

The androgen receptor as an emerging target in hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is one of the male-dominant liver diseases with poor prognosis, although treatments for HCC have been progressing in the past decades. Androgen receptor (AR) is a member of the nuclear receptor superfamily. Previous studies reported that AR was expressed in human HCC and non-HCC tissues. AR is activated both ligand-dependently and ligand-independently. The latter is associated with a mitogen-activated protein kinase–, v-akt murine thymoma viral oncogene homolog 1–, or signal-transducer and activator of transcription–signaling pathway, which has been implicated in the development of HCC. It has been reported that more than 200 RNA expression levels are altered by androgen treatment. In the liver, androgen-responsive genes are cytochrome P450s, transforming growth factor β , vascular endothelial growth factor, and glucose-regulated protein 78 kDa, which are also associated with human hepatocarcinogenesis. Recent studies also revealed that AR plays a role in cell migration and metastasis. It is possible that cross-talk among AR-signaling, endoplasmic reticulum stress, and innate immune response is important for human hepatocarcinogenesis and HCC development. This review shows that AR could play a potential role in human HCC and represent one of the important target molecules for the treatment of HCC.

Keywords: vascular endothelial growth factor, angiogenesis, glucose-regulated protein 78 kDa, hepatocarcinogenesis, molecular targets

Introduction

Hepatocellular carcinoma (HCC) is one of the male-dominant cancers with poor prognosis, although treatments are being developed.^{1–4} HCC usually occurs after the age of 40 years, reaching a peak at approximately 70 years of age.⁵ Irrespective of their etiology, rates of HCC among men are two to four times higher than those among women.⁵ HCC derived from hepatitis B virus (HBV) or hepatitis C virus infection and virus-unrelated HCC are male-dominant disorders.^{6,7} Similar sex difference is also observed in mice given a chemical carcinogen, diethylnitrosamine.⁸

In humans, androgen and estrogen are essential sex steroid hormones involved in many cellular processes such as cell metabolism and cell differentiation, as well as sex development.⁹ Both androgen receptor (AR) and estrogen receptor α , for androgen and estrogen, respectively, seem to be involved in hepatocellular carcinogenesis.^{8,10–12} There have been many reports concerning the expression of AR in HCC and its surrounding liver tissues.^{13–31} The association between AR and liver diseases is shown in Table 1. In this review article, we provide comprehensive insights regarding the association between ARs and HCC. We have been expecting that AR would become an emerging therapeutic target in HCC.

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Table I Androgen receptor (AR) and liver diseases from different etiologies

Etiology of HCC	Roles of AR	References
HBV	AR-CAG repeats may be associated with an increased risk of HCC	116
HBV	AR signaling may affect the risk of HBV-related HCC among men	117
HBV	AR exon I CAG repeat length may contribute to HCC predisposition among women	118,119
HBV	TNR of AR gene in male HCC	120
HBV	HBx enhances AR-responsive gene expression	10,11, 121–123
HBV	AR promotes HBV replication	124–126
HBV	CCRK-AR regulates HBV-associated HCC	127
HCV	HCV core augments AR-signaling	12
NAFLD	Association between AR, ER stress, and hepatic lipid deposition	86,128–130
Alcohol	AR associated with severity of liver diseases	56

Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; TNR, trinucleotide repeats; HBx, hepatitis B virus X; AR, androgen-responsive; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; ER, endoplasmic reticulum; CCRK, cell cycle-related kinase.

ARs and androgen action

Human AR is a member of the nuclear steroid receptor superfamily and AR gene is located on Xq11-12, indicating that males have a single copy of the gene.³² AR is a ligand-activated transcriptional factor with three domains: DNA-binding domain, C-terminal ligand-binding domain, and N-terminal transactivation domain.³³ Unliganded AR is inactive and is bound to cytoplasmic chaperones such as heat shock protein 90 (Hsp90).³⁴ Testosterone is produced in the testes and is converted to dihydrotestosterone. Ligands bind to AR and activate AR, inducing conformational change. Then, the AR dimerizes and the AR-dimers translocate to the nucleus, where AR binds to consensus-binding sequences (androgen-responsive elements [AREs]) in the DNA to regulate target gene expression.³⁴ Mitogen-activated protein kinase (MAPK)/extracellular signal-regulated protein kinase signaling increases the stability of AR.³⁴ Interleukin-6 is sufficient to activate AR in vitro, and steroid receptor coactivator-1 has been shown in interleukin-6-dependent signaling.³⁵ Steroid receptor coactivator-1 has been shown to interact with human AR and to modulate ligand-dependent AR transactivation, and it is regulated by phosphorylation by MAPK.³⁵ Growth and survival pathways such as MAPK, v-akt murine thymoma viral oncogene homolog 1 (AKT), and signal-transducer and activator of transcription (STAT) signaling are involved in the ligand-independent activation

of AR of prostate cancer, pancreatic cancer, and HCC.^{12,35–40} It is also known that MAPK, AKT, and STAT could activate AR signaling, and they also are involved in human hepatocarcinogenesis.^{41–48} In several human cancers, AR seems to be activated in an androgen-dependent and/or androgen-independent manner (Figure 1).

Target genes of AR in the liver AR and its target genes

Androgens and steroid hormones bind to the AR and, in turn, AR associates with genomic AREs (Table 2).⁴⁹ In LNCap prostate cancer cells, more than 200 RNA expression levels are altered by androgen treatment.^{49–51} Androgen plays a critical role for the cytoskeleton and extracellular matrix in transducing signals for growth, differentiation, and secretion in normal and cancerous prostate cells.^{50,52} Upregulation of NF- κ B and several DNA repair or stress-response gene expressions may be a secondary response to oxidative stress rather than a direct response to AR signaling.^{50,53} Bolton et al⁴⁹ reported that most androgen-responsive genes (ARGs) were associated with two or more AREs and that ARGs were sometimes themselves linked in gene clusters containing up to 13 AREs and 12 ARGs. Primary ARGs seem to produce effects on secondary target genes.⁵⁰

Androgen and the liver

Human liver microsomes and cytochrome P450s (CYP) are major sites of metabolism of drugs and hormones. The liver could have an impact on the metabolism of androgen and the activation of AR or on the metabolism of anti-androgenic drugs such as flutamide.^{54,55} It was reported that downregulation of AR activity correlates with the severity of alcoholic liver injury.⁵⁶ Hepatocyte nuclear factor-1 and CCAAT/enhancer-binding protein are responsible for liver specificity of the rat dehydroepiandrosterone sulfotransferase gene, which catalyzes sulfonation of androgenic steroids and certain aromatic procarcinogens.⁵⁷

AR and transforming growth factor β 1 (TGF- β 1) in the liver

TGF- β 1 expression increases during progression of HCC,^{58,59} hepatic cirrhosis,^{60,61} hepatic damage,^{62,63} and hepatic regeneration.^{64,65} Yoon et al⁶⁶ found that the promoter region of TGF- β 1 includes putative androgen response sequence and also in vivo and in vitro evidence of activation of TGF- β 1 expression by androgen and AR. They reported that androgen might regulate hepatocarcinogenesis by increasing

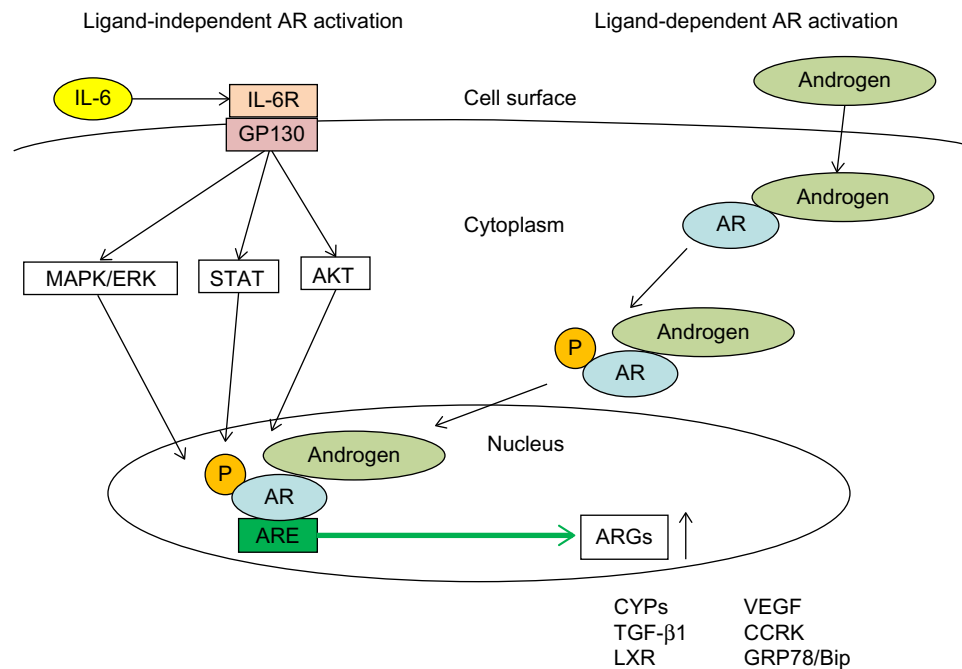


Figure 1 Ligand-dependent and ligand-independent androgen receptor (AR)-activation in hepatocytes.

Abbreviations: CYP, cytochrome P450; TGF- β 1, transforming growth factor β 1; LXR, liver-X-receptor; VEGF, vascular endothelial growth factor; CCRK, cell cycle-related kinase; GRP78/Bip, glucose-regulated protein 78 kDa; ARE, androgen-responsive element; ARGs, androgen-responsive genes; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated protein kinase; STAT, signal-transducer and activator of transcription; AKT, v-akt murine thymoma viral oncogene homolog 1; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; GP130, glycoprotein 130; P, phosphorylation.

transcription of TGF- β 1 through direct interactions with AR and ARE in the TGF- β 1 gene.⁶⁶

AR and cholesterol homeostasis in the liver

AR signaling plays a role in the development and progression of several liver diseases, including HCC and nonalcoholic fatty liver disease. Androgen control of growth hormone secretion also induces male-specific genes in the liver.⁶⁷ AR activation results in obesity and altered lipid metabolism in orchidectomized mice,⁶⁸ suggesting that the activation

of AR might be involved in HCC development in patients with nonalcoholic steatohepatitis, although there is also a contrary opinion.⁶⁹ But these studies showed that hepatic AR may play a role in the development of insulin resistance and hepatic steatosis.^{68,69} CYP27A1 is a key enzyme in cholesterol homeostasis and vitamin D₃ metabolism. AR could induce CYP27A1, which is a target for the JNK/c-Jun pathway. The JNK/c-Jun pathway is thought to be involved in AR-mediated upregulation of human CYP27A1.⁷⁰ Krycer and Brown⁷¹ showed that liver-X-receptor activity is down-regulated by AR. The cross-talk between AR and liver-X-receptor is important for cholesterol homeostasis.

AR and hepatocarcinogenesis

Vascular endothelial growth factor (VEGF) is a target gene of AR⁴⁹ and plays an important role in angiogenesis in the liver.¹² Hepatitis C virus core protein enhances AR signaling, upregulates VEGF expression in hepatocytes, and facilitates angiogenesis.¹² VEGF is one of the key molecules of treatment of HCC.^{72,73} Of interest, female sex was associated with better response to sorafenib in patients with unresectable HCC in Japan.⁷⁴ Feng et al reported that cell cycle-related kinase is a direct AR transcriptional target and that cell cycle-related kinase promotes hepatocarcinogenesis through the upregulation of β -catenin/TCF signaling.⁷⁵

Table 2 Representative ARGs in the liver

ARGs	Function	References
CYPs	Drug metabolism and alcohol metabolism	54–57,70
TGF- β 1	HCC development, hepatic fibrosis, hepatic damage, and hepatic regeneration	66
LXR	Cholesterol homeostasis	71
VEGF	HCC development and angiogenesis	12,49
CCRK	HCC development	75
GRP78/Bip	ER stress and HCC development	86,92

Abbreviations: ARG, androgen-responsive gene; CYP, cytochrome P450; ER, endoplasmic reticulum; HCC, hepatocellular carcinoma; TGF- β 1, transforming growth factor β 1; LXR, liver-X-receptor; VEGF, vascular endothelial growth factor; CCRK, cell cycle-related kinase; GRP78/Bip, glucose-regulated protein 78 kDa.

AR and aryl hydrocarbon (or dioxin) receptor

Both aryl hydrocarbon (or dioxin) receptor and aryl hydrocarbon (or dioxin) receptor nuclear translocator are known to interact with AR.^{39,76,77} AR might also be involved in hepatocarcinogenesis through aryl hydrocarbon (or dioxin) receptor pathways.³⁹ Li et al⁷⁸ reported that the vertebrae forkhead box A factors and their targets estrogen receptor α and AR play an important role in the sex difference of HCC. Nuclear receptors including AR and estrogen receptor and their related signaling pathways play a role in human hepatocarcinogenesis.⁴⁰

AR and cell migration

Recent studies revealed that AR is involved in cell migration and metastasis.⁷⁹ At present, it is not clear whether AR could promote cell migration^{81–83} or not.^{80,84,85} Although further studies will be needed regarding this point, AR is one of the important target molecules for treatment targeting metastasis or advanced HCC.

AR and endoplasmic reticulum stress

Dihydrotestosterone could induce RNA-dependent protein kinase/eukaryotic initiation factor-2 α activation in human hepatocytes.⁸⁶ Dai et al⁸⁶ reported that RNA-dependent protein kinase/eukaryotic initiation factor-2 α activation is involved in dihydrotestosterone-induced cell cycle arrest and that the eukaryotic initiation factor-2 α /GADD153 pathway, a branch of ER stress response, is enhanced. It is well known that the ER stress pathway is involved in human hepatocarcinogenesis.⁸⁷ Glucose-regulated protein 78 kDa (GRP78/Bip) is one of the androgen response genes in human prostate cells as well as in human hepatocytes.^{39,88–92} We reported that stronger positive correlations between the expressions of AR mRNA and GRP78 mRNA in stage I/II HCC samples, compared with stage III/IV HCC samples, indicated that AR-controlling GRP78 activation plays a role in hepatocarcinogenesis in especially earlier-stage HCC patients.⁹² We also observed that AR overexpression increased ER stress-responsive gene expression in human hepatocytes and that AR-knockdown led to the down-regulation of expression of ER stress molecules.⁹² We also confirmed that the double-knockdown of AR and GRP78 enhanced sorafenib-induced apoptosis in human hepatoma cell lines.⁹² The cross-talk between AR and ER stress response might be a potential target in the treatment of HCC.

AR and Toll-like receptor signaling pathways

Tissue expression of AR is associated with differential immune responsiveness.⁹³ Toll-like receptors (TLRs) are a family of transmembrane receptors and play central roles in innate immunity. TLR4 recognizes lipopolysaccharide, a cell wall component of gram-negative bacteria that activate innate immunity.⁹⁴ Lipopolysaccharide induced apoptosis in hepatocytes and reduced the hepatic expressions of ER stress-related proteins. ER stress response is important for hepatic cell damage from an innate immune response.⁹⁴

Testosterone downregulated the expression of several TLR genes, possibly resulting in the inhibition of the immune response.⁹⁵ MyD88, downstream of TLR4, may play a role in limiting prostate tumorigenesis by altering tumor-infiltrating immune populations.⁹⁶ We observed an increase of lipopolysaccharide-induced apoptosis (67%) in HepG2 stably expressing shAR as compared to that (47%) in HepG2 control cells.⁹² AR and ER stress response may be involved in innate immune response of hepatocytes.

AR and other signaling pathways

Several reports indicated that insulin-like growth factor (IGF), fibroblast growth factor (FGF), and VEGF, as well as mammalian target of the rapamycin (mTOR) signaling pathways are involved in human hepatocarcinogenesis.^{48,97–99} Cell surface receptors for IGF, FGF, and VEGF activate downstream signal transduction through the receptor-tyrosine kinases. These receptors are also important molecular targets for drugs against HCC such as sorafenib, brivanib, and everolimus.^{48,97–99}

IGF-1 and its binding proteins are also known as AR-targeting genes in prostate cancer cells.^{100,101} Tsuei et al¹⁰² showed that downregulation of IGF-1 and its binding protein-3 were observed in the RNA-binding motif gene on the Y chromosome-knockdown HepG2 cells, suggesting the enhancing effect of RNA-binding motif gene on the Y chromosome on AR transactivation activity in human HCC.

AR could control FGF and FGF-binding protein production and affect FGF signaling pathway in prostate cancer cells.¹⁰³ AR may have an impact on FGF signaling pathway as well as VEGF signaling pathways in human hepatocarcinogenesis.¹² PI3K/phosphatase and tensin homologs deleted on chromosome 10 (PTEN)/Akt/mTOR pathway are involved in many cellular processes of human HCC.⁴⁸ Everolimus and sirolimus could inhibit HCC

Table 3 Clinical trials targeting androgen in hepatocellular carcinoma

Drug (dosage)	Randomized study	Number of patients	Eligibility Child-Pugh class	Stage of HCC	Efficacy: mean survival or response	Ref
Leuporelin, flutamide, and tamoxifen	Yes	192	Child-Pugh Class A/B/C: 112/50/2; cirrhosis, 90%; ascites, 26%; HBV, 3%; HCV, 19%	Okuda's classification stage I/II/III: 81/107/4	135.5 d ($P=0.21$)	108
Tamoxifen (administered until death)	Yes	184	Child-Pugh Class A/B/C: 105/59/5; cirrhosis, 93%; ascites, 31%; HBV, 10%; HCV, 13%	Okuda's classification stage I/II/III: 93/83/8	176 d	108
Flutamide for 8 weeks	Phase II	32	Measurable advanced HCC patients; hepatitis-related, 88%	AJCC stage III/IV: 5/27	10 wks; 9 of 22 (41%), stable diseases; 13 (59%), progress diseases	109
Antiandrogen (Anandron) plus placebo	Yes	58	Unresectable HCC; cirrhosis, 76%; HBV, 25%	N/A	3.6 mo (NS); 1, complete response	110
LHRH agonist plus placebo	Yes	61	Unresectable HCC; cirrhosis, 85%; HBV, 21%	N/A	2.7 mo (NS); 1, partial response	110
Antiandrogen plus LHRH agonist	Yes	60	Unresectable HCC; cirrhosis, 82%; HBV, 14%	N/A	3.9 mo (NS); 1, partial response	110
Placebo plus placebo	Yes	59	Unresectable HCC; cirrhosis, 83%; HBV, 35%	N/A	5.8 mo	110
Cyproterone acetate	No	25	Cirrhotics with unresectable HCC	N/A	14 wks; 5, excess in 29 wks; 5, response	111
Ketoconazole	No	8	Unresectable HCC	N/A	6, <8 weeks	112
D-Tryptophan-6-luteinizing hormone-releasing hormone	No	17	Cirrhotics with HCC	N/A	No response	113
LHRH-analog triptorelin and tamoxifene	Yes	33	Child-Pugh: 7.7 ± 2.0 (untreated HCC); cirrhosis, 27; HBsAg (+), 69.7%; anti-HDV (+), 15.2%; anti-HCV (+), 12.1%	Okuda stage I/III (%): 27.3/18.2	282 d ($P=0.020$ vs placebo)	114
Triptorelin plus flutamide	Yes	23	Child-Pugh: 8.3 ± 1.6 (untreated HCC); cirrhosis, 18; HBsAg (+), 56.5%; anti-HDV (+), 8.7%; anti-HCV (+), 8.7%	Okuda stage I/III (%): 21.7/13.0	112 d (NS vs placebo)	114
Placebo	Yes	29	Child-Pugh: 8.9 ± 2.1 (untreated HCC); cirrhosis, 25; HBsAg (+), 58.6%; anti-HDV (+), 10.7%; anti-HCV (+), 20.0%	Okuda stage I/III (%): 24.1/17.2	127 d	114

Abbreviations: AJCC, American Joint Committee on Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus; HBsAg, hepatitis B virus surface antigen; LHRH, luteinizing hormone-releasing hormone; HCC, hepatocellular carcinoma; Ref, references; NS, not significant; N/A, not applicable; d, days; wks, weeks; mo, months; vs, versus.

growth through this signaling pathway.⁴⁸ Previous study in prostate cancer cell lines¹⁰⁴ showed AR-mTOR cross-talk is regulated by testosterone availability. Further study will be needed at a significance of AR-mTOR cross-talk in human hepatocarcinogenesis.

HBV and AR

Chen and Yehs' group has extensively studied the association between HBV infection and AR, or the association between HBx protein and AR, and reported that AR is involved in human hepatocarcinogenesis.^{38,39,105–107} Table 1 shows several mechanisms of the effects of AR in HBV-associated HCC. Many studies with human liver tissues^{13–31} also support

this concept. These data support the idea that AR could be one of the important molecular targets for the treatment of HCC with or without HBV infection.

Conclusion

AR could play critical roles in human HCC and be one of the important target molecules for the treatment of HCC. The previous controlled study shows the lack of efficacy of androgen treatment in unresectable HCC (Table 3).^{108–115} However, the present review clearly suggests that AR but not androgen could be an important target of hepatocarcinogenesis and HCC development, and more specific inhibitors of AR would shed light on the treatment of HCC.

Further studies concerning AR and ARGs in the liver should be carried out.

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Disclosure

The authors report no conflicts of interest in this work.

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