Medical Hypotheses 86 (2016) 67–70

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Hepatocellular carcinoma and estrogen receptors: Polymorphisms and isoforms relations and implications

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ARTICLE INFO

Article history:
Received 17 July 2015
Accepted 29 November 2015

ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary tumor of liver and its incidence continues to increase worldwide. HCC is a disease with multifactorial causes and genetic variability has been discussed as a risk factor for its development. Liver is a hormone-sensitive organ and therefore is influenced by gonadal hormones, such as estrogen. Estrogen is known to participate in various biological functions, but its role in development of HCC, on the other hand, is controversial and presents evidence suggesting a role as both a carcinogen and protective effect in liver. Estrogen way of action is mediated by estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), that belong to a family of nuclear receptors that may regulate the expression of many genes. The ER subtypes exert a variety of roles in many stages of liver disease and may play a part in the process of signal transduction, according to some studies. However, the many functions of ER subtypes in hepatic diseases, in special of the ERβ, are yet to be clarified.

The genetic modifications related to HCC are not yet fully clarified and accumulation of multiple genetic alterations appears to have an important role in carcinogenesis of HCC. The presence of some certain single nucleotide polymorphism (SNP) may have a functional repercussion related to final product of a gene, which can be measured and may participate in some alterations related to a pathological condition.

Our hypothesis is based on the fact that liver tissue express ER and its different variants exert multiple functions in various stages of liver disease and participate in an extremely complicated signal transduction process, therefore we believe that the presence of one or more SNPs of *ESR1* and *ESR2* genes may be related with the increase of risk in developing and the severity of HCC, as well as in the response to different treatments. The confirmation of our hypothesis by scientific studies may provide knowledge of markers that act as prognostic factors of this disease, as well as enabling alternatives to development of anti tumoral therapies.

Introduction

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary tumor of liver and its incidence continues to increase worldwide, especially in areas with low incidence [1]. HCC is a disease with multifactorial causes where 95% of patients have underlying chronic liver diseases, particularly of viral etiology [2,3]. The main etiological agents to HCC are liver diseases related to hepatitis B virus (HBV), hepatitis C virus (HCV) and alcohol intake. Other causes are also related, representing a minor global impact, and are nonalcoholic steatohepatitis (NASH), hemochromatosis, exposure to B1 aflatoxin, autoimmune hepatitis, primary biliary cirrhosis and some hepatic metabolic diseases [4,5].

The incidence of HCC varies considerably according to geographical region. In Asia and Africa, HBV is the predominant risk factor, whereas in the west and in Japan, HCV is the most relevant factor. The age group with the highest prevalence in the United States and Europe is between the 6th and 7th decade, whereas in areas of high incidence, tumor occurs in younger patients, between the 3rd and 5th decades [1,5,6]. In Brazil, annual incidence of HCC is 2.9% and the main causes were associated with HCV, HBV and alcohol [3].

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http://dx.doi.org/10.1016/j.mehy.2015.11.030
0306-9877/

Genetic variability has been discussed as a risk factor for development of HCC, since many of patients exposed to known environmental risk factors never develop cirrhosis or HCC, whereas a significant minority of cases of the disease has developed HCC without presenting any risk factor [7].

Epidemiological studies indicate that incidence of HCC is higher in men than in women, and the risk of HCC is 2–7 times higher in men, though this ratio varies between different countries. This is mainly for three reasons: (a) men would be more exposed to hepatic carcinogens (tobacco or alcohol) and hepatitis B virus infections; (b) the effects of estrogen may suppress the inflammatory process mediated by interleukin-6 (IL-6) in women, reducing hepatic injury and the compensatory proliferation of hepatocytes; and (c) the effects of testosterone may increase signaling androgen receptor in men, promoting proliferation of hepatocytes [5,8]. Given this characteristic gender-specific, significantly relevant, study of the role of sex steroids and their relationship with HCC is of great importance, since the mechanisms of action of these hormones in development of HCC are still poorly understood [8].

Estrogen receptors

Liver is a hormone-sensitive organ and therefore is influenced by gonadal hormones, such as estrogen [9]. Estrogen is a steroid hormone produced in greater amounts by ovary and placenta, and in lower quantities, by testicles, cortex of the adrenal, brain, adipose tissue, breast, skin, blood vessels, bone and cartilage [10]. It is known to participate in various biological functions such as growth, differentiation and metabolism in mammals [11], reproduction, bone integrity, cardiovascular function and liver function [12–14].

The role of estrogen in development of HCC is controversial and presents evidence suggesting a role as both a carcinogen and protective effect in liver [15–17].

The estrogen way of action is mediated by two receptors: estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), that belong to a family of nuclear receptors that may regulate the expression of many genes [8]. The estrogen receptor (ER) is a transcription factor activated by ligand, which is composed of one estrogen binding domain and one DNA binding domain. ERα and ERβ are encoded by distinct genes *ESR1* and *ESR2*, respectively, and are located on different chromosomes [11,14]. Both ER subtypes are expressed in HCC and interact with each other [18]. The ER subtypes exert a variety of roles in many stages of liver disease and may play a part in the process of signal transduction, according to some studies [19]. However, the many functions of ER subtypes in hepatic diseases, in special of the ERβ, are yet to be clarified and have been object of studies for a long time [19,20]. The majority of biological effects of the estrogen in the liver is also known as mediated by ERα [21] and that it presents different isoforms and their expressions vary depending if tissue is healthy, cirrhotic or with HCC [22]. The process by which ER subtype pattern expression, and its isoforms pattern expression, modifies in hepatocarcinogenesis, tough, is yet to be elucidated [19].

Estrogen receptors isoforms

As explained above, ER has two subtypes of receptors: ERα and ERβ. However, due to the splicing mechanism, the two subtypes of receptors may have different isoforms, since modification of pre-mRNA is capable of generating multiple products, diversifying the pattern of proteins produced [23,24]. The role and influence that these isoforms may play in signaling of ERs is still being studied [24].

In humans, more than twenty isoforms to ERα has been described in some tumors. Both ERα46 and ERα36 are the most studied isoforms. ERα46 isoform appears to be related with cell cycle arrest in the G0/G1 phase and a state of refraction to E2 stimulated growth, which is normally reached at hyperconfluency of cells [24]. It also appears to be involved in the role of inhibiting others transcripts involved in cell cycle control. ERα36, in turn, appears to be related to an increase of cell proliferation by MAPK–ERK activation [24].

As for ERβ, at least five isoforms has been described in human tissue, however its functional significance is not yet well understood [24]. Among the isoforms, stands out ERβ2 as the best studied. Its role appears to be associated with inhibition of ERα. A possible process suggested by authors is that, by degradation of ERα by ERβ2, occur less recruitment of ERα by estrogen-responsive promoters and that could leave to a suppression of genes responsible for ERα regulation [25].

Estrogen receptors and genetic variability

The genetic modifications related to HCC are not yet fully clarified. But, such as in others tumors, accumulation of multiple genetic alterations appear to have an important role in carcinogenesis of HCC [26].

Genetic polymorphisms are DNA sequence variations, which the least common allele must have a frequency of 1per cent or more in the population. One of the most studied types is single nucleotide polymorphism (SNP), which is resulting of a single nucleotide substitution. The presence of some certain polymorphisms may have a functional repercussion related to final product of a gene, which can be measured and may participate in some alterations related to a pathological condition. Thus, in some cases, a genetic polymorphism may increase susceptibility to cancer [27].

Several polymorphisms have been described to *ESR1* and *ESR2* genes and some studies demonstrated a clear association of some polymorphisms, as rs2234693 and rs9340799, with risk of breast and endometriosis cancer development ([28], see review in [18]), and a consistent association with development of prostate cancer (see review in [18]). In these cases, literature indicates that polymorphisms in genes involved with metabolic pathway of sex hormones may alter the exposure of body to exogenous sex hormones and affect the risk of tumor development. In addition, these genetic variations are pointed as possible contributors to aberrant expression of ERs, by modifying its structure and mechanism of action, which may be related to increased risk for such cancers ([28], review in [18]). Nonetheless, just a few studies on genetic variability of ERs and liver diseases were performed, besides, studies that aim to replicate previous findings of these associations, for various reasons, have found contradictory results [29].

In animal model, estrogen has been described as a tumor promoter, having the possibility of inducing hepatocarcinogenesis. A relation between ERs expression and estrogen-induced tumor formation was demonstrated in MT-mESR transgenic mouse [30]. Another study demonstrated that 8 per cent of female rats that received ethinyl-estradiol (EE) treatment for twelve months developed HCC, therefore revealing that EE causes mutation of hepatocytes that leads to adducts DNA formation and induces development of cancer in affected cells [8].

On the other hand, a genetic variation, such as a SNP, not always will lead to a modification of receptor structure and, consequently, lead to an effect. The lack of association between SNPs and cancer, for example, can be found in some studies that showed rs9340799 polymorphism had no association with the risk to HCC [30,31], as well as rs1801132 polymorphism had no association of cancer risk, in pooled analysis, in another study (see review in [32]). The rs2077647 variant, however, showed association with risk to HCC development, but not for others cancers such as colorectal, breast and prostate cancer (see review in [32]).