

DHCR24: A Novel HCC Biomarker at a Glance

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Abstract

The sustained increase of hepatocellular carcinoma (HCC) new cases and the failure of determining a “universal” biomarker for early detection are sounding the alarm about finding urgently new alternatives and develop new biomarkers in order to face this public health issue. Hereby, a highlight of new findings about the involvement of 3 β -hydroxysterol Δ 24-reductase (DHCR24) as a potential biomarker of hepatitis C disease progression to hepatocellular carcinoma and a valuable target for hepatitis C virus (HCV) related HCC therapy.

Keywords: HCV; DHCR24; Biomarker; HCC

HCV-Induced Hepatocellular Carcinoma

Chronic hepatitis C infection is a major public health issue with 150 million people chronically infected worldwide, since the infection with hepatitis C virus (HCV) persists in 70% of cases. Notwithstanding, several factors related to the virus, to the host, or to the virus-host interactions; modulate host response to hepatitis C infection and affect disease progression, leading ultimately to hepatocellular carcinoma (HCC). This form is the most frequent primary liver tumor, the fifth human malignancy and the second most common cause of cancer-related mortality, with an increasing rate of cases [1,2]. It is widely acknowledged that HCV viral proteins indirectly induce hepatocarcinogenesis throughout several pathways [3]. Recently, a rising interest to lipid metabolism pathways and the involvement of HCV in hijacking the process has emerged, since HCV relies on host lipids for its life cycle. The contribution of obesity, diabetes and nonalcoholic steato-hepatitis comorbidities in the observed increase in HCV-HCC incidence was established. With all the existing management strategies, the 5-years survival is still poor. The heterogeneity of HCC limits the performance of alpha-fetoprotein (AFP) as a classical HCC-biomarker and a list of other suggested biomarkers (AFP-L3, DCP, GP73, IL-17, Osteopontin). Furthermore, the curative therapy (surgical resection, RFA and liver transplantation) are limited to early stage of HCC, while Sorafenib and Transarterial chemoembolization (TACE) are optimal options for patients with advanced stage, though side effects are not negligible [4,5].

HCV Modulates DHCR24 Expression

3 β -hydroxysterol Δ 24-reductase (DHCR24) plays a crucial role in maintaining cellular physiology via the regulation of cholesterol synthesis and is one of newly discovered host markers of oxidative stress and HCV-induced HCC. Data on the localization of DHCR24 in the endoplasmic reticulum (ER), its multifunctional backbone, and HCV modulation of DHCR24-mediated cholesterol biosynthesis corroborate the direct role of this host protein in HCV-induced oxidative stress. Indeed, DHCR24 exerts a modulating function in the prevention of stress-induced apoptosis when it is expressed at high

levels and may exert an antioxidant role via scavenging of reactive oxygen species (ROS). The existence of a HCV-responsive region/Sp1 binding site in the promoter region of DHCR24 coding gene emphasize the suggested way that HCV modulates DHCR24 expression and induces oxidative stress. This specific region seems to be highly controlled by epigenetic mechanisms since it locates on a CpG island on the promoter region of DHCR24 gene, a fact that attests of the DHCR24 key implication in HCV-induced hepatocellular carcinogenesis [6].

New Insights on the Role of DHCR24 in HCV-Induced HCC

In a previous model of HCV-induced HCC, it has been shown that overexpression of DHCR24 impaired p53 activity by suppression of acetylation and increased interaction with MDM2 proto-oncogene. This impairment of p53 suppressed the hydrogen peroxide-induced apoptotic response in hepatocytes [7]. Recent data published by our team showed that high levels of anti-DHCR24 antibodies (Ab) have been detected in the sera of patients with HCV-related HCC. A set of patients with HBV/HCV ongoing liver disease has been analyzed for serum DHCR24 Abs using enzyme-linked immunosorbent assay. The serum DHCR24 Ab levels were significantly higher in patients with chronic hepatitis C (CHC) than in healthy controls, and interestingly, in early HCC-C than CHC or Liver cirrhosis (LC)-C patients and in late HCC-C compared to early HCC-C patients, which demonstrate a stage-related overexpression of DHCR24. The comparison of the sensitivity of DHCR24 Ab for HCC-C detection was higher than that of alpha-fetoprotein (70.6% vs. 54.8%) and protein induced by vitamin K absence or antagonist-II (70.6% vs. 42.5%). Moreover, DHCR24 was up regulated in HCV-positive, but not HBV-positive tissues or HBV/HCV free HCC specimens [8]. In a study of Satoh et al., it has been demonstrated that DHCR24 expression was upregulated in HCC cell lines and tissues from IFN-non responders LC and HCC patients; and that 2-152a MAbs possessed agonistic activity against HCV replication [9]. Recently, a published paper of Saito et al., demonstrates that DHCR24 was specifically expressed on the surface of HuH-7 HCC cell lines, and that the DHCR24 enzymatic activity in the cholesterol transport process triggers the DHCR24 surface expression. Moreover, they showed that DHCR24 possess a recognition Site in 2-152a MAbs

and using a 152a Chimera Ab (ChAb), they demonstrate that the binding of 2-152a MAb to surface DHCR24 exerts anti-HCV activity. As well, examined the effector function of 2-152a MAb for antitumor activity mediated through complement-dependent cytotoxicity. Strikingly, they found that in response to 2-152a MAb binding, the expression of surface DHCR24 in HCC cell lines was downregulated, which means that HCC-surface expressed DHCR24 on might function as a carrier of target anti-tumor agents. This has been confirmed using a 2-152a MAb/saporin-conjugated secondary antibody [10].

DHCR24 as a Novel Biomarker of HCV-Induced HCC

Taken together, all these available data are substantially useful to sketch a new model of HCV-induced HCC; in the light of the pivotal role played by DHCR24 in HCV life cycle.

The importance of DHCR24 as a novel biomarker of interest rises from its usefulness for early detection of disease progression and specifically HCC. On the other hand, it might represent a new target for HCC therapy leaning on its property of binding to 2-152a MAb, which may be promising tool in the future for the HCC targeting approaches. Nonetheless, still too much to learn about DHCR24 biology in the context of HCC, especially post-translational modifications, how it could affect the HCV life cycle and the disease progression, the human population context and how it determines DHCR24 expression and functional profile.

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