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RESEARCH ARTICLE

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Molecular mechanisms of hepatitis C virus (HCV) triggering normal cell transformation into cancer: A mini review

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Abstract

HCV infection has become a serious concern because it can trigger the severity of complications leading to HCC. HCV is a virus with ssRNA type genetic material, with virions composed of structural proteins such as glycoprotein, envelope, and core, as well as non-structural proteins such as NS3, NS4, NS4B, NS5A, and NS5B. The development of HCV infection therapy has been carried out through DAAs with the hope of achieving a reduction in mortality and HCC risk. However, these strategies cannot fully reduce the risk of HCC in patients who have recovered from HCV infection. This review briefly reviews several factors from the virus and host to trigger cellular transformation of hepatocytes into HCC. HCV infection can trigger the transformation of hepatocytes into cancer in the case of HCC influenced by two factors consisting of pro- oncogenic and growth factors. Pro-oncogenic of HCV initiates HCC through the release of ROS that triggers genetic mutations and upregulation of proliferation in hepatocytes; it allows internal cell factors to also work in the process of transformation into cancer such as increased growth factor activity for anti-apoptotic response, survival, and proliferation to trigger increased severity of HCC.

Keywords: HCC; HCV; Hepatitis; Liver Cancer

Introduction

Liver cancer is one of the cancers with a high mortality rate in the world. Liver cancer or hepatocellular carcinoma (HCC) cases are mostly due to hepatitis C virus (HCV) infection has been identified as a major factor. HCV infection in the liver is both acute and chronic, both of which can lead to severe liver damage such as cirrhosis and HCC[1,2]. HCV is a single-stranded ribonucleic acid (ssRNA) type virus, with virions composed of structural proteins such as glycoprotein, envelope (E), and core, and nonstructural proteins such as NS3, NS4, NS4B, NS5A, and NS5B[3,4].

The development of HCV infection therapy has been carried out through direct-acting antiviral agents (DAAs) with the hope of achieving reduced mortality and risk of HCC. However, these strategies cannot fully reduce the risk of HCC in patients who have recovered from HCV infection. The transformation of hepatocytes into cancer is still being studied and much research has been done by scientists. Several studies have shown that the risk of HCC severity increases due to two factors: viral proteins from HCV and growth factors in host cells[5,6]. This review describes the molecular mechanism of several factors from the virus and the host to trigger cellular transformation of hepatocytes into HCC in a concise manner.

Brief on HCV

HCV is a virus with an envelope consisting of ssRNA from the Flaviviridae family, the virus was originally discovered in 1989[7]. The virus has a heterodimeric glycoprotein form on the envelope consisting of E1 and E2, these two proteins are the main targets of the antibody neutralization process. HCV has a structure called lipoviral particle formation on the virion surface, although the density is low, this structure can reduce the effectiveness of antibody binding and form a protective shield. The identified host cells of HCV are hepatocytes, dendritic, B, and Tcells[8,9].

When HCV performs the entry process, it requires various factors from the host cell to trigger the next stages such as binding to receptors, endocytosis, and internal fusion and then affect the signaling pathway of host cell proliferation and survival[10,11]. The role of microRNAs (miRNAs) such as miR-122 in HCV is used to stabilize the translational process of viral genes in the endoplasmic reticulum. The virus has NS2/NS3 and NS3/4 proteases for the formation of structural proteins such as core, E1, E2 and non-structural proteins are p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B. HCV takes over a kinase enzyme from the host cell such as lipid kinase phosphatidylinositol 4-kinase III to trigger the formation of replication complex or membranous web which can then produce lipoproteins for the virus assembly process. The new virus particles are released through the Golgi apparatus then go to the extracellular region through the mechanism of exocytosis[12,13].

HCV pro-oncogenic proteins

HCV does not have oncogenic proteins that directly trigger the transformation of host cells into cancer like HPV and Rous sarcoma virus. HCV infection can trigger changes in the regulation of biological pathways in host cells to produce increased tumor growth through cell proliferation and survival. This is played by a type of pro-oncogenic proteins such as core protein, NS3, and NS5A. NS3 is identified as a protease, RNA helicase, and nucleoside triphosphatase (NTPase) in HCV[14,15].

Core protein composed of RNA-binding protein is one of the pro-oncogenic parts of HCV because it can trigger hepatocyte proliferation through the release of reactive oxygen species (ROS) production that leads to disruption of β-oxidation signalling, increased ROS leads to genetic mutations in host cells that trigger a high risk of HCC[16,17]. The pro-oncogenic ability of NS3 was identified through in vivo experiments through NS3 overexpression in experimental animal models such as mice can trigger the growth of ectopic tumors. NS5A plays an important role during RNA replication, virion assembly, and causes HCV to have an interferon resistance mechanism[18,19]. Excessive NS5 activity can lead to an increased risk of HCC as proven by *in vivo* research in transgenic mice (**Figure 1**).

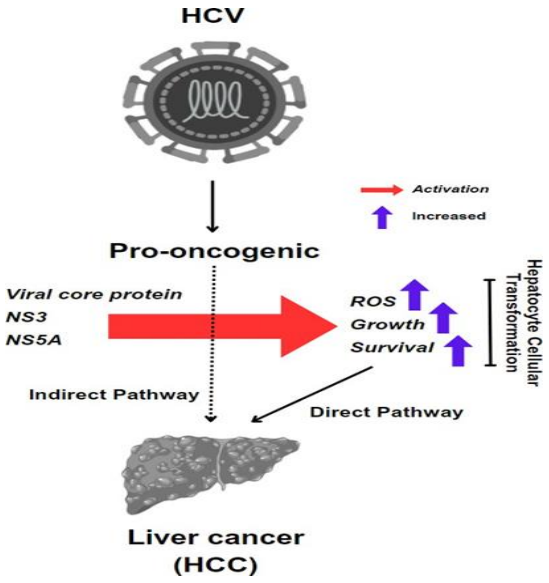

Figure 1. HCV pro-oncogenic triggers liver cancer or HCC through an indirect pathway. HCV has specific proteins consisting of viral core protein, NS3, and NS5 that are encoded pro-oncogenic. The activity of the three proteins can trigger an increase in ROS release, growth signalling, and survival that leads to cellular transformation of normal hepatocytes into HCC through the direct pathway.

How HCV turn normal cells into cancer?

HCV infection has been identified to trigger changes in signalling regulation in host cells that contribute to the development and increased risk of HCC. Several signalling pathways play an important role in the mechanism of HCV transforming normal cells into cancer consisting of vascular endothelial growth factor (VEGF), signal transducer and activator of transcription 3 (STAT3), epidermal growth factor (EGF), and transforming growth factor beta (TGF-β)[20,21]. EGFR may act as a host cell factor that regulates viral entry into hepatocytes. In the early stages of HCV replication, it binds to host receptor complexes such as CD81 and claudin-1 (CLDN1) and triggers phosphorylation of EGFR for HCV internalization. During viral entry and replication, sustained EGFR signalling can trigger viral evasion of natural antiviral response mechanisms through interferon. Increased EGF expression also triggers increased liver fibrosis and HCC[22,23].

Similar to EGF, STAT3 also acts as a factor from the host to drive the HCV replication process. HCV triggers STAT3 activation directly through binding to core proteins, STAT3 is also involved in increasing ROS production in host cells through signalling with NS5A. STAT3 activation in hepatocyte cells is not limited, it is proven through experiments that cells with HCV infection trigger the release of miR-19a when in exosomes, it promotes increased STAT3 phosphorylation through downregulation of SOCS3 (signalling for the effectiveness of immune responses, regulation of balance, and suppression of inflammation). This makes STAT3 signaling increase the malignancy of HCC[24,25].

Activation of the TGF-β signaling pathway triggers increased progression of liver fibrosis. When HCC occurs, the cytokine has two roles: suppressing tumor progression at an early stage and as a tumor driver through stimulation of antiapoptotic gene activation. Interestingly, oncogenic TGF-β activity can trigger EGFR activation as well to promote increased replication and entry in HCV. TGF-β can trigger increased liver fibrosis and accelerated tumor growth through angiogenesis by interacting with core-

stimulated expression of endoglin (CD105)[21,26]. The process of new tissue formation in cancer cells or angiogenesis is influenced by VEGF signalling, which can trigger the development of cancer into solid tumors. Increased VEGF occurs during HCV infection through hypoxia-inducible factor 1 alpha (HIF-1α) and STAT3 transcription factor activity. VEGF signalling can be a facilitator of HCV for tumor cell entry and survival, suggesting VEGF activity can trigger the transformation of hepatocytes into HCC[27–29].

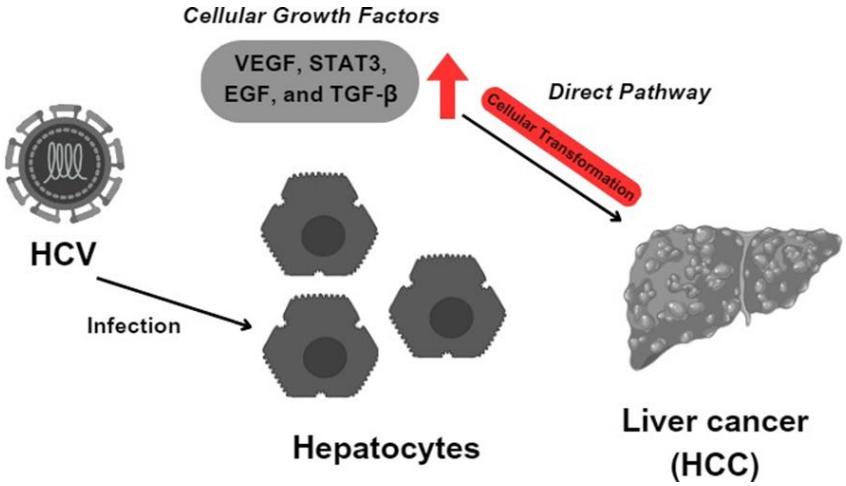

Figure 2. Growth factor mechanisms in host cells trigger cellular transformation into cancer. HCV infection triggers changes in the regulation of growth factors such as VEGF, STAT3, EGF, and TGF-β in hepatocytes, triggering the mechanism of cellular transformation into liver cancer or HCC.

In summary, HCV infection in hepatocyte cells can trigger transformation into HCC influenced by two factors, namely from the virus such as pro-oncogenic (core protein, NS3, and NS5A) and growth factors in host cells consisting of VEGF, STAT3, EGF, and TGF-β. Most oncogenic factors that trigger the transformation of hepatocytes into HCC indirectly affect the immortalization process through increased cell proliferation. The ability of HCV to evade immune response has been identified such as inhibition of regulation of interferon response, and increased disruption of balance in immune response. Interestingly, HCV infection can trigger an increase in ROS release by inhibiting the regulation of antioxidant responses by mitochondria to trigger the transformation of hepatocytes into HCC based on previous research has also been reported (**Figure 2**).

Conclusions

HCV infection can trigger the transformation of hepatocytes into cancer in the case of HCC influenced by two factors consisting of pro-oncogenic and growth factors. Pro-oncogenic of HCV initiates HCC through the release of ROS that triggers genetic mutations and increased regulation of proliferation in hepatocytes, it allows internal cell factors to also work in the process of transformation into cancer such as increased growth factor activity for anti-apoptotic response, survival, and proliferation to trigger an increase in the severity of HCC.

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Conflicts of Interest

The authors declare no conflict of interest in any capacity, including competing or financial.

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