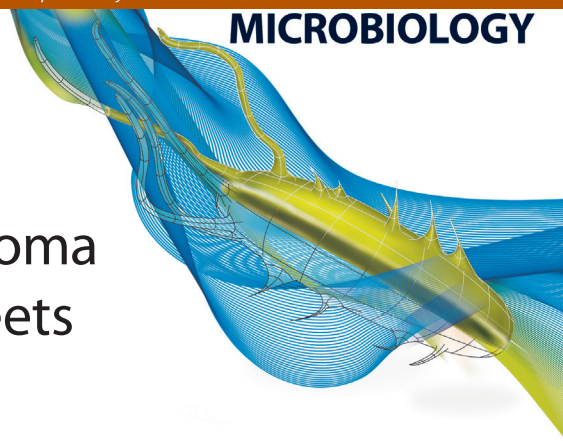
REVIEW
For reprint orders, please contact: reprints@futuremedicine.com



Residual risk of hepatocellular carcinoma after HCV eradication: more than meets the eye

Fabio Salvatore Macaluso*[,1], Vincenza Calvaruso[1] & Antonio Craxì[1]

ABSTRACT Eradication of HCV in patients with advanced liver fibrosis or cirrhosis reduces, but does not altogether abolish, the risk of development of hepatocellular carcinoma. The reasons underlying this residual risk remain elusive. Even if HCV clearance eliminates its direct and indirect carcinogenic effects, the persistence of cirrhosis and the possible coexistence of metabolic factors (diabetes, obesity and insulin resistance) and of alcohol abuse can promote the development of hepatocellular carcinoma acting as autonomous, nonviral carcinogenic factors. Lessons learned in the IFN era may still assist in predicting the forthcoming scenario, when IFN-free regimens will obtain high rates of viral clearance even at the most advanced stages of liver disease.

KEYWORDS
• cirrhosis • HCV
• hepatocarcinogenesis
• hepatocellular carcinoma
• IFN-free regimens
• sustained virological response

Hepatocellular carcinoma (HCC) is a challenging malignancy of global importance, being the second cause of cancer-related death worldwide [1]. The majority of HCCs occur in the context of chronic infection with HBV and HCV, and the cancer risk is directly related to the histological and clinical stage of the underlying liver disease [2]. In particular, HCV infection stands today as the leading risk factor for HCC in many industrialized countries [3], occurring at a rate between 3 and 8%, according to the geographic area, in patients with HCV-related cirrhosis [4]. On these assumptions, prevention of population exposure to HCV can be regarded as the most effective tool to reduce liver-related mortality from HCC due to chronic HCV infection. In the HCV scenario, where an effective vaccine is not currently available, antiviral treatments have stood as the real backbone of prophylaxis strategy in the prevention of HCC, of course together with all procedures implemented to prevent HCV transmission [5].

However, the evidence that patients with chronic hepatitis C (CHC) are completely protected against occurrence of HCC by successful IFN-based treatments is controversial, mainly due to methodological limitations of available literature. All in all, HCC risk seems to be sharply attenuated, although not completely eliminated – especially in patients with advanced fibrosis – following eradication of HCV infection, and the causes for this residual HCC risk in patients who achieved a sustained virological response (SVR) remain receding. Moreover, the intrinsic limitations of the use of IFN to patients with less advanced liver disease have curtailed the potential benefit, due to the fact that HCC in HCV cirrhosis becomes more prevalent at the more advanced stages of liver disease.

In this review, we discuss the available clinical evidence of the role of antiviral treatment against chronic HCV infection for the prevention of HCC, and the residual risk existing in patients successfully treated. In addition, we focus on the molecular mechanisms that might explain the pathophysiological rationale of the reduction, but not elimination, of HCC risk after HCV eradication. The lesson from the IFN era may be extremely useful to predict the near-future scenario, when

[1]Sezione di Gastroenterologia & Epatologia, DiBiMIS, University of Palermo, Italy
*Author for correspondence: Tel.: +39 091 655 2274; Fax: +39 091 655 2156; fsmacaluso@gmail.com

Future Medicine part of fsg

the IFN-free regimens will determine extremely high rate of SVR and will also be administered to patients with advanced or decompensated cirrhosis, thus reducing dramatically liver-related events – including HCC – and mortality due to HCV infection.

The role of antiviral treatment for the prevention of HCV-related HCC

As previously mentioned, the evidence that patients with CHC are effectively protected against HCC risk by IFN-based regimens is rather controversial, due to several methodological concerns in the literature on this topic [6]. First, most of the available evidence examining the relationship between SVR and HCC is observational and retrospective, so that treatment outcomes could not properly be adjusted for important risk factors for HCC such as age, HCV genotype, coinfections with HBV or HIV, fibrosis stage, other well-known potential carcinogenic factors (for example diabetes, obesity and alcohol abuse) and presence of advanced liver disease and comorbidities – the latter two causes of ineligibility to IFN-based treatments. Indeed, it should be noted that the exclusion to IFN-based treatments of patients with severe comorbidities and advanced/decompensated chronic liver disease, in other words, the closest to develop HCC, might have caused an overestimation of risk reduction of HCC and all-cause mortality in the cohorts of HCV patients who achieved an SVR [7]. In addition, long-term outcomes of treatments against chronic HCV infection are difficult to assess because, on the one hand, the diagnosis of HCV infection often occurs after symptoms appearance, in other words, at a late stage of disease, and, on the other hand, natural history studies of cohorts successfully treated for HCV typically have inadequate length of follow-up in relation to the outcomes of interest, which may occur after several decades. Nonetheless, the evidence seems sufficient to state that HCV-related HCC is more likely to be prevented in young patients with mild fibrosis achieving an SVR, rather than in elderly patients with cirrhosis [8].

One of the first studies regarding the potential role of antiviral therapy in preventing HCV-related HCC in cirrhotic patients derived from a small Japanese trial published in 1995 [9]: HCC occurred only in two out of 90 patients (4%) with HCV-related cirrhosis treated with IFN-α, a much smaller proportion if compared with untreated controls (38%), resulting in a risk ratio of IFN-α treatment versus no treatment of 0.067. Along this line, the Inhibition of hepatocarcinogenesis by interferon therapy (IHIT) – a Japanese national surveillance program conducted during the 1990s – provided further evidence for a significant reduction of HCC risk in patients with any histological stage of hepatitis C capable to achieve an SVR [10]. Similarly, several subsequent observational studies conducted both in Western and Asiatic cohorts confirmed this chemopreventive effect of IFN-based treatments on HCC occurrence [11–31] **(Table 1)**. However, it was initially debated if this clinical benefit could be gained with antiviral treatment only, independent from the achievement of an SVR, in other words, also in nonresponder patients. Indeed, IFN has potential antitumor effects, being likely associated to its immunomodulatory action as well as to the *in vitro* ability of IFN to influence cellular differentiation and proliferation of neoplastic cells [32]. This issue was subsequently clarified by several large cohort studies, which highlighted how the risk reduction of HCC development was substantial in SVR patients only compared with non-SVR ones. A multicenter retrospective study conducted on 920 Italian patients with histologically proven cirrhosis, who received IFN monotherapy and were followed up for a median period of 96 months after the end of treatment, showed not only lower rates of liver-related complications (0 vs 1.88 per 100 person-years), but also of HCC occurrence (0.66 vs 2.10 per 100 person-years) in SVR patients compared with non-SVR [20]. Along the same line, Cardoso *et al.* performed a cohort study on 307 French patients with bridging fibrosis or cirrhosis followed up for a median of 3.5 years after the end of antiviral treatment, showing that incidence rates of HCC were lower in SVR patients compared with non-SVR (1.24 vs 5.85 per 100 person-years), and that the lack of SVR was a strong independent predictor of HCC (hazard ratio [HR]: 3.06) [26]. Similar conclusions were argued by Veldt *et al.* with their retrospective cohort study performed on North American patients with advanced fibrosis, where an SVR was associated to a reduced risk of any liver-related events (adjusted HR: 0.21), and with a lower occurrence of HCC, although this reduction was not statistically significant, probably due to the limited follow-up of the study (median 2.1 years) [27]. Finally, our group

Table 1. Summary of the main studies on the prevention of hepatocellular carcinoma in HCV patients who achieved a sustained virological response.

Study (year)	Country	Main findings	Ref.
Nishiguchi *et al.* (1995)	Japan	Reduced HCC occurrence in patients with HCV-related cirrhosis treated with IFN-α compared with untreated controls (4 vs 38%)	[9]
Yoshida *et al.* (1999)	Japan	Association of IFN therapy with a reduced risk for HCC, especially among patients with SVR and among those with persistently normal serum ALT or with ALT levels less than two-times the upper limit of normal	[10]
Okanoue *et al.* (2002)	Japan	Reduction of HCC development among patients treated with IFN and improvement of long-term survival	[11]
Kawamura *et al.* (2010)	Japan	Higher cumulative rates of HCC in diabetic patients than in nondiabetics; inpatients with SVR, no significant impact of diabetes on the rate of hepatocarcinogenesis; lack of SVR and diabetes as independent risk factors for hepatocarcinogenesis	[12]
Braks *et al.* (2007)	France	In patients with HCV-related cirrhosis, association of SVR with a significant decrease in the incidence of HCC and mortality during a follow-up period of 7.7 years	[13]
Asahina *et al.* (2010)	Japan	Although SVR was independently associated with a reduced risk of HCC, HCV eradication had a smaller effect on hepatocarcinogenesis in older patients	[14]
Velosa *et al.* (2011)	Portugal	Association of SVR with lower risk of HCC, liver transplantation and any event in patients with HCV-related cirrhosis	[15]
Kurokawa *et al.* (2009)	Japan	Association of SVR and continuous normalization of ALT levels after IFN therapy with lower risk of HCC occurrence in HCV-infected patients	[16]
Hung *et al.* (2006)	Taiwan	Association between lack of SVR, male gender and old age with HCC development after IFN-α-2b plus ribavirin therapy in patients with HCV-related cirrhosis	[17]
Sinn *et al.* (2008)	Korea	In patients treated with anti-HCV therapy, treatment response, platelet level and APRI were independent factors associated with disease progression, including HCC development	[18]
Coverdale *et al.* (2004)	Australia	Throughout 9 years of follow-up, IFN treatment *per se* did not influence the rate of liver complications. However, response to IFN was a significant predictor of liver-related complications at univariate analysis	[19]
Bruno *et al.* (2007)	Italy	Association of SVR after IFN-α therapy with a reduction – but not elimination – of HCC development in Italian patients with HCV-related cirrhosis	[20]
Shindo *et al.* (2001)	Japan	After a long-term follow-up, annual incidence of HCC was 0.37% in patients with SVR after IFN therapy, 0.50% in patients with HCV-RNA positivity but persistently normal ALT, while higher frequencies were reported in nonresponders	[21]
Morgan *et al.* (2010)	USA	Adjusted hazard ratio for time to death/liver transplantation or development of liver-related morbidity/mortality or HCC was significant lower for SVR compared with nonresponders, although a residual risk of HCC persisted despite SVR (prospective data from the HALT-C trial)	[22]
Hung *et al.* (2011)	Taiwan	Diabetes was an independent predictor of HCC in SVR patients without cirrhosis at baseline, despite a low HCC incidence, after IFN-based therapy	[23]
Van der Meer *et al.* (2012)	The Netherlands	After a median follow-up of 8.4 years, SVR after IFN-based treatment was associated with lower all-cause mortality and reduced occurrence of HCC among patients with chronic HCV infection and advanced hepatic fibrosis	[24]

ALT: Alanine aminotransferase; APRI: Aspartate aminotranferase to platelet ratio index; HCC: Hepatocellular carcinoma; SVR: Sustained virological response.

Table 1. Summary of the main studies on the prevention of hepatocellular carcinoma in HCV patients who achieved a sustained virological response (cont.).

Study (year)	Country	Main findings	Ref.
Hasegawa *et al.* (2007)	Japan	Among patients with cirrhosis due to genotype 1b low viral load or genotype 2 HCV who received IFN from 1989 to 2005, the rate of development of HCC was significantly lower in patients with SVR	[25]
Cardoso *et al.* (2010)	France	During a median follow-up of 3.5 years after treatment completion, the incidence rate per 100 person-years of HCC was lower in SVR compared with non-SVR patients (1.24 vs 5.85) among subjects with advanced fibrosis or cirrhosis at baseline	[26]
Veldt *et al.* (2007)	The Netherlands	Association of SVR with a reduced risk of any liver-related event, and with a lower occurrence of HCC, although this reduction was not statistically significant	[27]
Osaki *et al.* (2012)	Japan	Identification of lack of SVR after PEG-IGN plus Ribavirin therapy as an independent predictor of HCC development	[28]
Imai *et al.* (1999)	Japan	Risk ratios for development of HCC in patients with sustained response, relapse and nonresponse equal to 0.06, 0.51 and 0.95, respectively, compared with untreated controls	[29]
Ikeda *et al.* (1999)	Japan	Hepatocellular carcinogenesis rates in patients treated with IFN and untreated groups were 2.1 and 4.8% after 5 years of follow-up, and 7.6 and 12.4% after 10 years; rates were lower in patients with undetectable HCV-RNA or normal ALT values	[30]
Tanaka *et al.* (2000)	Japan	Hazard rate ratios for development of HCC in sustained responders, transient responders and nonresponders of 0.16, 0.27 and 0.74, respectively, compared with untreated controls	[31]
Di Marco *et al.* (2012)	Italy	After a median follow-up of 87 months, SVR was associated with a significant reduction in the incidence of HCC in cirrhotic patients with and without esophageal varices at baseline, and the global incidence of HCC was not statistically different between the two subgroups, i.e., not affected by the degree of portal hypertension	[33]

ALT: Alanine aminotransferase; APRI: Aspartate aminotranferase to platelet ratio index; HCC: Hepatocellular carcinoma; SVR: Sustained virological response.

recently performed a prospective cohort study aiming to evaluate the long-term clinical benefit of HCV eradication in patients with compensated cirrhosis with or without esophageal varices [33]. The outcomes of 440 patients consecutively treated with Peg-IFN and Ribavirin were recorded and analyzed. After a median follow-up of 87 months, the incidence of HCC in patients without esophageal varices at baseline was 0.77 per 100 person-years for SVR patients versus 3.45 per 100 person-years for non-SVR patients, while in patients with esophageal varices at baseline the incidence of HCC was 0.95 per 100 person-years for SVR patients and 4.77 per 100 person-years for non-SVR ones. Thus, SVR was associated with a significant reduction in the incidence of HCC in both groups, even if the global incidence of HCC was not statistically different between the two subgroups, in other words, not affected by the degree of portal hypertension. Furthermore, analysis of data has identified the variables independently associated with a higher risk of HCC development, and among them (age, male gender, gGT value and SVR) the presence of varices and the Child-Pugh score did not appear. Of note, different results were observed about the role of SVR in preventing the '*de novo*' occurrence of esophageal varices. Indeed, SVR was the unique variable independently associated with a reduction of the risk of esophageal varices development in patients without varices at baseline. Conversely, SVR patients with small varices at baseline may experience a progression to large varices even if an SVR was achieved. Regarding liver decompensation and mortality, we have observed a significant association between virological response and the occurrence of liver events in both patients with and without EV, although the formers maintained a risk to develop liver decompensation and to die in consequence of liver events even after SVR achievement. Further evidences were provided from three randomized controlled trials – HALT-C [34], COPILOT [35] and EPIC-3 [36] – that investigated the effectiveness of a long-term maintenance therapy with pegylated-IFN in nonresponder HCV patients with advanced fibrosis or cirrhosis. The outcomes assessed were death, hepatic decompensation, HCC development and an increase in hepatic fibrosis for non-cirrhotic patients: overall, a poor benefit of maintenance therapy on clinical outcomes – including HCC – was observed, despite the reduction of viral load and the improvement of inflammatory

markers. Of note, data from HALT-C trial with an extended follow-up (up to 8 years) showed that the cumulative rate of HCC was lower in treated cirrhotic patients compared with controls, thus demonstrating a modest benefit of long-term pegylated-IFN treatment in decreasing the incidence of HCC in patients with cirrhosis [37]. Furthermore, several meta-analyses have resumed and emphasized the relationship between achievement of SVR and subsequent risk reduction of HCC [38–41]; the most recent one by Morgan *et al.* [42], including 30 observational studies on this topic, led to quantify in almost 80% the reduction of the HCC risk across all clinical stages of CHC occurring in SVR patients compared with non-SVR.

All in all, these studies universally concluded that SVR is associated with a robust reduction of HCC occurrence, also among persons who have progressed to advanced liver disease. However, as previously stated, the strength of this association remains undefined, mainly due to the methodological issues affecting original, uncontrolled, studies producing incorrect effect estimates [6].

The residual risk of HCC among SVR patients

It should be pointed out that all the aforementioned reports highlighted only a significant reduction, but never a complete elimination, of the risk of HCC development after HCV eradication. Indeed, common to all these studies was the persistence of HCC occurrence in a minority of patients despite their achievement of an SVR. Several studies focused specifically on this issue **(Table 2)**, showing that HCC develops in 2.5–4% of SVR patients [43–45]. In this line, a large multicenter, retrospective study of 1124 Japanese patients followed for a median period of 66 months [46] reported an incidence of HCC of 3.5% among 373 SVR patients. About the temporal relationship between SVR achievement and diagnosis of HCC, some groups reported that HCCs are usually detected within 5 years after the end of therapy – thus speculating that HCC was already present but too small to be detected before the start of therapy [43,44] – while Kobayashi *et al.* emphasized how in 8 of their 13 SVR patients who developed HCC, the tumor was detected more than 5 years (up to 12 years) after the end of IFN therapy, and the temporal interval to the detection of HCC was not significantly different between SVR and non-SVR patients [46]. Common to all these reports, older age, male sex and advanced histologic stage were identified as the main independent risk factors for the future development of HCC among patients with an SVR.

Although the reasons why some SVR patients will develop HCC are still unclear, it is likely that a certain degree of fibrosis regression/cirrhosis reversal might be a key factor. This issue was suggested by Mallet and colleagues in their retrospective study of 96 HCV cirrhotic patients who had at least one liver biopsy after antiviral treatment completion [47]. After a median follow-up of 118 months, cirrhosis regression was observed in 19% of patients (all but one achieved SVR) and was associated with significant reduction of liver decompensation and HCC development, whereas patients without signs of cirrhosis regression developed liver complications (0% in patients with cirrhosis regression, 22.1% in patients without, $p = 0.036$), including HCC; furthermore, all three SVR patients who developed HCC despite viral eradication had persistent cirrhosis on the follow-up biopsy [47]. However, independent of histological features, the identification of clinical risk factors associated with a high risk of HCC development in sustained responders stands as the most relevant issue in order to detect those patients who need to be closely monitored after the end of treatment. Some of these risk factors have been easily identified, namely patient age – possibly reflecting a long duration of infection or an increased prevalence of cirrhosis and other risk factors for HCC in aged population – and advanced fibrosis/cirrhosis [14,24]. Interestingly, some of the features able to predict HCC development in viremic patients – such as advanced age, advanced fibrosis, degree of portal hypertension and elevated α-fetoprotein levels – have been identified as independent predictors of HCC also in SVR patients [48]. In addition, recent data have emphasized the potential role of metabolic and exogenous players, such as diabetes, obesity, insulin resistance and alcohol abuse, in promoting the development of HCC in SVR patients, acting as autonomous, nonviral carcinogenic factors [49,51]. In this line, a recent Taiwanese study [50], performed among 642 patients who achieved an SVR after pegylated-IFN plus Ribavirin therapy, showed that the strongest predictive factor of HCC occurrence in this cohort was liver cirrhosis, followed by age and gamma-glutamyl transpeptidase (GGT) levels – a well-known marker of metabolic syndrome

Table 2. Summary of the main studies focused specifically on the residual risk of hepatocellular carcinoma among HCV patients who achieved a sustained virological response.

Study (year)	Country	Main findings	Ref.
Toyoda *et al.* (2000)	Japan	HCC was detected in 8 out of 392 SVR patients: in seven patients HCC developed within 5 years after completion of IFN therapy, and after 7–8 years in one patient	[43]
Makiyama *et al.* (2004)	Japan	Among 1197 sustained responders, 27 patients developed HCC (2.3%). Compared with sustained responders who did not develop HCC, patients who developed the disease more often were male, older and had advanced-stage histologic disease before IFN therapy	[44]
Ekonimura *et al.* (2003)	Japan	Among 142 SVR patients, six (4.2%) developed HCC after an average interval between IFN therapy and diagnosis of HCC of 59.2 months. Five of the six cases were single HCC, and the remainder were multifocal	[45]
Kobayashi *et al.* (2007)	Japan	HCC developed in 3.5% of SVR patients. As compared with SVR patients without HCC, SVR patients with HCC were predominantly male, older and at a more advanced histologic stage of disease; three of the 13 SVR HCC patients had mild fibrosis	[46]
Mallet *et al.* (2008)	France	Among 96 HCV cirrhotic patients with at least one liver biopsy after antiviral treatment completion, cirrhosis regression was associated with significant reduction of liver decompensation and HCC development, whereas patients without signs of cirrhosis regression developed liver complications; all three SVR patients who developed HCC despite viral eradication had persistent cirrhosis on the follow-up biopsy	[47]
Chang *et al.* (2012)	Taiwan	Older age, high α-fetoprotein levels, low platelet count and advanced fibrotic stage were independent risk factors for HCC development among 871 SVR patients and were used to compute a risk score	[48]
Arase *et al.* (2013)	Japan	Type 2 diabetes causes an approximately 1.7-fold enhancement in the development of HCC and malignancies other than HCC in HCV-positive patients treated with IFN	[49]
Huang *et al.* (2014)	Taiwan	A 5.1% of SVR patients developed HCC over 2324.8 person-years of follow-up. Risk factors for HCC occurrence were cirrhosis, age and γGT levels; the incidence of HCC was significantly higher in noncirrhotic patients with high γGT levels compared with those with low γGT levels	[50]

HCC: Hepatocellular carcinoma; SVR: Sustained virological response.

and its features, of liver fibrosis and its progression and of malignancies [52]. Although the incidence of HCC did not differ between cirrhotic patients with high and low baseline GGT levels, the incidence of HCC was significantly higher in noncirrhotic patients with high GGT levels compared with those with low GGT levels. Thus, the authors suggested that GGT levels may be a potential novel marker of high risk of HCC development in noncirrhotic SVR patients. Another interesting study on this topic analyzed 871 SVR patients [48]: authors computed a numerical score based on age, sex, platelet count, serum α-fetoprotein levels, Metavir stage and diabetes – the most intriguing factor. This score allowed to estimate the 5-year HCC risk after SVR achievement so to stratify all patients into low-, medium- and high-risk patients [48].

In conclusion, despite the majority of SVR patients benefit a substantial reduction of HCC risk, particularly those young, with mild fibrosis and/or with fibrosis regression/cirrhosis reversal, a residual risk exists, particularly in older patients with advanced fibrosis and comorbidities linked to diabetes, overweight and alcohol abuse. Predictors of high risk of HCC development in responder patients should be promptly identified in order to provide cost-effective screening programs of HCC also in SVR patients.

HCV-induced carcinogenesis & residual risk of HCC after SVR achievement: pathophysiological insight

Unlike in an HBV scenario, a successful antiviral treatment against HCV infection results in viral clearance. As discussed above, this translates in an approximately threefold reduction in the risk of HCC in cirrhotic patients, and in a much greater benefit, in other words, almost the elimination of any risk, in noncirrhotic ones [39,42]. Therefore, it is obvious that HCV infection is a risk factor for liver cancer, even if it is still unclear whether HCV is directly carcinogenic or if simply triggers an inflammatory/profibrotic response that favors cancer development [53]. The most accepted hypothesis is that HCV is able to elicit both direct and indirect effects on liver cells that may promote their neoplastic transformation. Regarding direct effects, it is established how a constitutive expression of a viral oncogene or the integration of viral sequences into the genome of host cells are not involved in

HCV-related HCCs. Instead, *in vitro* models led to hypothesize that HCV is able to interfere with several cellular functions in order to promote its survival in the liver, resulting in an enhancement of all processes involved in viral replication, and in the dismantlement of the immune responses of the host. Interestingly, some of these interactions involve cellular proteins with critical roles in controlling cell proliferation checkpoints and thus with tumor-suppressor properties [54]. The most studied interaction involves the binding between the viral nonstructural protein NS5B and the retinoblastoma (Rb) protein, which results in the fast degradation of cellular Rb. Rb is a relevant protein for host cells, since it controls the G1 to S-phase transition and other crucial checkpoints of cell cycle. HCV takes advantage of such mechanism to overcome possible blocks to cell-cycle progression [55,56]; unfortunately, Rb also regulates several cellular responses to DNA damages, all of them being critical controls in the prevention of neoplastic transformation [57], so that its impaired function may promote genomic instability [58]. Furthermore, typical of HCV-related HCCs is the expression of the liver-specific microRNA (miR)-122, a host cell factor that is necessary for HCV replication and has also relevant tumor-suppressor properties in the liver [59]. In addition, the artificial overexpression of HCV proteins – including core, NS3 and NS5A – causes cellular proliferation and tumor formation in mice, thus suggesting a potential direct contribution in activating oncogenic molecular pathways [60–63]. Therefore, the replicative cycle of HCV seems to be directly linked to procarcinogenic cellular phenomena [53]. Regarding indirect mechanisms, it is well known how viral replication itself stands as a continuous stimulus to the induction of pro-inflammatory and pro-apoptotic signals [64]. Apoptosis is compensated by a marked cellular proliferation occurring in a background of oxidative stress and inflammation due to the release of several mediators by the infected liver cells. As a consequence, DNA damage may occur also in uninfected liver cells [64]. All in all, HCV proteins – both directly and indirectly – promote immune evasion, cellular deregulation and inflammation, thus producing fibrogenesis, oxidative stress, DNA damage and genetic instability: these phenomena altogether are capable to create and expand tumor-initiating/cancer stem cells [63].

On this basis, it may be easily understood why a successful HCV eradication – erasing both direct and indirect HCV-induced carcinogenic effects – results in a significant reduction of HCC risk. However, as previously discussed, this risk is not completely eliminated **(Figure 1)**. Of course, the occurrence of HCC in SVR patients may reflect the interval of time necessary for pre-existing small HCCs to become clinically evident [37]; however, this hypothesis could explain only a fraction of HCC occurring after SVR, in other words, those developed early after completion of antiviral therapy. For all others, it should be noted that the persistence of residual procarcinogenic effects of cirrhosis, whose structural and vascular alterations constitute an environmental background able to produce hepatocyte proliferation and cell cycle dysregulation. In other words, established cirrhosis serves as fertile soil for all processes of initiation and promotion of neoplastic clones by promoting genetic aberration pathways and cellular transformation [65], so that cirrhosis-driven carcinogenesis is regarded as the main mechanism involved in the development of HCV-related HCCs [66]. This statement is coherent with the above-discussed evidences revealing the greatest reduction of HCC risk in patients who experienced a histological reversion of cirrhosis [47]. In addition, animal models have shown that chronic immune-mediated liver damage is overall sufficient for the development of HCC, and that viral mechanisms of carcinogenesis are not required [67]. So, persistence of liver necroinflammation likely serves as a relevant cause of the increased risk of HCC associated with the presence, after SVR achievement, of well-known nonviral carcinogenic risk factors such as obesity, insulin resistance, steatosis, Type 2 diabetes and alcohol [68]. Furthermore, molecular pathways of fibrogenesis – the result of the wound healing response induced by necroinflammation – are tightly associated with the development of DNA damage in the hepatocytes. The interplay between mechanisms of inflammation, fibrosis and carcinogenesis is complex and still elusive. A central role could be played by NF-κB, a master regulator of inflammation and all linked processes acting as key factor on cellular cycle and survival of parenchymal and nonparenchymal liver cells [69], although other several mediators – including JNK, TGF-β, PDGF-β, COX-2 and many more – and related pathways could be potentially involved [65]. Even if eradication of HCV strongly reduces these pathological mechanisms, the first steps in liver

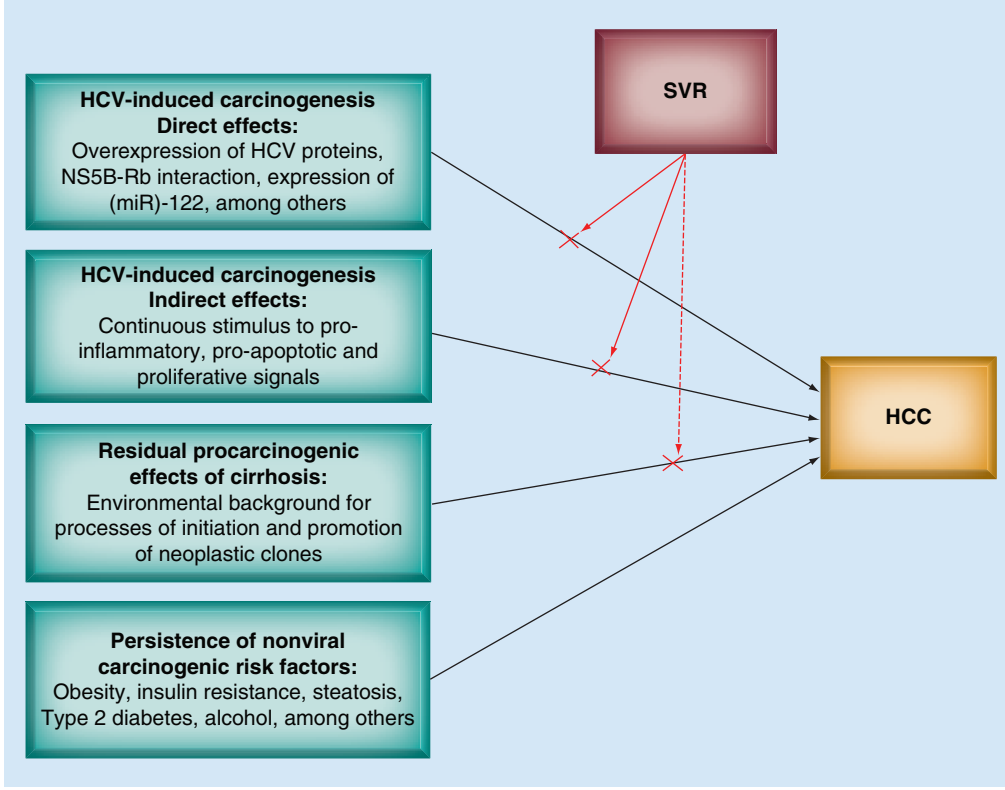


Figure 1. A successful HCV eradication erases both direct and indirect HCV-induced carcinogenic effects, and can induce a certain degree of histological reversion of cirrhosis in a proportion of patients. However, the persistence of residual procarcinogenic effects of cirrhosis and the presence of nonviral carcinogenic risk factor acting as a continuous stimulus to the induction of inflammation-fibrosis-carcinogenesis pathways do not eliminate completely the risk of HCC despite the achievement of an SVR.
HCC: Hepatocellular carcinoma; SVR: Sustained virological response.

carcinogenesis probably occur at early stages of CHC, so that a certain risk of HCC persists even if fibrosis has decreased. However, it is important to note that most of these observations have been derived from cell cultures or animal models overexpressing single proteins. Consequently, the real relevance of these findings for human hepatic carcinogenesis needs to be confirmed [63].

Conclusion

Current data are enough to state that a substantial reduction of the risk for future HCC development occurs following eradication of HCV infection, as a result of the suppression of both direct and indirect carcinogenic effects induced by HCV. However, a residual risk of HCC exists in SVR patients. Indeed, some HCCs could be already present, but too small to be detected, before the start of antiviral therapy, so we have to consider that a certain time interval can be required for small HCCs to become clinically evident. In addition, physicians should keep in mind that the residual risk of HCC in SVR patients correlates with patient age, possibly reflecting the increased prevalence of cirrhosis and other risk factors for HCC in aged population, and with the amount of histological injury, as reflection of the typical procarcinogenic effects of cirrhosis. Furthermore, evidence is growing that failure of HCC prevention in SVR patients may be also consequent to the persistence of necroinflammatory/fibrogenetic mechanisms driven by nonviral carcinogenic factors like diabetes, obesity and alcohol abuse. On these assumptions, it seems reasonable that patients with hepatitis C and advanced fibrosis/cirrhosis should continue to undergo surveillance despite the achievement of an SVR [70], and that all proper lifestyle modifications be implemented in order to avoid all preventable carcinogenic risk factors

such as alcohol drinking, insulin resistance and steatosis.

Future perspective

The next availability of safe IFN-free regimens will certainly lead to an expansion of the current criteria of anti-HCV therapy that have excluded patients unfit to IFN/ribavirin regimens due to decompensated cirrhosis and/or severe comorbidities, who are closest to HCC occurrence. This revolution in the HCV scenario will overcome one of the past methodological issues for the evaluation of the burden of SVR on the reduction of HCC risk, as ineligibility of patients with severe comorbidities and those with advanced or decompensated CHC might have caused two competing risk factors of shortened survival – HCC and all-cause mortality – to appear reduced in the cohorts of HCV patients who achieved an SVR. Similar to what has been observed with the advent of nucleos(t)ide analog therapy in HBV, patients with decompensated HCV – cirrhosis may show a clinical improvement, and a sharp reduction of deaths for liver decompensation can be expected.

EXECUTIVE SUMMARY

HCV-related hepatocellular carcinoma

- Hepatocellular carcinoma (HCC) is the second cause of cancer-related death worldwide.
- HCV infection stands today as the leading risk factor for HCC in many industrialized countries.
- Antiviral treatment is regarded as the main prophylaxis strategy for the prevention of HCV-related HCC.

The role of antiviral treatment for the prevention of HCV-related HCC

- The evidence that patients with chronic hepatits C are effectively protected against HCC risk by IFN-based regimens is rather controversial due to several methodological concerns of the literature.
- A real clinical benefit is gained only in patients achieving a sustained virological response (SVR) rather than in nonresponders.
- SVR confers an almost 80% reduction of the HCC risk across all the clinical stages of chronic hepatitis C compared with non-SVR.
- HCV-related HCC is more likely to be prevented in young patients with mild fibrosis achieving an SVR, rather than in elderly patients with cirrhosis.

The residual risk of HCC among SVR patients

- The risk for HCC is not completely eliminated following HCV eradication.
- Older age and advanced histologic stage have been identified as the main independent risk factors for the future development of HCC among patients with SVR.
- Lack of a certain degree of fibrosis regression/cirrhosis reversal after SVR might be a risk factor for HCC occurrence.
- Recent evidences have emphasized the potential role of metabolic factors such as diabetes, obesity, insulin resistance and alcohol abuse, in promoting the development of HCC in SVR patients.
- Predictors of high risk of HCC development in SVR patients should be promptly identified in order to provide cost-effective screening programs of HCC also in SVR patients.

Pathophysiological insight

- HCV proteins – both directly and indirectly – promote immune evasion, cellular deregulation and inflammation, thus producing fibrogenesis, oxidative stress, DNA damage and genetic instability: these phenomena altogether are capable to create and expand tumor-initiating/cancer stem cells.
- The persistence of residual procarcinogenic effects of cirrhosis and the potential presence of mechanisms of liver injury due to metabolic factors can promote the development of HCC in SVR patients acting as autonomous, nonviral carcinogenic factors.
- Several mediators – including JNK, TGF-β, PDGF-β, COX-2 and NF-κB – are involved and intimately related in processes of fibrogenesis, necroinflammation and carcinogenesis.

The next years will clarify whether the risk of HCC occurrence will decline drastically also in patients with decompensated cirrhosis after SVR achievement, or if there will be a sort of point of no return beyond which the risk of HCC will be poorly affected by the SVR. Anyways, further efforts should be done in order to identify the patients carrying real risk factors associated with a high risk of HCC development even after HCV eradication, who could ideally benefit from other chemopreventive therapies targeting the molecular basis of liver oncogenesis. Finally, the broad applicability of IFN-free regimens will clarify if HCV eradication could be a tool also for tertiary chemoprevention of HCC – in other words, if it will produce a delay or prevention of second primary tumors in patients who have undergone a successful tumor eradication with resection or ablation.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 International Agency for Cancer Research. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide. http://globocan.iarc.fr/Pages/fact_sheets

2 Bosch FX, Ribes J, Cléries R, Diaz M. Epidemiology of hepatocellular carcinoma. *Clin. Liver Dis.* 9, 191–211 (2005).

3 El-Serag HB. Hepatocellular carcinoma. *N. Engl. J. Med.* 365, 1118–1127 (2011).

4 Thomas DL, Seeff LB. Natural history of hepatitis C. *Clin. Liver Dis.* 9, 383–398 (2005).

5 Cabibbo G, Maida M, Genco C, Antonucci M, Cammà C. Causes of and prevention strategies for hepatocellular carcinoma. *Semin. Oncol.* 39, 374–383 (2012).

6 Colombo M, Lavarone M. Role of antiviral treatment for HCC prevention. *Best Pract. Res. Clin. Gastroenterol.* 28, 771–781 (2014).

7 McCombs J, Matsuda T, Tonnu-Mihara I *et al.* The risk of long-term morbidity and mortality in patients with chronic hepatitis C: results from an analysis of data from a Department of Veterans Affairs Clinical Registry. *JAMA Intern. Med.* 174, 204–212 (2014).

8 Aghemo A, Lampertico P, Colombo M. Assessing long-term treatment efficacy in chronic hepatitis B and C: between evidence and common sense. *J. Hepatol.* 57, 1326–1335 (2012).

9 Nishiguchi S, Kuroki T, Nakatani S *et al.* Randomised trial of effects of interferon-a on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 346, 1051–1055 (1995).

10 Yoshida H, Shiratori Y, Moriyama M *et al.* Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and non cirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann. Intern. Med.* 131, 174–181 (1999).

• **Provides one of the first evidence on the role of antiviral treatment for the prevention of HCV-related hepatocellular carcinoma (HCC).**

11 Okanoue T, Itoh Y, Kirishima T *et al.* Transient biochemical response in interferon therapy decreases the development of hepatocellular carcinoma for five years and improves the long-term survival of chronic hepatitis C patients. *Hepatol. Res.* 23, 62–77 (2002).

12 Kawamura Y, Arase Y, Ikeda K *et al.* Diabetes enhances hepatocarcinogenesis in noncirrhotic, interferon-treated hepatitis C patients. *Am. J. Med.* 123, 951–956 (2010).

13 Braks RE, Ganne-Carrie N, Fontaine H *et al.* Effect of sustained virological response on long-term clinical outcome in 113 patients with compensated hepatitis C-related cirrhosis treated by interferon alpha and ribavirin. *World J. Gastroenterol.* 13, 5648–5653 (2007).

14 Asahina Y, Tsuchiya K, Tamaki N *et al.* Effect of aging on risk for hepatocellular carcinoma in chronic hepatitis C virus infection. *Hepatology* 52, 518–527 (2010).

15 Velosa J, Serejo F, Marinho R, Nunes J, Gloria H. Eradication of hepatitis C virus reduces the risk of hepatocellular carcinoma in patients with compensated cirrhosis. *Dig. Dis. Sci.* 56, 1853–1861 (2011).

16 Kurokawa M, Hiramatsu N, Oze T *et al.* Effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with chronic hepatitis. *Hepatol. Res.* 39, 432–438 (2009).

17 Hung CH, Lee CM, Lu SN *et al.* Longterm effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. *J. Viral Hepat.* 13, 409–414 (2006).

18 Sinn DH, Paik SW, Kang P *et al.* Disease progression and the risk factor analysis for chronic hepatitis C. *Liver Int.* 28, 1363–1369 (2008).

19 Coverdale SA, Khan MH, Byth K *et al.* Effects of interferon treatment response on liver complications of chronic hepatitis C: 9-year follow-up study. *Am. J. Gastroenterol.* 99, 636–644 (2004).

20 Bruno S, Stroffolini T, Colombo M *et al.* Italian Association of the Study of the Liver Disease (AISF). Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology* 45, 579–587 (2007).

• **Excellent study emphasizing the clinical benefit due to sustained virological response (SVR) achievement in HCV-related cirrhosis.**

21 Shindo M, Hamada K, Oda Y, Okuno T. Long-term follow-up study of sustained biochemical responders with interferon therapy. *Hepatology* 33, 1299–1302 (2001).

22 Morgan TR, Ghany MG, Kim HY *et al.* HALT-C Trial Group. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology* 52, 833–844 (2010).

23 Hung CH, Lee CM, Wang JH *et al.* Impact of diabetes mellitus on incidence of

hepatocellular carcinoma in chronic hepatitis C patients treated with interferon-based antiviral therapy. *Int. J. Cancer* 128, 2344–2352 (2011).

24 van der Meer AJ, Veldt BJ, Feld JJ *et al.* Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 308, 2584–2593 (2012).

25 Hasegawa E, Kobayashi M, Kawamura Y *et al.* Efficacy and anticarcinogenic activity of interferon for hepatitis C virusrelated compensated cirrhosis in patients with genotype 1b low viral load or genotype 2. *Hepatol. Res.* 37, 793–800 (2007).

26 Cardoso AC, Moucari R, Figueiredo-Mendes C *et al.* Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J. Hepatol.* 52, 652–657 (2010).

27 Veldt BJ, Heathcote EJ, Wedemeyer H *et al.* Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann. Intern. Med.* 147, 677–684 (2007).

28 Osaki Y, Ueda Y, Marusawa H *et al.* Decrease in alpha-fetoprotein levels predicts reduced incidence of hepatocellular carcinoma in patients with hepatitis C virus infection receiving interferon therapy: a single center study. *J. Gastroenterol.* 47, 444–451 (2012).

29 Imai Y, Kawata S, Tamura S *et al.* Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka Hepatocellular Carcinoma Prevention Study Group. *Ann. Intern. Med.* 129, 94–99 (1998).

30 Ikeda K, Saitoh S, Arase Y *et al.* Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology* 29, 1124–1130 (1999).

31 Tanaka H, Tsukuma H, Kasahara A *et al.* Effect of interferon therapy on the incidence of hepatocellular carcinoma and mortality of patients with chronic hepatitis C: a retrospective cohort study of 738 patients. *Int. J. Cancer* 87, 741–749 (2000).

32 Ferrantini M, Capone I, Belardelli F. Interferon-alpha and cancer: mechanisms of action and new perspectives of clinical use. *Biochimie* 89, 884–893 (2007).

33 Calvaruso V, Bavetta MG, Ferraro D *et al.* Risk of disease decompensation and HCC in patients with HCV cirrhosis nonresponder to PEG IFN plus RBV. *Hepatology* 56(Suppl. S1), 35 (2012).

34 Di Bisceglie AM, Shiffman ML, Everson GT *et al.* HALT-C Trial Investigators. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. *N. Engl. J. Med.* 359, 2429–2441 (2008).

35 Afdhal NH, Levine R, Brown B Jr, Freilich B, O'Brien M, Brass C. Colchicine versus Peg-Interferon alfa-2b long-term therapy: results of the 4-year COPILOT trial. *J. Hepatol.* 48(Suppl. 2), S4 (2008).

36 Bruix J, Poynard T, Colombo M *et al.* EPIC3 study group. Maintenance therapy with peginterferon alfa-2b does not prevent hepatocellular carcinoma in cirrhotic patients with chronic hepatitis C. *Gastroenterology* 140, 1990–1999 (2011).

37 Lok AS, Everhart JE, Wright EC *et al.* HALT-C Trial Group. Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. *Gastroenterology* 140, 840–849 (2011).

38 Cammà C, Di Bona D, Craxì A. The impact of antiviral treatments on the course of chronic hepatitis C: an evidence-based approach. *Curr. Pharm. Des.* 10, 2123–2130 (2004).

39 Singal AK, Singh A, Jaganmohan S *et al.* Antiviral therapy reduces risk of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. *Clin. Gastroenterol. Hepatol.* 8, 192–199 (2010).

40 Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. *Clin. Gastroenterol. Hepatol.* 9, 923–930 (2011).

41 Zhang CH, Xu GL, Jia WD, Li JS, Ma JL, Ge YS. Effects of interferon treatment on development and progression of hepatocellular carcinoma in patients with chronic virus infection: a meta-analysis of randomized controlled trials. *Int. J. Cancer* 129, 1254–1264 (2011).

42 Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann. Intern. Med.* 158, 329–337 (2013).

•• **Excellent meta-analysis of 30 observational studies showing the relationship between SVR and the development of HCC.**

43 Toyoda H, Kumada T, Tokuda A *et al.* Long-term follow-up of sustained responders to interferon therapy, in patients with chronic hepatitis C. *J. Viral Hepat.* 7, 414–419 (2000).

44 Makiyama A, Itoh Y, Kasahara A *et al.* Characteristics of patients with chronic hepatitis C who develop hepatocellular carcinoma after a sustained response to interferon therapy. *Cancer* 101, 1616–1622 (2004).

45 Enokimura N, Shiraki K, Kawakita T *et al.* Hepatocellular carcinoma development in sustained viral responders to interferon therapy in patients with chronic hepatitis C. *Anticancer Res.* 23, 593–596 (2003).

46 Kobayashi S, Takeda T, Enomoto M *et al.* Development of hepatocellular carcinoma in patients with chronic hepatitis C who had a sustained virological response to interferon therapy: a multicenter, retrospective cohort study of 1124 patients. *Liver Int.* 27, 186–191 (2007).

• **Large retrospective study focusing specifically on SVR patients who developed HCC.**

47 Mallet V, Gilgenkrantz H, Serpaggi J *et al.* Brief communication: the relationship of regression of cirrhosis to outcome in chronic hepatitis C. *Ann. Intern. Med.* 149, 399–403 (2008).

•• **Provides evidence about the relevance of cirrhosis regression for HCC prevention.**

48 Chang KC, Hung CH, Lu SN *et al.* A novel predictive score for hepatocellular carcinoma development in patients with chronic hepatitis C after sustained response to pegylated interferon and ribavirin combination therapy. *J. Antimicrob. Chemother.* 67, 2766–2772 (2012).

• **Provides a useful score to predict the risk for HCC in patients who achieved an SVR.**

49 Arase Y, Kobayashi M, Suzuki F *et al.* Effect of type 2 diabetes on risk for malignancies includes hepatocellular carcinoma in chronic hepatitis C. *Hepatology* 57, 964–973 (2013).

50 Huang CF, Yeh ML, Tsai PC *et al.* Baseline gamma-glutamyl transferase levels strongly correlate with hepatocellular carcinoma development in non-cirrhotic patients with successful hepatitis C virus eradication. *J. Hepatol.* 61, 67–74 (2014).

51 Macaluso FS, Maida M, Minissale MG *et al.* Metabolic factors and chronic hepatitis C: a complex interplay. *Biomed. Res. Int.* 2013, 564645 (2013).

52 Petta S, Macaluso FS, Barcellona MR *et al.* Serum γ-glutamyl transferase levels, insulin resistance and liver fibrosis in patients with chronic liver diseases. *PLoS ONE* 7, e51165 (2012).

53 Lemon SM, McGivern DR. Is hepatitis C virus carcinogenic? *Gastroenterology* 142, 1274–1278 (2012).

•• **Excellent review on direct and indirect HCV-induced carcinogenic effects.**

54 McGivern DR, Lemon SM. Virus-specific mechanisms of carcinogenesis in hepatitis C virus associated liver cancer. *Oncogene* 30, 1969–1983 (2011).

55 Kannan RP, Hensley LL, Evers L, Lemon SM, McGivern DR. Hepatitis C virus infection causes cell cycle arrest at the level of entry to mitosis. *J. Virol.* 85, 7989–8001 (2011).

56 Walters KA, Syder AJ, Lederer SL *et al.* Genomic analysis reveals a potential role for cell cycle perturbation in HCV-mediated apoptosis of cultured hepatocytes. *PLoS Pathog.* 5, e1000269 (2009).

57 Hernando E, Nahle Z, Juan G *et al.* Rb inactivation promotes genomic instability by uncoupling cell cycle progression from mitotic control. *Nature* 430, 797–802 (2004).

58 Munakata T, Liang Y, Kim S *et al.* Hepatitis C virus induces E6AP-dependent degradation of the retinoblastoma protein. *PLoS Pathog.* 3, 1335–1347 (2007).

59 Chang J, Nicolas E, Marks D *et al.* miR-122, a mammalian liver-specific microRNA, is processed from hcr mRNA and may downregulate the high affinity cationic amino acid transporter CAT-1. *RNA Biol.* 1, 106–113 (2004).

60 Fukutomi T, Zhou Y, Kawai S, Eguchi H, Wands JR, Li J. Hepatitis C virus core protein stimulates hepatocyte growth: correlation with upregulation of wnt-1 expression. *Hepatology* 41, 1096–1105 (2005).

61 Zemel R, Gerechet S, Greif H *et al.* Cell transformation induced by hepatitis C virus NS3 serine protease. *J. Viral Hepat.* 8, 96–102 (2001).

62 Arima N, Kao CY, Licht T, Padmanabhan R, Sasaguri Y. Modulation of cell growth by the hepatitis C virus nonstructural protein NS5A. *J. Biol. Chem.* 276, 12675–12684 (2001).

63 Hoshida Y, Fuchs BC, Bardeesy N, Baumert TF, Chung RT. Pathogenesis and prevention of hepatitis C virus-induced hepatocellular carcinoma. *J. Hepatol.* 261, S79–S90 (2014).

•• **Comprehensive review on molecular mechanisms of hepatocarcinogenesis occurring in chronic hepatitis C.**

64 Qiu W, Wang X, Leibowitz B, Yang W, Zhang L, Yu J. PUMA-mediated apoptosis drives chemical hepatocarcinogenesis in mice. *Hepatology* 54, 1249–1258 (2011).

65 Aihara T, Noguchi S, Sasaki Y, Nakano H, Imaoka S. Clonal analysis of regenerative nodules in hepatitis C virus-induced liver cirrhosis. *Gastroenterology* 107, 1805–1811 (1994).

66 Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 127, S35–S50 (2004).

67 Nakamoto Y, Guidotti LG, Kuhlen CV, Fowler P, Chisari FV. Immune pathogenesis of hepatocellular carcinoma. *J. Exp. Med.* 188, 341–350 (1998).

68 Borena W, Strohmaier S, Lukanova A *et al.* Metabolic risk factors and primary liver cancer in a prospective study of 578,700 adults. *Int. J. Cancer* 131, 193–200 (2012).

69 Luedde T, Schwabe RF. NF-kappaB in the liver–linking injury, fibrosis and hepatocellular carcinoma. *Nat. Rev. Gastroenterol. Hepatol.* 8, 108–118 (2011).

• **Provides a complete scenario on the central role of NF-κB in processes of liver injury, fibrogenesis and carcinogenesis.**

70 Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 53, 1020–1022 (2011).