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Repurposing Antiallergic Drug Desloratadine as a Potential Treatment for Hepatocellular Carcinoma: Short Commentary

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Abstract: **Hepatocellular carcinoma (HCC) remains a significant global health challenge despite advancements in treatment. Drug repurposing offers a promising approach to discovering novel therapies efficiently. Desloratadine, an FDA-approved antiallergic medication, has shown anticancer properties in HCC. This Short commentary elucidates desloratadine's mechanisms in HCC treatment, identifying its inhibition of N-myristoyl transferase 1 (NMT1) as pivotal. Through disrupting NMT1-mediated myristoylation, desloratadine inhibits the NFκB/Bcl-2 signaling pathway, suppressing HCC progression. Additionally, NMT1 and Visinin-like protein 3 (VILIP3) are identified as significant in HCC, offering potential prognostic biomarkers and therapeutic targets. The findings advocate for exploring desloratadine's efficacy in clinical trials, potentially revolutionizing HCC therapy and underscoring the value of drug repurposing in oncology. Further research is warranted to validate biomarkers, optimize treatment strategies, and enhance drug delivery systems for improved patient outcomes.**

Keywords: Hepatocellular carcinoma, Potential Treatments, **Desloratadine, Antiallergic Drugs, Cell Proliferation.**

1. INTRODUCTION

Hepatocellular carcinoma (HCC) poses a significant global health burden, being one of the most prevalent and lethal malignancies worldwide. Despite advancements in treatment options, including surgical resection and targeted therapies like sorafenib, the prognosis for advanced-stage HCC remains grim. Consequently, there's an urgent need to explore novel therapeutic strategies to combat this aggressive cancer[1]. Drug repurposing, which investigates existing drugs for new therapeutic applications, presents a promising avenue in oncology research. By leveraging approved drugs with known safety profiles, drug repurposing can expedite the drug development process and potentially overcome the challenges associated with traditional drug discovery. Desloratadine, an FDA-approved antiallergic medication, emerged as a candidate for repurposing based on its demonstrated anticancer properties in hepatocellular carcinoma. This article delves into a study that elucidated the anticancer mechanisms of desloratadine in HCC and explored its therapeutic potential as a repurposed drug. The study, which was published in Signal Transduction and Targeted Therapy (2023) at www.nature.com/sigtrans, commenced with screening a compound library comprising 419 FDA-approved drugs to identify potential anticancer agents for HCC treatment. Desloratadine exhibited significant inhibitory effects on HCC cell proliferation across various in vitro and in vivo models, prompting further investigation into its mechanism of action[2].

2. RESULTS

Desloratadine's anticancer activity has been attributed to its inhibition of N-myristoyl transferase 1 (NMT1), a key enzyme involved in protein myristoylation. Through drug affinity responsive target stability (DARTS) and mass spectrometry analysis, NMT1 was identified as a target protein of desloratadine. By disrupting NMT1-mediated myristoylation, desloratadine impedes the activation of the NFκB/Bcl-2 signaling pathway, thereby suppressing HCC progression. Mechanistic studies have unveiled that desloratadine exerts its anticancer activity by targeting N-myristoyl transferase 1 (NMT1), a critical enzyme involved in protein myristoylation[3]. Through drug affinity responsive target stability (DARTS) and mass spectrometry analysis, NMT1 emerged as a direct target of desloratadine. By disrupting NMT1-mediated myristoylation, desloratadine effectively impedes the activation of the NFκB/Bcl-2 signaling pathway, thereby suppressing HCC progression. By targeting NMT1-mediated myristoylation and downstream signaling pathways, desloratadine exhibits potent anticancer effects both in vitro and in vivo. Moreover, the identification of NMT1 and VILIP3 as key players in HCC progression highlights their potential as prognostic biomarkers and therapeutic targets. Furthermore, the study elucidated a significant correlation between elevated NMT1 expression and poor prognosis in HCC patients, underscoring the clinical relevance of targeting NMT1 as a therapeutic strategy. Additionally, the identification of Visinin-like protein 3 (VILIP3) as a novel substrate of NMT1 provided insights into the intricate molecular pathways driving HCC pathogenesis[4].

Implications of The Study

The findings of this study hold significant implications for the treatment landscape of hepatocellular carcinoma (HCC). The repurposing of desloratadine, an FDA-approved antiallergic drug, as a potential anticancer agent underscores the importance of exploring alternative therapeutic avenues for cancer treatment. If validated in clinical trials, desloratadine could offer a novel and accessible treatment option for HCC patients, particularly those who are refractory to current therapies or ineligible for surgical intervention. The identification of N-myristoyl transferase 1 (NMT1) and Visinin-like protein 3 (VILIP3) as key molecular targets in HCC sheds light on the intricate mechanisms driving hepatocarcinogenesis. These insights have implications for the development of precision medicine approaches in HCC management[5]. Targeting NMT1-mediated myristoylation and downstream signaling pathways, either alone or in combination with existing therapies, could pave the way for personalized treatment strategies tailored to the molecular profiles of individual patients. The study's findings regarding the prognostic significance of NMT1 and VILIP3 in HCC underscore the potential utility of these molecules as prognostic biomarkers. Their expression levels could serve as valuable indicators of disease progression and treatment response, aiding in patient stratification and clinical decision-making. Further validation of these biomarkers in larger patient cohorts could facilitate their integration into routine clinical practice, enabling more precise prognostication and personalized treatment selection in HCC[6]. The success of desloratadine as a repurposed drug for HCC exemplifies the potential of drug repurposing as a cost-effective and time-efficient strategy in drug discovery and development. By leveraging existing drugs with known safety profiles, researchers can expedite the translation of promising therapeutic candidates from bench to bedside, addressing unmet medical needs promptly. This paradigm shift in drug development emphasizes the importance of reimagining the therapeutic potential of existing pharmacological agents across diverse disease contexts, fostering innovation and improving patient care.

Future Directions

The next step involves conducting clinical trials to validate desloratadine's efficacy and safety in treating hepatocellular carcinoma (HCC) patients. These trials should encompass diverse patient populations to assess the drug's effectiveness across different HCC subtypes and stages. Exploring the potential synergistic effects of desloratadine with existing HCC treatments, such as sorafenib or immunotherapy, could enhance therapeutic outcomes. Combinatorial approaches may overcome drug resistance and improve patient responses. Further research is needed to validate NMT1 and VILIP3 as prognostic biomarkers for HCC. Assessing their expression levels in larger patient cohorts and correlating them with clinical outcomes would strengthen their utility in predicting disease progression and guiding treatment decisions. Delving deeper into the molecular mechanisms underlying desloratadine's anticancer effects can uncover additional therapeutic targets and pathways implicated in HCC progression. Comprehensive mechanistic studies may identify novel drug targets for future therapeutic interventions. Investigating optimal dosing schedules and treatment durations for desloratadine administration in HCC patients is crucial. Understanding the pharmacokinetics and pharmacodynamics of desloratadine can optimize treatment regimens to maximize efficacy and minimize adverse effects. Exploring innovative drug delivery systems, such as nanoparticles or hydrogels, to enhance the bioavailability and tumor-targeting efficiency of desloratadine could improve therapeutic outcomes while minimizing systemic toxicity.

3. CONCLUSION

The study highlights desloratadine as a promising candidate for repurposing in HCC therapy. By targeting NMT1-mediated myristoylation and downstream signaling pathways, desloratadine demonstrates potent anticancer effects both in vitro and in vivo. Moreover, the identification of NMT1 and VILIP3 as key players in HCC progression underscores their potential as prognostic biomarkers and therapeutic targets. The findings offer valuable insights into the repurposing of existing drugs for cancer treatment, emphasizing the importance of exploring alternative therapeutic avenues to improve patient outcomes in hepatocellular carcinoma. Further clinical studies are warranted to validate the efficacy and safety of desloratadine as a repurposed drug in HCC patients, potentially paving the way for innovative therapeutic strategies in liver cancer management.

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Abbreviations

HCC Hepatocellular Carcinoma

NMT1 N-myristoyl Transferase 1

VILIP3 Visinin-like Protein 3

DARTS Drug affinity responsive target stability

FDA Food and Drug Administration

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