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HBV Covalently Closed Circular DNA Targeting by Plant-Derived Chemical Agent: Exploring the Potential of Coumarins

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Abstract

Hepatitis B virus (HBV) infection remains a global health concern, with persistent covalently closed circular DNA (cccDNA) hindering curative treatments. Coumarin is one of these natural compounds that could be utilized as a pharmaceutical agent due to its stability, solubility, availability and low toxicity. Previous studies demonstrate their efficacy, but the challenges of specificity and resistance remain unexplored. Further research is needed to unlock coumarins full potential as antiviral agents for chronic HBV infection and removal of cccDNA from infected hepatocytes.

Keywords: Hepatitis B Virus; HBV cccDNA; Chronic HBV infection; coumarins; Antiviral Therapy; Combination Therapy

Introduction

Chronic HBV infection is a major public health challenge, affecting an estimated 257 million individuals globally. The fact that cccDNA, a stable and persistent form of HBV DNA that reside in the nuclei of hepatocytes as an HBV minichromosome, is present is a key factor in how long the infection lasts. The cccDNA serves as a reservoir for viral replication and transcripts, allowing the virus to persist despite antiviral treatments. Antiviral treatments have gotten a lot better over the years, but the fact that covalently closed circular DNA (cccDNA) stays in hepatocytes is still one of the biggest problems in finding a cure for chronic HBV infection.

Coumarin (2H-1-benzopyran-2-one) comes from plants and is anti-inflammatory, anticoagulant, antibacterial, antifungal, antiviral, anticancer, antihypertensive, antitubercular, anticonvulsant, antiadipogenic, antihyperglycemic, antioxidant, and neuroprotective. Previous research has shown promising results of coumarins in targeting HBV replication, such as 7-Methoxy-8-prenylcoumarin Ostho, 6-Hydroxyl-7-methoxyl-coumarin, and Coumarin lignan, which suppressed coumarin glycoside suppressed HBV antigens [1,2]. In this opinion, we will explore the potential of coumarins in the context of HBV cccDNA targeting, discussing the mechanism of action, challenges, and future prospects. We concentrate on three coumarins despite the fact that several coumarins have different therapeutic applications; here, we only discuss their activity against HBV cccDNA and have documented that they may impact chronic HBV replication. We apologize to colleagues who defined additional coumarin potential that may also be crucial for other complications but were unable to be discussed due to space restrictions.

HBV cccDNA Degradation by Coumarins

Coumarin derivatives such as dicoumarol, sphondin, and esculetin, effectively target HBx, inhibit associated transcriptional activities, and promote the degradation of c cccDNA [3-5]. Owever, recent studies have revealed their potential to target viral DNA, including HBV cccDNA,

via degradation of HBx proteins, which is essential for the maintenance of cccDNA. Esculetin inhibits HBV replication effectively both in vitro and in vivo, providing potential for its further development as an antiviral agent. After treatment with esculetin, the levels of DHBV DNA, duck hepatitis B surface antigen (DHBsAg), duck hepatitis B e-antigen (DHBeAg), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) decreased significantly in ducklings infected with duck hepatitis B virus (DHBV). Moreover, Sphondin is a potent inhibitor of HBsAg synthesis and HBV RNA levels. It is a new, natural antiviral drug that also targets the HBx protein and promotes the degradation of it, resulting in a decline in the level of cccDNA and HBsAg production [3]. While, Dicoumarol is known for the inhibition of NAD (P) H Quinone Dehydrogenase 1 (NQO1), the result dramatically decreased HBx expression. In HBV-infected cells and a humanized liver mouse model, dicoumarol inhibited HBV RNAs, DNA, HBsAg, and HBc proteins. Endogenous NQO1 protects HBx protein from 20S proteasome degradation.

NQO1 knockdown or dicoumarol therapy dramatically decreased HBx recruitment to cccDNA and hindered its transcriptional activity, resulting in repressive chromatin. Additionally, Dicumarol decreased lentiviral episome DNA. Dicumarol also suppressed HBV replication in NTCP-expressing HepG2 and primary human hepatocytes. Dicumarol also decreased cccDNA in HBV-infected cells but did not influence HBV adsorption or entry [4]. Our group also identified two coumarin derivatives called FC-31, and FC-20, which also interacted with HBx and enhanced the degradation of HBx in a concentration dependent manner unpublished data Tyagi P, et al.

As with any antiviral agent, the emergence of viral resistance is a concern. HBV is known for its high mutation rate, and continued exposure to currently used nucleotide analogues might lead to the development of various resistant viral strains. Due to their advantages, coumarins are non-toxic, non-mutagenic at higher concentrations, and they are plant-derived, so there is no issue with their availability. Combination therapies or alternative treatment approaches might be necessary to address this issue effectively.

Conclusion

Given the clinical significance of chronic HBV infection and liver damage, as well as the fundamental role of HBx in HBV replication, it is critical to consider targeting HBx to disrupt virus replication. Coumarins may be able to break down HBV cccDNA via targeting HBx, which is a promising step in the search for a cure for chronic HBV infection. While challenges remain, further research and clinical investigations may pave the way for more effective and targeted HBV therapies. At present, it is difficult to pinpoint a specific coumarins that could be targeted. More robust HBV-infection models are required in the future to explore coumarins potential against to virus replication and cccDNA degradation. As continue to explore the interplay between coumarins and HBV cccDNA, collaboration between researchers, clinicians, and the pharmaceutical industry will be crucial in advancing this potential treatment strategy.

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