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Molecular events of hepatitis C in hepatocellular carcinoma

Abstract

Cancer is defined by a set of more than 100 diseases that have in common disordered autonomous growth of abnormal cells and genetic alterations, including acquired mutations and genetic instability. The infectious etiology of cancer, on the other hand, is the result of virus activity, which induce tumor cell transformation. This transformation results in activation or deactivation of key regulatory genes, cell proliferation and differentiation. The alterations of these events leads to important modulatory changes in the expression of several proteins and/or their structure, causing profound modifications on cellular metabolism. Carcinomas are cancers that occur in epithelial tissues, as skin or mucous. Among those, the hepatocellular carcinoma (HCC) is one of the most relevant carcinomas and is the sixth most common cancer worldwide. Several factors are associated with progression of HCC, among them diabetes, obesity, metabolic syndrome, alcohol, tobacco, aflatoxins, genetic predisposition and hepatitis B and C virus. The hepatitis C virus (HCV) it is one of the most important etiological agents of HCC, resulting in virus induced liver necroinflammation. The infection of hepatitis C virus (HCV) in hepatocytes is an orchestrated event involving viral oncogenic factors and its development in the host cell, which involve viral envelope glycoprotein structures such as E1 and E2. The most interesting trade is that the HCV genetic material does not invade the nucleus of the infected cell, it acts directly as a mRNA in the cytoplasm, where virus transmission is initiated by the internal ribosome entry site. Numerous events are involved in the molecular pathogenesis of HCC by HVC. In this review, we highlight those involved in p53 signaling pathway; Wnt signaling and E-cadherina/β-catenin activation and TGF-β/activin pathway regulation. As these molecular alterations derived from host-pathogen interactions interfere in hepatocyte normal effectors expression, to understand the interactome behind these well-driven mechanistic events could lead to more realistic molecular targets, as well to early screening for possible biomarkers molecules.

Keywords: Hepatitis C virus, cancer, hepatocellular carcinoma, molecular events, liver

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Introduction

According to the Instituto Nacional do Câncer (INCA), the cancer is a set of more than 100 diseases that are caracterized by the uncontrolled growth of cells that invade tissues and organs and can spread to nearby areas (lymph nodes) or other body regions (metastasis). When it begins in epithelial tissues, such as skin or mucous membranes, they are named carcinomas; when in connective tissue, such as cartilage or bone, they are called sarcomas.[1] The evolutionary process of the cancer can be described as a phenomenon in which genetically altered cells lose the ability to renew themselves every cycle in a non-pathological form, resulting in cell trait loss, causing damage to one or more genes from a single cell and genetic instability. Metabolic changes occur in cell growth, allowing the rise of cell populations that do not follow a standard construction and maintenance of normal tissue. The structure of tumor tissues presents a disorganized combination, indicating that the cancer is a disease formed by heterotypic malfunctioning.[2,3] The cell multiplication occurs by the cell division processes, in which the cell grows, replicates its DNA and divides. There are checkpoints where the cell assesses the cellular environment and it defines whether to continue the cell cycle. Thus, the genetic alteration may cause uncontrolled cell proliferation.[4,5]

The infectious etiology of cancer, on the other hand, is the result of virus activity, which induce tumor cell transformation. This pathogen-driven transformation results in activation or mutation of key regulatory genes, cell proliferation and differentiation.[6] Thus, the machinery responsible for DNA repair and maintenance can be affected by mutations. The alterations of these events leads to important modulatory changes in the expression of several proteins and/or their structure, causing profound modifications on cellular metabolism.[7]

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) is a primary liver cancer derived from hepatocytes mutation that causes an impair at cellular and metabolic levels, in which defective cells multiply uncontrolled.[8] The HCC is the sixth most common cancer worldwide. It is the fifth most common malignancy among men and the eighth among women.[9] Within the various etiologies already identified, which causes HCC appearance, chronic hepatitis caused by virus B (HBV) and C (HCV) are among those most important in HCC genesis.[9] Regarding the HCC infectious etiology, hepatitis virus C (HVC) is estimated chronically to affect 130–170 million people and several conditions, causing long-term complication of HCV infection.[10] The severity of the disease could be increased by advanced fibrosis phenotype, development of cirrhosis and hepatocellular carcinoma, making HCV carriers the most common subjects for liver transplantation.[11,12]As causes of these mutations that leads to HCC development, the recurring regeneration in chronic hepatitis and the excessive multiplication of cells, is a positive feedback on HCC progression. Within this scenario, HCC is considered a highly aggressive cancer with incidence/mortality ratio of 0.93.[13]

Hepatitis C virus (HCV)

The hepatitis C virus (HCV) is a member of the *Flaviviridae* family, within the *Hepacivirus* gender. The *Flaviviridae* family has other important pathogens, such as dengue and yellow fever virus.[10]. The HCV is a spherical shaped virus with 50mm in diameter, enveloped nucleocapsid and its genetic material consists of a linear strand of RNA with positive polarity.[14]

The HCV genetic material is composed by approximately 9.6-kb genome and consists of a single large open reading frame (ORF) encoding a polyprotein of 3,000 amino acids involved in two noncoding regions.[2]. This polyprotein is processed by viral proteases and host cells in the N-terminal pole, in three structural proteins:

i. the nucleocapsid (core),

ii. glycoprotein core structure one (E1) and

iii. glycoprotein core structure two (E2).[15]

The HCV penetrates a susceptible host entering the bloodstream towards the liver and by going through several tissues such as pancreas, thyroid, adrenals, spleen, bone marrow and to peripheral B-cells and T-cells, that can be infected by the virus, allowing its multiplication.[16] The liver is the major site to HCV replication, where the virus infects about 10% of the liver cells.[15] In 60% to 85% of cases of HCV infection, the chronic liver disease may progress and cause liver cirrhosis and/or hepatocellular carcinoma.[16,17]

Virological aspects of hepatitis C

HCV is a single-stranded RNA virus that has the hepatocytes, as primary target.[18] This is an important pathogen that induces chronic hepatitis and activates the host immune response to viral infections.[19] The infectious virus particle encode two glycoproteins, E1 and E2 which are initially originated as part of the virus protein.[20] The HCV infection requires the interaction of E1 and E2 with the hepatocytes cell membrane.[18]

Nonetheless, the entire host-pathogen process is not fully elucidated, it is known that the entry of hepatitis C virus (HCV) in hepatocytes is an organized event involving oncogenic viral factors and their development in the host cell.

The viral envelope structures are involved in this process (such as glycoprotein E1 and E2) and also the recognition of the CD81 receptor, present at hepatocytes cell membrane. Low density lipoprotein receptors (LDLr) and scavenger receptors class B type I (SR-BI) play also an important role in the host-pathogen interactions. Other important structures have been nowadays described in these events, such as adhesion protein claudin-1 (CLDN1) and occludin (OCLN).[18]

Studies have discussed the characteristics of HCV entry receptors into cells. One of these important molecules mentioned in the literature is a member of the superfamily of tetraspanin, the CD81. This receptor has been identified as a direct binder of the recombinant HCV protein envelope, the E2 glycoprotein, resulting in a potential cell receptor or co-receptor for HCV entry into hepatocytes.[20]

The HCV structural proteins are attacked by enzymes of the infected cell, the hepatocytes, and these viral envelope proteins are glycosylated and then involved in the binding with CD81 and LDLr receptors, responsible for fusing the virus.[21].

The activation of signaling pathways initiate after the binding of these CD81 and LDLr receptors. The HCV genetic material does not invade the nucleus of the infected cell, it acts directly as a mRNA in the cytoplasm, where virus transmission is initiated by the internal ribosome entry site.[9]. Subsequently to the connection to several cell surface molecules, HCV acts directed into adhesion proteins, where it interacts with CLDN1 and OCLN, facilitating their adsorption.[21]

The HCV enters the cell cytoplasm by endocytosis and after the fusing process and adsorption of RNA, triggers the synthesis and maturation of the nonstructural proteins (NS2, NS3, NS4 and NS5) forwarding to replication complexes.[15] The viral RNA and envelope proteins combine to form the nucleocapsid, which is transported in cytoplasmic vesicles to the surface of the host cell, passing through the Golgi complex, to meet other particles, in which undergoes to exocytosis, releasing the newly formed HCV viral particles to complete a new cycle. The HCV expresses high replication rate, and high rate of mutation, which leads to the great heterogeneity of manifestations.[14,15]

The HCV lifecycle

Cellular attachment of HCV virions and entry

The HCV lifecycle is not yet fully comprehend and several cell surface molecules have been proposed to mediate HCV binding or HCV binding and internalization.

CD81

Among all putative HCV receptor molecules, CD81 has been the most extensively studied. Human CD81 (target of antiproliferative antibody 1, TAPA-1) is a 25-kDa molecule belonging to the tetraspanin or transmembrane 4 superfamily. The CD81 has been shown to mediate binding of HCV through its envelope glycoprotein E2.[22] The site of interaction appears to involve CD81 residues 163, 186, 188 and 196 which also need a two disulfide bridges for the CD81-HCV interaction to occur.[23-25] Several studies argue that cellular factors other than CD81 are required for HCV infection. The expression of human CD81 in a CD81-deficient human hepatoma cell line restored permissiveness to infection with HCV pseudo-particles, but a murine fibroblast cell line expressing human CD81 remained resistant to HCV entry.[25] In addition, expression of human CD81 in transgenic mice did not confer susceptibility to HCV infection.[26]

SR-BI

The scavenger receptor B type I (SR-BI) has been proposed as another candidate receptor for HCV.[27] It is expressed at high levels in hepatocytes and steroidogenic cells.[28,29] The natural ligand of SR-BI is high density lipoproteins (HDL). HDLs are internalized through a non-clathrin-dependent endocytosis process that mediates cholesterol uptake and recycling of HDL apoprotein.[30] HCV genotypes 1a and 1b recombinant E2 envelope glycoproteins were shown to bind HepG2 cells (a human hepatoma cell line that does not express CD81) by interacting with an 82 kDa glycosylated SR-BI molecule. The SR-BI appeared to be responsible for HCV binding, and HVR1 was recently suggested to be the E2 envelope region involved in the interaction, which was facilitated by serum HDLs.[27,31,32] However, the fact that antibodies against SR-BI resulted only in a partial blockade of binding suggests that SR-BI is not the only cell surface molecule involved in HCV binding to hepatocytes.[27]

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LDL-R

The low-density lipoprotein (LDL) receptor (LDL-R) is an endocytic receptor that transports lipoproteins, mainly the cholesterol-rich LDLs, into cells through receptor-mediated endocytosis.[33,34] Virus-like particles complexed with LDLs have been reported to enter into cells via the LDL receptor.[35,36] Thus, binding of low-density HCV particles recovered from plasma by sucrose gradient sedimentation correlated with the density of LDL receptors at the surface of MOLT-4 cells and fibroblasts. The binding was inhibited by LDL but not by soluble CD81.[37]

Mechanisms of cell entry and fusion

After attachment, the nucleocapsid of enveloped viruses is released into the cell cytoplasm as a result of a fusion process between viral and cellular membranes. Fusion is mediated by specialized viral proteins and takes place either, directly at the plasma membrane or following internalization of the particle into endosomes. The entry process is controlled by viral surface glycoproteins that trigger the changes required for mediating fusion. At least two different classes of fusion proteins (I and II) can be distinguished.[38] In general, the flaviviruses enter target cells by receptor-mediated endocytosis and use MHC class II fusion proteins.[39] By analogy, researchers believe that HCV events resemble the other viruses from the family.[40] However, in contrast with other class II fusion proteins, HCV envelope glycoproteins do not appear to require cellular protease cleavage during their transport through the secretory pathway.[41] HCV entry into cells is pH-dependent and endocytosis dependent,[35] but the identity of the HCV fusion peptide remains unknown. E1 appeared as a good candidate because sequence analysis suggested the presence of a fusion peptide in its ectodomain.[42]

After the viral genome is liberated from the nucleocapsid (uncoating) and translated at the rough ER, NS4B (perhaps in conjunction with other viral or cellular factors) induces the formation of membranous vesicles (referred to as the membranous web). These membranes are supposed to serve as scaffolds for the viral replication complex. After genome amplification and HCV protein expression, progeny virions are assembled. The site of virus particle formation has not yet been identified. The biological significance of these protein-RNA interactions remains unknown.[43,44]

HCV replication

The HCV replication complex

Infection with a positive-strand RNA virus leads to rearrangements of intracellular membranes, a prerequisite to the formation of a replication complex that associates viral proteins, cellular components and nascent RNA strands.[45,46] Overall, the membranous web consists of small vesicles embedded in a membranous matrix, forming a membrane-associated multiprotein complex that contains all of the nonstructural HCV proteins.[47]

Mechanism of HCV replication

The precise mechanisms of HCV replication are still poorly understood. By analogy with other positive-strand RNA viruses, HCV replication is thought to be semi-conservative and asymmetric process.[47,48] The positive-strand genome RNA serves as a template for the synthesis of a negative-strand intermediate of replication during the first step. In the second step, negative-strand RNA serves as a template to produce numerous strands of positive polarity.[49] This template will subsequently be used for polyprotein translation, synthesis of new intermediates of replication or packaging into new virus particles.[48] Initiation of RNA replication is triggered by an interaction between proteins of the replication complex that forms a pseudoknot structure with a stem-loop.[50,51]

Virus assembly and release

Little is known about HCV assembly and release due to the lack of appropriate study models. Different variants of the HCV core protein, which can exist as dimeric, and probably multimeric forms as well, have been shown to be capable of self assembly in yeast in the absence of viral RNA, generating virus-like particles with an average diameter of 35 nm.[52] Particle formation is probably initiated by the interaction of the core protein with genomic RNA; HCV core can indeed bind positive-strand RNA in vitro through stem-loop domains I and III.[53]

Discussion

Hepatitis C virus (HCV), and hepatocellular carcinoma (HCC)

The HCV-related HCC is the result of liver necroinflammatory virus induced, and there is recent evidence suggests the virus may also act as a direct carcinogenic factor causing direct mutation in the DNA of the hepatocytes, as well as in carcinogenesis caused by B viruses (HBV).[21] The HCV protein might act by repressing the p53 activity, because after the virus-host interactions, the HCV protein is preserved. This structure operates modulating of cell proliferation, apoptosis and immune response and plays an important role in hepatocarcinogenesis, favoring tumor growth.[20] In typical cases of chronic hepatitis C there is a quiescent state for 10 years or more and the mean time of HCC onset, after the viral infection, is 30 years in most cases.[9,54]

The influence of hepatitis c molecular events in hepatocellular carcinoma

The causative mechanisms of HCC in people infected with HCV remains poorly understood, however it has been shown that the infection leads to persistent inflammation (chronic inflammation), steatosis, fibrosis, cell regeneration and proliferation, acquiring pre-neoplastic characteristics in an oxidative metabolic processes that affect DNA (production of reactive oxygen species) turning into a positive feedback to the malignant transformation.[55]

Numerous genetic and environmental changes are involved in the molecular pathogenesis of HCC. The p53 tumor suppressor gene when mutated requires only the modification of one allele to have its function altered, since the mutant protein is unable to protect the cell cycle functions.[7,56] The p53 gene is involved in various cellular homeostasis maintenance functions. It is responsible for inflammatory response to stress, at lower levels of DNA damage in the cell cycle.[56]

The proteins encoded by the HCV RNA bind to p53 to form protein-protein complex and inactivate p53 dependent-events. This effect of the virus on p53 provides the basis for malignant cell transformation.[13] Mutations that occur in the hepatocytes genome are identified and repaired by p53. Its auditing function in cell division events become dysfunctional with the assembly described previously,[57] inducing errors in gene expression. Therefore, the mutation of p53 may lead to failure in DNA repair causing the onset of mutated hepatocytes.[58,59]

Another important component in the development of HCC is β-catenin, a protein with multiple functions essential in the cell-cell

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adhesion process, cell communication and cellular signals transducing, fundamental processes in the regulation of cellular functions such as growth, differentiation, migration, proliferation and cell death.[60] Some studies have shown that β-catenin downregulation expression is present in several types of malignancies, including HCC.[61,62]

β-catenin is rapidly phosphorylated and degraded in the cytoplasm, but when there is activation of Wnt signaling pathway, the E-cadherina/β-catenin complex became stabilized, thereby facilitating β-catenin translocation towards the nucleus.[61,63] Recent studies have shown that the frequency of genetic mutations of β-catenin in HCC patients with HCV is usually twice, compared to other cancers.[13]

Other important effectors were also reported in the literature due to the carcinogenesis process in patients infected with HCV, such as transforming growth factor beta, TGF-β, and reactive oxygen species (ROS).[64] TGF-β plays an important role in apoptosis and liver fibrosis.[65] TGF-β and activin are members of the TGF superfamily and play a wide role in development, proliferation and apoptosis. These growth factors exert their biological effects by binding to the type I and II membrane receptors to transduce their signaling through the nucleus by phosphorylation of R-SMADs (SMAD 2/3) and co-SMADs (Smad 4). The proper control of TGF-β/activin pathway is negatively regulated by inhibitory SMAD (SMAD7) and by E3 ubiquitination enzymes (Smurfs). Alterations in the receptors and components of SMAD signaling pathway are associated with several types of tumors. Since TGF-β and activin generate their intracellular signaling through the same components of the SMAD pathway, in the susceptible HCC cells, the unbalance of this pathway impairs may play also an important role on both of the described above anti-mitogenic signals on the HCC development and progression.[66]

ROS act directly on essential biomolecules, inducing hepatotixicty, and also indirectly activating the cascades of redox-sensitive transcription factors which leads to the production of cytotoxic, pro-inflammatory and fibrogenic mediators. The chronic hepatitis phenotype increases with fibrotic events and higher degree of necroinflammatory.[65] When those events are associated with downregulation of the tumor suppression signals - p53, p16 and p21 pathways - the mechanisms that impel hepatic fibrosis, ROS-dependent increase the risk of HCC occurrence.[66,67]

Conclusion

Understand the cellular and molecular basis of neoplastic transformations that occur in the liver, represents an important key in the development of effective strategies for the prevention and/or treatment of HCC. In update description through this work, we demonstrated important signaling pathways in the development of HCC carcinogenesis throughout HCV pathogenesis and its molecular mechanisms. It was possible to highlight, at molecular level, that HCV influences chronic hepatitis, evolving into the HCC phenotype.

These molecular alterations derived from host-pathogen interactions interfere the hepatocyte normal effectors expression leading to severe, and most of the times, irreversible changes in liver cell metabolism. To understand the interactome behind these well-driven mechanistic events could lead to more realistic molecular targets, as well to early screening for possible biomarkers molecules.

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Conflict of interest

None.

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