# HEPATITIS C VIRUS ONCOGENESIS

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**Abstract**

Hepatitis C virus (HCV) is a principal cause of liver-related mortality worldwide. Recent estimates have shown an increase in its prevalence over the last decade to 2.8%, with approximately 185 million infections worldwide. HCV was considered as oncogenic to humans by the International Agency for Research on Cancer (IARC) in 1993. Four HCV proteins (core, NS3, NS5A and NS5B) appear to deregulate potentially oncogenic signaling pathways. Proliferative signaling pathways of mammalian cells are altered by extracellular factors that incorporate specific programs of gene transcription and protein regulation. Physiological feedback systems like contact inhibition, controlled availability of growth factors and others ensure a firm regulation of the proliferative signaling pathways. Uncontrolled cell proliferation is the principal aspect of most cancer types. The dedifferentiation of hepatocytes, which is accompanied by significant changes in intracellular communication and nutrient supply, is a key aspect of HCC development. The current understanding of tumor formation has greatly benefited from the discovery and study of stem cell-like cells in cancers. NF-κB participates in the immune system's role in the removal of transformed cells. This is supported by the finding that NF-κB activation during the acute inflammatory response is strongly correlated with the response of cytotoxic immune cells. Once phosphorylated, STAT3 joins forces with STAT1 or STAT5 to form homo- or heterodimers that move to the nucleus and bind particular DNA sequences. Without a doubt, STAT3 transcriptional activity depends on phosphorylation. However, unphosphorylated STAT3 also performs biological activities like regulating the expression of genes involved in cell cycle progression.

**Keywords:** Hepatitis C virus (HCV)

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## BACKGROUND:

Hepatitis C virus (HCV) is a principal cause of liver-related mortality worldwide. Recent estimates have shown an increase in its prevalence over the last decade to 2.8%, with approximately 185 million infections worldwide [1]. One-third of chronic HCV infections may develop to cirrhosis and hepatocellular carcinoma (HCC) [2]. Meanwhile, nearly 350,000 patients will die from HCV-related complications [3].

Tumor-inducing viruses represent a significant field of study for the understanding of molecular oncogenesis. Several oncogenes were discovered at first in association with retroviruses and then associated with most types of cancer [4,5]. Oncogenic viruses have direct and indirect effects on oncogenesis [6].

HCV was considered as oncogenic to humans by the International Agency for Research on Cancer (IARC) in 1993 [7]. Four HCV proteins (core, NS3, NS5A and NS5B) appear to deregulate potentially oncogenic signaling pathways [8]. It is questionable that HCV creates a pro-carcinogenic environment in the liver by initiation of a chronic inflammatory condition [9]. The study of the HCV life cycle declared numerous host dependencies of the virus that involve signaling molecules [10,11].

Multiple studies have illustrated signaling cascades that are altered by chronic HCV infection and are engaged in carcinogenesis. These cascades are categorized into three categories according to their role in cell proliferation and survival, differentiation, adhesion, angiogenesis and inflammatory response [12].

### 1- HCV stimulates persistent proliferative and anti-apoptotic signals inside infected cells:

Proliferative signaling pathways of mammalian cells are altered by extracellular factors that incorporate specific programs of gene transcription and protein regulation [13,14].

Physiological feedback systems like contact inhibition, controlled availability of growth factors and others ensure a firm regulation of the proliferative signaling pathways. Uncontrolled cell proliferation is the principal aspect of most cancer types [15].

Usually, growth factor and cytokine signaling pathways fundamentally stimulate all the principal steps of tumor progression which consist of clonal expansion, invasion, angiogenesis and metastatic formation [16].
Tumor suppressors - as the cellular tumor antigen p53 and the retinoblastoma-associated protein (pRb) - regulate cell proliferation and their perturbation promotes a continuing activation of the cell cycle [15].
Although Hepatocellular carcinoma proliferative index is generally low, there is an obvious association between HCC risk and proliferative signals in a pre-tumor condition [17].

**2- HCV affects signaling pathways of differentiation, adhesion and angiogenesis:**

The dedifferentiation of hepatocytes, which is accompanied by significant changes in intracellular communication and nutrient supply, is a key aspect of HCC development. The current understanding of tumor formation has greatly benefited from the discovery and study of stem cell-like cells in cancers [18].
CSCs are similar to normal tissue stem cells in some important ways (e.g., unlimited proliferative and differentiation ability), but they also have the potential to replicate many aspects of the development, spread, and recurrence of cancer [19, 20].
In the case of hepatocellular carcinoma, tumor tissues contain large numbers of liver cancer stem cells that promote malignant transformation and chemotherapeutic resistance [21].
Numerous liver cancer stem cell markers that affect the signaling circuits and are thought to be potential therapeutic targets for HCC therapy have been identified [22].

**3- HCV modifies inflammatory response signaling:**

An important physiological reaction to a variety of upsetting stimuli, such as infection, is inflammation. Additionally closely related to the mechanisms of both cancer and tissue regeneration is inflammation. NF-B and STAT3 are key regulators of liver inflammation during chronic inflammation and are frequently linked to an increased risk of cancer [23].
NF-κB participates in the immune system's role in the removal of transformed cells. This is supported by the finding that NF-κB activation during the acute inflammatory response is strongly correlated with the response of cytotoxic immune cells [24].
Numerous cancers have constitutively active NF-κB, which supports oncogenic processes [25].
Leukemia inhibitory factor (LIF), interleukin 6 (IL-6), cardiotrophin-1 (CT-1), oncostatin M (OSM), IFN-, and IFN- are examples of many ligands that can activate STAT3 [26].
When these ligands bind to their receptors, Janus kinases (JAK1, 2, and 3) and tyrosine kinase 2 (TYK2) are then recruited and they phosphorylate STAT3 as a result [12].
Once phosphorylated, STAT3 joins forces with STAT1 or STAT5 to form homo- or heterodimers that move to the nucleus and bind particular DNA sequences. Without a doubt, STAT3 transcriptional activity depends on phosphorylation. However, unphosphorylated STAT3 also performs biological activities like regulating the expression of genes involved in cell cycle progression [27, 28].
STAT3 signaling is closely related to NF-κB signaling. STAT3 signaling and hepatic IL-6 production are induced by NF-κB -mediated inflammation [29].
In cancer cells, activated STAT3 binds to the NF-κB complex proteins RelA/p65 and the nuclear histone acetyltransferase p300. As a result, RelA/p65 dimers are reversibly acetylated by p300, resulting in RelA nuclear retention [30].
NF-κB can also reduce oxidative stress, which is a STAT3 activator, at the same time [31].

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