheless, additional experiments are required to definitively determine the suitability of ARHGAP12 as a therapeutic target for HCC.

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