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Review Article

Targeting PIN1 enzyme for pancreatic cancer

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Abstract: Hepatocellular carcinoma (HCC) is a major global health concern, ranking as the fourth most common cancer in men and eighth in women, with an alarming mortality rate. Despite advances in medical interventions, including surgical resection, liver transplantation, and molecular-targeted therapies like sorafenib and lenvatinib, outcomes for advanced HCC remain suboptimal. Protein phosphorylation and isomerization have emerged as critical regulators of cancer progression, with the peptidyl-prolyl cis-trans isomerase PIN1 playing a significant role in hepatocarcinogenesis. PIN1 is implicated in the stability and activity of key oncogenic and tumor suppressor proteins, driving uncontrolled cell proliferation and tumor growth in HCC. This review explores the molecular mechanisms by which PIN1 facilitates HCC progression, focusing on its interaction with cyclin D1 and its role in oncogenic signaling pathways. The research also highlights the potential of targeting PIN1 as a therapeutic strategy. Preclinical studies showed that PIN1 inhibition reduces tumor growth, induces cell death, and enhances survival in animal models. Moreover, PIN1 inhibitors like API-1, ATRA, and ATO have demonstrated promising anti-proliferative effects on HCC cells, paving the way for novel treatment avenues. Given the resistance challenges to current therapies like sorafenib, combining PIN1 inhibitors with existing drugs may offer enhanced efficacy and mitigate resistance. Further research is essential to understand PIN1-mediated pathways in drug resistance and to optimize PIN1-targeted therapies for clinical use. This review underscores the therapeutic potential of PIN1 inhibition in improving outcomes for HCC patients.

Keywords: Hepatocarcinogenesis PIN1; PIN 1 and cyclin D1; PIN 1 and sorafenib; PIN 1 and Atra; PIN 1 and ATO; PIN 1 and API-1

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Hepatocellular carcinoma (HCC) ranks fourth most commonly occurring cancer in men and eighth most commonly occurring cancer in women worldwide. At about 750,000 new cases per year, it is also the third most often occurring cause of cancer-related mortality. Having a 4-year overall survival rate of just 20%, HCC patients have a poorer prognosis than other common malignancies like stomach (29%), breast (85%), colon (70%), and prostate (92%)[1]. Strong risk factors for HCC are liver cirrhosis, frequent alcohol consumption, and prior infection with either hepatitis B or C. Genetic modifications and metabolic anomalies trigger many signaling pathways supporting malignancy, thereby directing the cellular level growth of HCC. The complex network of cancer cell signaling pathways causes unfavorable therapeutic results and quick clinical development of the illness. Early-stage HCC can be treated curatively with radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), liver transplantation, and surgical resection[2]. For advanced HCC, the molecular-targeting medications authorized by the Food and Drug Administration (FDA) include regorafenib, lenvatinib, and cabozantinib. Regorafenib and cabozantinib are second-line therapies for those exhibiting resistance to sorafenib; sorafenib, similar to lenvatinib, is advised as a first-line treatment for advanced cases[3]. Aiming for a spectrum of tyrosine kinases, these inhibitors boost general survival and enhance therapeutic effectiveness over sorafenib. Protein phosphorylation and dephosphorylation are essential for the control of cancer signaling pathways. Protein regulation involves the addition of phosphate groups to serine or threonine residues that come before proline (pSer/Thr-Pro) by mitogen-activated protein kinases (MAPKs) and cyclin-dependent kinases (CDKs). Conformational changes brought forth by PIN1-mediated isomerization influence the interactions, subcellular localization, and stability of these proteins[4]. Among the biological processes under the impact of this system are cell cycle progression, differentiation, proliferation, death, and transformation. PIN1 has so been connected to various diseases, including Alzheimer's and cancer as well. Its overexpression connects uncontrolled cell proliferation, carcinogenesis, and the advancement of cancer to each other[5]. More than 45% of HCC patients were revealed to have PIN1 overexpression. Advanced HCC does not currently have any effective molecular-targeted treatments or conventional chemotherapy replacements. One interesting approach for treating HCC is targeting PIN1[6]. This review explores PIN1 in the development of HCC and emphasizes the likely advantages of PIN1 inhibition as a therapy strategy.

2. HEPATOCARCINOGENESIS: PIN1'S FUNCTIONS

The fact that non-tumorigenic human liver cells become malignantly under overexpression of PIN1 marks the first hint that PIN1 is involved in promoting HCC formation. Driven by PIN1, a process known as isomerization helps PIN1 regulate the related proteins' oncogenic activity, hence contributing to hepatocarcinogenesis. Furthermore, PIN1 is identified to control the stability and activity of various significant tumor suppressors and oncogenes related to HCC. The disruption of these crucial proteins by PIN1 eventually leads to uncontrolled cell proliferation and cancer growth. Thus, a reasonable therapeutic approach to treat HCC and retard its spread seems to be PIN1 targeting. Two favorable outcomes of preclinical research on animal models of HCC include lowering tumor development and increasing survival rates when PIN1 activity is inhibited[7]. In targeting PIN1, researchers hope to interrupt the complex network of protein interactions causing hepatocarcinogenesis, hence retarding tumor development and its spread. Particularly for treating liver cancer, further research is required to completely grasp PIN1's function in HCC and create efficient therapy plans specifically targeting this protein. Targeting drugs specifically target PIN1 for HCC might significantly raise patient outcomes.

3. PIN1 AND CYCLIN D1

Cyclin D1 is pivotal as a cell cycle regulator and a key target of the peptidyl-prolyl cis-trans isomerase PIN1[8]. Dysregulation of cyclin D1 is frequently associated with various types of cancers, including hepatocellular carcinoma (HCC). Cyclin D1 production is critical for cell cycle progression, particularly the transition from the G1 to S phase, which drives cellular proliferation. PIN1 interacts with cyclin D1 to enhance its stability through isomerization, promoting its accumulation in the nucleus and facilitating its role in transcriptional activation[9]. This stabilization also impacts key signaling pathways, such as NF-κB, c-Jun, and β-catenin, further amplifying cyclin D1 expression and boosting cell proliferation. In the context of HCC, PIN1 overexpression has been strongly correlated with elevated levels of cyclin D1. This interaction promotes tumor growth by enhancing cell division and plays an initiating role in hepatocarcinogenesis. Evidence from multiple studies stresses this relationship, showing that PIN1-mediated stabilization of cyclin D1 contributes significantly to the development and progression of HCC. These findings highlight the critical role of the PIN1-cyclin D1 axis in cancer biology, suggesting that targeting this pathway could offer a novel therapeutic approach. Future research must unravel the precise mechanisms by which PIN1 modulates cyclin D1 in HCC and identify potential inhibitors that could disrupt this interaction. Such advancements could pave the way for targeted therapies aimed at mitigating cyclin D1-driven tumor progression in liver cancer.

4. DESIGN OF PIN1 INHIBITORS FOR TREATMENT OF HCC

PIN1 is a desired therapeutic target for HCC therapy. Early studies have shown that reducing PIN1 expression in HCC cells by RNA interference slows cell proliferation, stops colony growth on soft agar, and causes caspase-mediated death[10]. Furthermore, in a xenograft mouse model of HCC, PIN1 knockdown delays tumor development and results in tumor cell death[11,12]. Changing the catalytic structure allows covalent inhibitors of PIN1 to block its PPIase domain, reducing its activity[13] permanently. On the other hand, non-covalent inhibitors usually bind competitively to the PIN1 domain, lowering its effect. Among them are API-1, PiB, ATRA, and ATO. These non-covalent inhibitors show promise as HCC treatments according to preclinical studies. Competitively reducing PIN1 activity has significantly reduced tumor formation in xenograft mice models[14]. Before clinical trials for patients with HCC, further study is required to completely understand the activities of these inhibitors and related negative effects. For this aggressive form of liver cancer, targeting PIN1 with covalent or non-covalent inhibitors is a promising treatment. The novel covalent PIN1 inhibitor KPT-6566 has demonstrated the ability to degrade PIN1 proteins, inhibiting the proliferation of cancer cells, including those originating from the breast, prostate, lung, and pancreas[15]. Furthermore, demonstrating that KPT-6566 has

more selective PIN1 inhibitory activity, PIN1-expressing cells show higher anti-proliferative impact than PIN1-silenced cells. However, its strong anti-proliferative effects on cancer cells and extensive clinical and preclinical investigations in humans and animal models have not yet confirmed the safety and effectiveness of these inhibitors for treating cancer in humans.

5. PIN1 AND SORAFENIB

Sorafenib, a multi-tyrosine kinase inhibitor, is approved for advanced HCC by the FDA for first-line treatment. In HCC, sorafenib lowers VEGF receptor tyrosine kinase signaling pathways and RAF/MEK/ERK, producing cell death, inhibition of cell division, tumor development, and angiogenesis reduction[16]. This process drives death, reduces Mcl-1 protein expression, and ends cell development. Although there is no evidence between PIN1 and Mcl-1 in human breast tissue, HCC usually shows abnormal Mcl-1 expression. Furthermore, lowering Rb phosphorylation in HCC cells by sorafenib lowers PIN1 mRNA and protein levels. Since phosphorylated Rb releases E2F, targeting the Rb-E2F pathway helps sorafenib to reduce PIN1 expression. Moreover, cell death induced by sorafenib is more obvious in HCC cells lacking PIN1, indicating that sorafenib might not affect all PIN1-interacting proteins involved in HCC pathogenesis. Although the response rate is still modest, clinical studies showed that sorafenib monotherapy increases general survival for patients with HCC, even with a 12-week survival rate[17]. Either sorafenib monotherapy may induce sorafenib resistance to develop or help reduce the HCC cells' metastases. Combining studies on sorafenib and other PIN1 inhibitors could lower the incidence of treatment resistance and metastases in patients with HCC and boost general survival. Targeting many pathways connected to tumor development and metastases, sorafenib may be more effective in treating HCC when administered with PIN1 inhibitors. Apart from overcoming sorafenib resistance, this combo therapy strategy lowers the possibility that HCC cells become more aggressive and spread to other body organs. Investigating the safety and efficacy of treating HCC patients with sorafenib in combination with PIN1 inhibitors is still much needed.

6. PIN1 AND ATRA

First found to be a therapy for acute promyelocytic leukemia (APL), All-Trans Retinoic Acid (ATRA) stops APL cells from multiplying via the promotion of terminal differentiation[18]. Direct binding of ATRA to the PIN1 PPIase domain produces PIN1 protein degradation and inhibition of PIN1 isomerase[19]. ATRA-induced degradation of PIN1 inhibits many cancer-promoting pathways and APL cell proliferation, both *invivo* and *in vitro*. The fact that ATRA does not affect healthy liver cells indicates its selective behavior for HCC cancer cells even more. Using PIN1 protein degradation, ATRA reduces HCC cell motility, invasion, and lung metastases. Encapsulating ATRA in vitamin A pellets in their acidic state has produced a slow-release version. Comparatively, to free ATRA, this showed more stability in animals and maintained constant plasma ATRA levels over time. A minimal effective dosage can minimize the negative effects of the slow-releasing ATRA formulation on animals. More importantly, in the xenograft mouse model of HCC, it has been demonstrated that the slow-releasing ATRA formulation reduces tumorigenicity in addition to causing PIN1 degradation[20]. ATRA's novel controlled release formulation has demonstrated an enhanced anti-proliferative action on HCC cells. ATRA is a potential therapeutic agent aiming at PIN1 for treating HCC; thus, producing a stable, encapsulated version of ATRA is a good approach to improve its effectiveness and safety.

7. PIN1 AND ATO (ARSENIC TRIOXIDE)

The FDA has approved arsenic trioxide (ATO) as therapy for acute promyelocytic leukemia (APL) resistant to or recurrences following ATRA treatment. To combat cancer, ATO mainly aids in the degradation of several carcinogenic proteins, such as cyclin D1 in mantle cell lymphoma, PML-RARA in APL, and NPM-ALK in anaplastic large cell lymphoma[21]. ATO inhibits the *invivo* and *invitro* proliferation of breast cancer cells through the degradation of PIN1[22]. It affects several carcinogenic processes under the control of PIN1 genic pathways. ATO induces caspase-dependent death in hepatocellular carcinoma (HCC) cells, thereby arresting the cell cycle and suppressing the growth of the xenograft tumor. The transmembrane arsenic transporter Aquaporin 9 (AQP9) regulates cellular uptake of ATO, hence reducing its detrimental impact[23]. The expression level of AQP9, which varies by cancer cell type, is strongly linked with ATO-induced cell death. Raising of AQP9 expression, ATO could have a stronger cytotoxic effect on cancer cells. In addition to its PIN1-inhibitory effect, ATRA was demonstrated to enhance AQP9 expression, facilitating ATO uptake into the cells. ATO and ATRA increase cellular absorption of ATO more effectively than each treatment itself. In laboratory and animal trials, this generates lower PIN1 expression, blockage of various PIN1-regulated oncogenic pathways, and suppresses breast cancer cell development[24].

8. PIN1 AND API-1

Most PIN1 inhibitors have a PIN1-dependent anti-proliferative effect on cancer cells; cells expressing PIN1 exhibit more decline in cell proliferation than those lacking PIN1. Recent research indicates that the strong anti-proliferative activity of API-1, a new PIN1 inhibitor, on HCC cells needs PIN1 expression and XPO5 phosphorylation. In HCC cells expressing more PIN1, API-1 treatment reacts better than those with either declining XPO5 phosphorylation or lower PIN1 levels[25]. Pre-miRNA export from the nucleus to the cytoplasm has been enabled by inhibiting PIN1, which also restores the synthesis of tumor-suppressive miRNAs in HCC cells. Thus, API-1 treatment of HCC cells stops the development of xenograft tumors and lowers cell proliferation via restoring PIN1-impaired miRNA synthesis. Since API-LP does not necrotize the tissues of the main organs of mice—including the kidney, liver, spleen, heart, or lung—it does not seem to be fatal to mice[26]. The liposomal formulation presents fresh approaches to create a powerful PIN1 inhibitor that is more efficient against HCC in people and animals and better absorbed by the body[27]. More studies are thus required to ascertain how API-LP treats HCC patients safely and effectively. This hopeful study suggests that API-LP could one day be a suitable therapeutic option for HCC sufferers. The absence of toxicity in key organs of API-LP suggests that it might be well tolerated in clinical trials involving people, offering one significant advantage. With more study and development, API-LP might offer a fresh and effective treatment for HCC sufferers, therefore offering hope for improved outcomes in the fight against this aggressive form of cancer. Furthermore, API-LP has encouraging effects in retarding tumor development and encouraging cell death in HCC cells.

9. CONCLUSION

Targeting PIN1 is a viable therapeutic strategy against HCC due to its carcinogenic influence on hepatocarcinogenesis. High-throughput screening technologies facilitate the identification of novel and potent PIN1 inhibitors from various chemical compound libraries. Nonetheless, the therapeutic significance of PIN1 inhibitors is contingent not only upon their anti-cancer efficacy but also on them in vivo bioavailability. The limited water solubility and chemical instability of certain PIN1 inhibitors constrain their therapeutic uses. According to a randomized clinical study, regorafenib improved overall survival in patients with HCC who had progression after first-line sorafenib therapy. The correlation between PIN1 expression and acquired regorafenib resistance in HCC remains unclear; nonetheless, investigating PIN1's role in drug resistance in HCC is an intriguing avenue for research. Before exploring the potential of further PIN1 inhibitors as a second-line treatment for drug-resistant HCC, we must enhance our understanding of the molecular mechanisms via which PIN1 facilitates drug-resistant malignancy. Further investigation into the correlation between PIN1 expression and regorafenib resistance may yield interesting novel therapeutic strategies for patients unresponsive to first-line medications. Targeting PIN1 is a promising strategy to mitigate medication resistance and enhance patient outcomes in hepatocellular carcinoma (HCC). Examining the mechanisms behind PIN1-mediated resistance will assist doctors in improving treatment options and the effectiveness of second-line therapies for this aggressive cancer type.

10. AUTHORS CONTRIBUTION STATEMENT

Aswinprakash Subramaniam, Vinoth Kumar Selvaraj wrote the initial draft. Jagadeesh Dhamodharan, and Ragesh Gurumoorthy contributed to critical revision and supervision. All authors reviewed the manuscript.

11. CONFLICT OF INTEREST

Conflict of interest declared none.

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