Androgen Receptor and Hepatocellular Carcinoma

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Abstract

The androgen receptor (AR) exists in normal liver as well as in human hepatocellular carcinoma (HCC) tissues. Recent studies revealed that AR plays an important role in hepatitis B viral as well as hepatitis C viral hepatocarcinogenesis. The targeting of AR might be developed as a new therapeutic option against HCC. This article provides information regarding the association between AR and HCC.

Keywords: Androgen receptor; Foxa; HBV; HCV; STAT3; VEGF

Abbreviations: HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HCC: Hepatocellular Carcinoma; AR: Androgen Receptor; DBD: DNA-Binding Domain; ARE: Androgen Response Element; LBD: Ligand-Binding Domain; VEGF: Vascular Endothelial Growth Factor; STAT3: Signal Transducer and Activator of Transcription-3; Foxa: Vertebræ Forkhead Box A

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most commonly implicated risk factors of hepatocellular carcinoma (HCC) [1-3]. Irrespective of its cause, gender differences also exist in its prevalence [4].

Androgen receptor (AR), belonging to nuclear receptors, is putatively involved in the development of cancers such as prostate cancer, HCC and pancreatic cancer [5-7]. Androgen as a ligand interacts with AR, leading to a suggested link between transcriptional control and physiology. AR is characterized by a central DNA-binding domain (DBD), which targets AR to specific DNA sequences known as androgen response elements (AREs). The C-terminal half of the receptor encompasses the ligand-binding domain (LBD), which possesses the essential property of androgen recognition and ensures both specificity and selectivity of the physical response: LBD can be thought of as a molecular switch that, upon binding with ligand, shifts the receptor to a transcriptionally active state [8-10].

ARE is present in regulatory elements on target genes such as vascular endothelial growth factor (VEGF) and transforming growth factor beta-1, and regulates the growth and proliferation of hepatocytes [11,12]. Sorafenib, a molecular-targeted agent that inhibits tumor cell proliferation and angiogenesis by inhibiting Raf serine-threonine kinase (MAPKK kinase, MAPK KK), and VEGF, platelet-derived growth factor beta (PDGF), fms-related tyrosine kinase 3 (FLT3), and v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (C-Kit) receptor tyrosine kinase, was approved for treatment of advanced HCC in Europe, USA, Japan and other countries [13,14]. A selective transforming growth factor beta-1 receptor inhibitor inhibits phosphorylation of the beta 1 integrin intracytoplasmic tail, blocking invasion of HCC cells [15].

Nagasue et al. reported that HCC had a significantly higher concentration of androgen receptors than did the surrounding liver tissue [6]. There are several reports concerning the expression of AR mRNA and AR protein in tumor and in non-tumor parts of liver, suggesting that AR plays an important role in hepatocarcinogenesis [6,16-35].

Androgen Receptor-Mediating Signaling in HCV-related Hepatocarcinogenesis

HCV core protein, which has a size of ~20 kDa, is one of the structural proteins. It has been reported that HCV core protein is involved in hepatocarcinogenesis [36-42]. Expression of HCV core protein as well as HCV full-length protein leads to activation of the AR signaling pathway in the presence of androgen [43]. Cell culture-grown HCV infection in human hepatocytes also augments AR-mediated signaling in the presence of androgen [43,44]. These results showed that HCV core protein might cross-talk with the AR signaling pathway for promotion of carcinogenesis.

Signal transducer and activator of transcription-3 (STAT3) is often constitutively phosphorylated and activated in human cancers and in transformed cell lines and is implicated in tumorigenesis [45]. HCV core increased STAT3 phosphorylation both at Ser-727 and at Tyr-705, which in turn activates AR [43]. HCV infection also enhances VEGF, one of the target genes of AR [11], and induces in vitro angiogenesis in the presence of androgen [43]. HCV core protein could be an activator of AR in the male-dominant disease HCC.

Androgen Receptor-Mediating Signaling in HBV-related Hepatocarcinogenesis

The male predominance in HBV-related HCC is significantly high, with a ratio of 5-7:1 [4]. HBx is the only HBV nonstructural gene that functions as a multifunctional regulator modulating gene transcription, cell responses to genotoxic stress, protein degradation, apoptosis, and several signaling pathways [46-48]. HBx, which has a size of ~17 kDa, can physically bind to AR [49]. HBx-mediated enhancement of AR activity is androgen-dependent and could be mediated through indirect mechanism involving calcium and c-Src signaling pathways [50]. HBx enhances the AR transcriptional activity through two kinases: c-Src and glycogen synthase kinase-3beta kinase [51]. AR promotes HBV-induced hepatocarcinogenesis through modulation of HBV RNA transcription [52]. The androgen pathway can increase the transcription of HBV...
through direct binding to the ARE sites in HBV enhancer I, leading to a higher HBV titre in male carriers and increased risk of HCC [53]. These facts together suggest that the targeting of AR might be developed as a new therapeutic strategy against HBV-related HCC [54].

Ma et al. [54] reported that mice lacking hepatic AR developed later and less HCC than their wild-type littermates with comparable serum testosterone in both males and females when using the Cre-Lox conditional knockout mouse model injected with carcinogen and that AR may promote hepatocarcinogenesis via increased cellular oxidative stress and DNA damage, as well as by suppression of p53-mediated DNA damage sensing/repairing system and cell apoptosis. Recently, it has been shown that vertebrae forkhead box A (Foxa) factors and their targets estrogen receptor (ERα) and/or AR play an important role in the sexual dimorphism of HCC [55]. In conclusion, AR as well as ERα targets estrogen receptor (ERα) and/or AR play an important role in hepatocarcinogenesis. Targeting AR might be developed as a new molecular-target therapy against not only HBV-related but also HCV-related HCC.

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