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TOPIC HIGHLIGHT

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Hepatitis C-associated liver carcinogenesis: Role of PML nuclear bodies

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Abstract

Successful escape from immune response characterises chronic hepatitis C virus (HCV) infection, which results in persistence of infection in about 80% of the patients. The deleterious consequences are cirrhosis and hepatocellular carcinoma. HCV accounts the most frequent cause for hepatocellular carcinoma (HCC) and liver transplantation (LT) in the western world. The underlying molecular mechanisms how HCV promotes tumor development are largely unknown. There is some *in vitro* and *in vivo* evidence that HCV interferes with the tumor suppressor PML and may thereby importantly contribute to the HCV-associated pathogenesis with respect to the development of HCC. The tumor suppressor protein "promyelocytic leukemia" (PML) has been implicated in the regulation of important cellular processes like differentiation and apoptosis. In cancer biology, PML and its associated nuclear bodies (NBs) have initially attracted intense interest due to its role in the pathogenesis of acute promyelocytic leukemia (APL). More recently, loss of PML has been implicated in human cancers of various histologic origins. Moreover, number and intensity of PML-NBs increase in response to interferons (IFNs) and there is evidence that PML-NBs may represent preferential targets in viral infections. Thus, PML could not only play a role in the mechanisms of the antiviral action of IFNs but may also be involved in a direct oncogenic effect of the HCV on hepatocytes. This review aims to summarise current knowledge about HCV-related liver carcinogenesis and to discuss a potential role of the nuclear body protein PML for this this hard-to-treat cancer.

Key words: Hepatitis C virus; Promyelocytic leukemia; Nuclear bodies; Hepatocellular carcinoma; Apoptosis

Core tip: Escape from immune response and non-responsiveness to interferon-therapy are frequently observed in hepatitis C virus (HCV) infection. HCV infection leads to severe liver disease like cirrhosis and hepatocellular carcinoma and is the major cause for hepatocellular carcinoma and liver transplantation in the western world. Interestingly, HCV interferes with tumor suppressor promyelocytic leukemia (PML) function in apoptosis. PML localises to multi-protein complexes termed nuclear bodies (NBs). The number and the size of PML NBs are increased upon interferon-treatment and PML NBs represent preferential targets in viral infection. Accordingly, PML plays an important role in the antiviral action of interferons.

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HEPATOCELLULAR CARCINOMA

The HCC, which accounts for 80%-90% of primary liver tumors is the fifth most common cancer worldwide and the third most common cause of cancer mortality[1]. While therapeutic options are scarse, liver transplantation has become the treatment of choice for the early stage of unresectable HCC patients because it offers complete tumor excision along with the removal of the carcinogenic liver[2].

Chronic viral hepatitis B and C infections are the most important risk factors, responsible for the majority of HCC worldwide[3]. While cirrhosis accounts as precarcinogenic condition as such, hepatocarcinogenesis is a multistep process and hepatitis viruses are supposed to excert a direct oncogenic effect in hepatocytes[4]. It has been proposed that HCC development requires a combination of two mechanisms implying cell lysis and stimulation of mitosis, leading to an accumulation of molecular events necessary for transformation, followed by increased neoplasia mediated by induction of recombinogenic proteins during chronic hepatitis. Thus, HCV-related HCC is a consequence of accumulative somatic mutations in the genome of virus-infected liver cells[5]. However, the exact mechanisms are either diverse or not elucidated yet, making current available therapeutic modalities for HCC largely inadequate. So far, cytotoxic chemotherapy has proven ineffective and no first-line therapy has emerged for advanced HCC[6]. Despite major efforts to improve diagnosis and treatment of HCC, therapeutic options remain limited to local ablative procedures like transarterial chemoembolization (TACE) and selective interne radiotherapy (SIRT) with liver transplantation (LT) being the only curative treatment approach. Thus, the need for novel therapeutic agents and strategies is obvious.

Chronic infection with hepatitis C virus (HCV) has been causally associated with HCC[7]. Advances in imaging and treatment gave rise to some improvement in prognosis of patients with HCV-related HCC, but outcomes are still unsatisfactory. Reasons for this unfavourable prognosis are considered to include high intrahepatic tumor recurrence rates and sustained hepatic damage, both resulting from HCV infection. Underlying HCV-related hepatic damage may also impair liver function and consecutively clinical outcome. Thus, prevention of HCC recurrence and preservation of liver function are both central issues for improving prognosis of patients with HCV-related HCC.

The combination of pegylated interferone (PegIFN) plus ribavirin (RBV) was the standard of care for HCV infection for 10 years until 2011, when the first generation protease inhibitors boceprevir (BOC) and telaprevir (TVR) were approved. For the other genotypes, the PegIFN plus RBV treatment regimen remained the standard of care. This treatment fails to eradicate HCV in many chronically infected patients with additional side effects. In those patients for who PegIFN was effective in eradicating HCV, this treatment could have value in minimizing hepatic necrosis, inflammation and fibrosis, and thus, reducing the incidence of HCC[8]. Several studies have reported that IFN therapy, even after curative treatment for HCV-related HCC, could prevent HCC recurrence and improve survival[9]. Moreover, PegIFN-alpha has been shown to effectively treat advanced hepatocellular carcinoma (HCC), even more so in combination with 5-fluorouracil (5-FU)[10]. However, the mechanisms by which IFN suppresses HCC recurrence, including possible direct anti-tumor and anti-inflammatory effects, remain uncertain.

Recently we described that the IFN-α increases the expression of the tumor suppressor TNF-related apoptosis-inducing ligand (TRAIL) in hepatoma cells, a mechanism that is mediated bei the promyelocytic leucemia protein (PML)[11] indicating that enhanced expression of PML and TRAIL and subsequent activation of death receptors is a central feature in IFN-associated regulation of apoptosis in liver tumor cells[12]. Thus, TRAIL and PML may account central components in IFN-mediated apoptosis regulation and prevention of hepatocarcinogenesis.

Since the recent approval of several new direct acting antivirals (DAAs), IFN might become dispensable and HCV therapy achieves currently a new milestone, as some highly effective antiviral substances are now available and more are awaited[13]. Experts promise complete eradication of the virus in the coming years. Thus, 2014 is the beginning of a new era of treatment options for HCV infection and the consequences on the incidence of HCC can eagerly be awaited.

PML NUCLEAR BODIES

Tumor suppressor protein PML localizes predominantly to distinct nuclear domains termed PML-nuclear bodies (PML-NBs), multiprotein complexes implicated in apoptosis regulation, cellular senescence and antiviral response. PML-NBs are present in almost every human cell type and appear as discrete nuclear dots. More than 50 different proteins have been localized to PML NBs, which are defined by the two molecular marker proteins PML and Sp100. PML-NBs can contain ribosomal proteins, transcription factors, transcriptional cofactors, as well as oncoproteins and also viral proteins, which are transiently associated with PML-NBs[14].

In leukemic blast of patients suffering from acute promyelocytic leukemia, the PML gene is reciprocally fused with the *retinoic acid receptor* α gene, thus resulting in expression of an oncogenic PML-RARα fusion protein. PML-RARα protein leads to disruption of PML-NBs in numerous tiny microspeckles, and its expression leads to cellular transformation and induction of leukemia. Treatment of APL patient with all-trans retinoic acid or arsenic trioxide (As_2O_3) causes reformation of PML-NBs and triggers either terminal differentiation, apoptosis or senescence of the blasts, which finally results in disease remission. Investigations of *PML-RARα* transgenic and *PML*$^{-/-}$ mice have demonstrated that PML inactivation results in impaired induction of apoptosis by multiple

apoptotic pathways, and *PML*$^{-/-}$ mice are highly susceptible to developing tumors when challenged by carcinogens[15]. Recently, comprehensive studies have shown that PML protein is frequently lost in human cancers of various histologic origins[16]. These observations demonstrate that PML is crucial for critical tumor-suppressive pathways although its exact mechanism of action in most tumors is largely unknown.

Remarkably, the promyelocytic leukemia (*PML*) gene is a target of IFNs that is specifically up-regulated at the transcriptional level. Multiple isoforms of PML have been identified, most of which are found in the nucleus where they can assemble to PML-NBs[17]. In addition, PML deficiency has been linked to increased susceptibility to viral pathogens[18]. Recent reports suggest that suppression of PML by hepatitis B virus surface antigen interferes with cellular mechanisms responding to double-strand DNA damage repair or apoptosis induction, potentially contributing to hepatocarcinogenesis associated with chronic hepatitis B virus infection[19,20].

Furthermore, it is well established that PML-NBs act as platforms which are involved in the control of p53 activity[21]. PML isoform Ⅳ (PML-Ⅳ) serves as a p53 coactivator and colocalizes with numerous factors regulating p53 post-translational modification, in particular its phosphorylation and acetylation, in PML-NBs, thereby regulating p53 target gene expression and effector function. Although previous studies showed that HCV core protein interacts with p53 and affects its function, the reported effects of HCV core on p53 activity are not consistent[22,23]. We were, however, able to observe that HCV core interacts with PML, thereby interfering with p53-phosphorylation and activation and, thus, induction of apoptosis which might result in HCV-associated hepatocarcinogenesis.

HCV INFECTION AND PML

Chronic infection with HCV is a major risk factor for the development of HCC and, moreover, is considered as the leading cause for liver transplantation in the western world[24]. Some authors suggest the Hepatitis C virus-induced chronic inflammation and the effects of cytokines in the development of fibrosis and liver cell proliferation as major pathogenic mechanisms for HCV-associated HCC development. On the other side, the HCV is an RNA virus that does not integrate into the host genome but HCV proteins interact in the cytoplasm with many host-cell proteins, thereby influencing cell signalling, transcription, cell proliferation, apoptosis and translational regulation[25]. Some convincing experimental evidence suggests that HCV contributes to HCC development by direct interference with pathways that promote the malignant transformation of hepatocytes[26]. At least four of the HCV gene products, namely HCV core, NS3, NS4B and NS5A, have been shown to exhibit transformation potential in tissue culture[26]. Several studies have investigated a potential role of the core protein in regulating apoptotic cell death. It has been demonstrated to exert both, pro- and anti-apoptotic activities[27] and in liver derived cells opposite and controversial effects were observed. It was demonstrated that the core protein might physically interact with the cytoplasmic domains of CD95, TNF-R1 and the lymphotoxin-β receptor and thereby enhances downstream signalling events of these receptors[28]. Moreover, the core protein did also interact with the death domain of FADD and with c-FLIP[29]. Because of the presence of a putative DNA-binding motif and nuclear localisation signals, a possible function of the core protein as a gene regulatory mediator has been suggested. However, interpretation of these data is difficult. In the different studies, only scarse attempts have been made in order to understand how HCV proteins could interfere with apoptosis at the molecular level.

As a central apoptosis-modulating mechanism, HCV core has also been reported to bind to p53. However, in the different reports it either activates or inactivates p53 and its downstream target p21. As mentioned above, our lab was able to shed some light on this controversy demonstrating that HCV core inhibits p53-mediated target gene expression through targeting predominantly the coactivator function of promyelocytic leukemia protein (PML)-Ⅳ[30]. These findings strongly suggest that in hepatoma cells the HCV core protein predominantly interferes with p53 function through targeting PML and not only p53, as suggested by previous reports[31-35]. Furthermore, these findings could provide an explanation for the contradictory reports about the effect of HCV core expression on p53 function, since they demonstrate a prominent role of PML in this scenario, which might be differentially expressed in the particular cell system used in these studies.

In an attempt to reduce potential artifacts caused by non-physiological overexpression in cell culture, HCV transgenic mice have been generated. In those mice, liver cell apoptosis was significantly reduced[36]. These and other data suggest that HCV proteins might directly or indirectly inhibit apoptosis rather than facilitate apoptosis. Moreover, after crossing those mice with PML knock out mice, the resulting HCV-transgenic PML-deficient mice show a significantly higher sensitivity towards induction of liver tumors[37]. These observations confirm a central role of PML in HCV-associated development of liver cancer.

CONCLUSION

While it is well established that PML mediates tumor suppressive functions, including induction of apoptosis and growth arrest, and PML has been reported to suppress the growth of breast and prostate cancer cells[38,39], it is not known whether this protein modulates key tumor suppressive pathways in the pathogenesis of liver tumors. While HCV core impairs PML function but IFN-a induces PML expression, these observations might explain the anti-hepatocarcinogenic effect of therapeutically ap-

plied IFN in HCV infection: IFN -induced PML might compensate the PML which is trapped by the virus.

These data support the potential usefulness of PML in cancer gene therapy, including the treatment of various types of liver cancers, and suggest that the PML gene can be effective in tumor cells resistant to p53-mediated apoptosis, such as advanced liver cancer in adults. In addition, it will be interesting to treat tumors in HCV-transgenic PML-deficient mice with a liver-specific adenovirus recombinantly expressing PML. Speculations that PML-reconstitution has a not only therapeutic but also preventive effect on hepatocarcinogenesis is intriguing and thus, we would postulate a therapeutic potential for PML in this setting.

An immunohistologic study of PML expression in hepatocarcinogenesis describes differential overexpression of PML in dysplastic nodules versus in carcinoma suggesting a differential regulation during the multistep hepatocarcinogenesis[40]. To further elucidate a functional role for PML in HCC, it would be interesting to address the question, whether PML expression in HCCs is associated with chronic HCV infection and whether velocity of disease progression correlates with alterations in PML expression or defects in the PML gene.

While the induction of PML appears important for enhanced expression of death receptors and apoptosis in liver cancer, the binding partners of PML appear to be quite diverse in different cell types. To understand its role in transcriptional control, a major focus in the future will therefore be to identify transcription factors with which PML interacts upon IFN stimulation.

The availability of both IFN-responsive and non-responsive lines together with availability of the HCV replicon system in combination with techniques such as array analyses will contribute to identify PML-regulated target genes, which are involved in HCV replication. Subsequently, additional tumor suppressive pathways that are regulated by PML upon IFN treatment might be identified in order to elucidate molecular mechanisms of HCV-associated hepatocarcinogenesis. Finally, new generation DAAs must be assessed with respect to their potential to influence the expression of tumor suppressors. Those studies will provide new insights into the understanding of the use of old versus new HCV therapeutics with respect to their potential for not only the treatment of HCV infection but also to prevent hepatocarcinogenesis.

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