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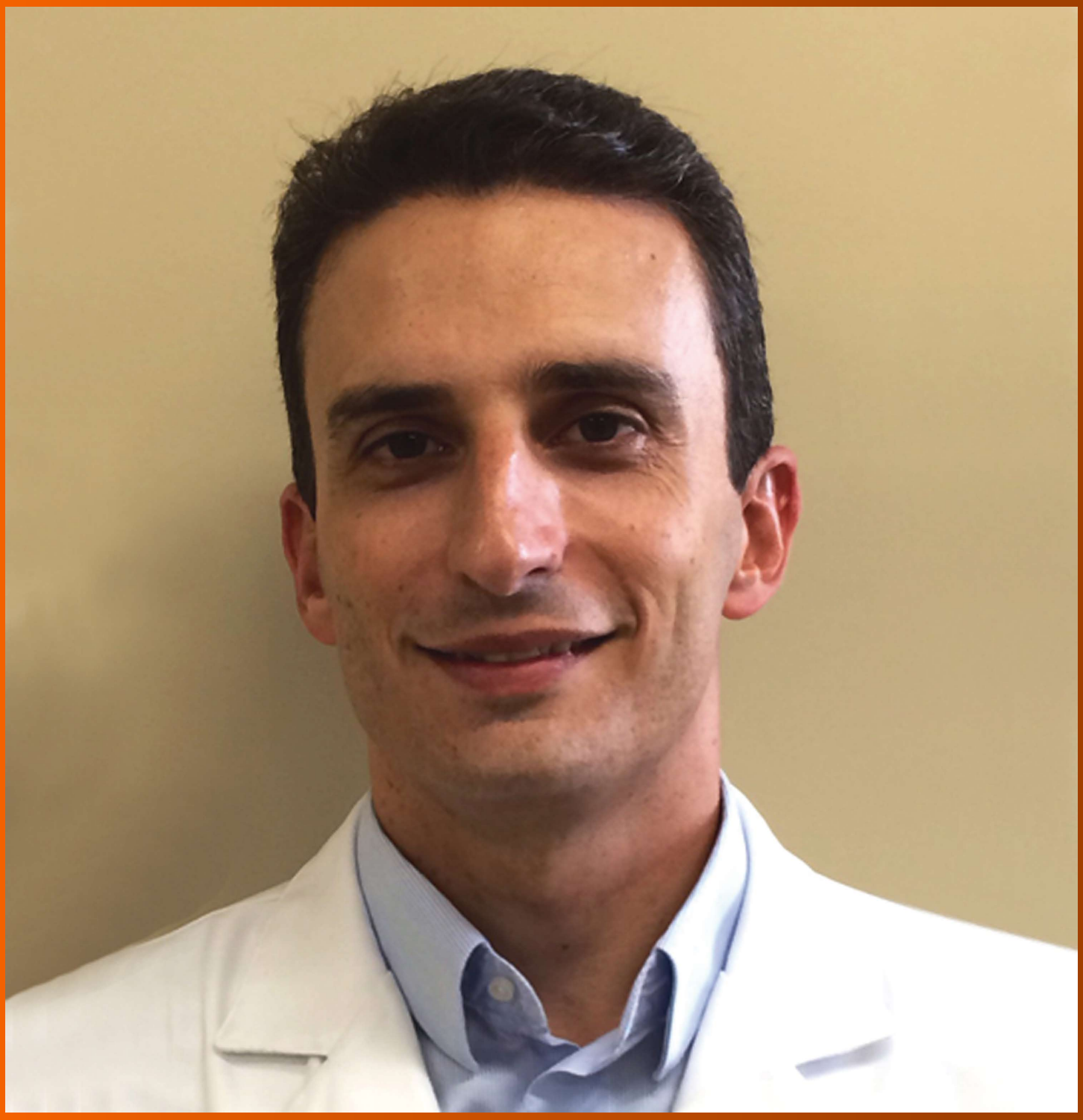

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AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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LETTERS TO THE EDITOR

Responsibility of hepatitis C virus in the development of hepatocellular carcinoma: From molecular alterations to possible solutions

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Abstract

There are several causes of hepatocellular carcinoma (HCC), but certainly the hepatitis C virus (HCV) is one of the most common. The HCV is able to contribute, both directly and indirectly, to the development of HCC. Determining early HCV clearance before an advanced liver disease develops, is absolutely necessary as this prevents the initiation of the cascade of events induced by HCV that may result in the development of HCC. The early treatment of the infection and the clearance of HCV represents today, in the age of the direct antiviral agents (DAAs), an extraordinary opportunity for true prevention of the development of HCV-related HCC.

Key words: Hepatitis C virus; Hepatocellular carcinoma;

Inflammation; Fibrosis; Insulin-resistance; Oxidative stress; Direct acting antivirals

Core tip: The hepatitis C virus (HCV) is able to contribute, both directly and indirectly, to the development of hepatocellular carcinoma (HCC). The early treatment of the infection and the clearance of HCV represents today, in the age of the direct antiviral agents, an extraordinary opportunity for true prevention of the development of HCV-related HCC.

Bertino G, Malaguarnera G, Frazzetto E, Sciuto A, Inserra G, Zanghì GN, Malaguarnera M. Responsibility of hepatitis C virus in the development of hepatocellular carcinoma: From molecular alterations to possible solutions. *World J Hepatol* 2018; 10(6): 448-451 Available from: URL: http://www.wjgnet.com/1948-5182/full/v10/i6/448.htm DOI: http://dx.doi.org/10.4254/wjh.v10.i6.448

TO THE EDITOR

I read with great interest the paper by Mohammad Irshad, Priyanka Gupta and Khushboo Irshad, published in *World J Hepatol* on 28 December 2017; 9(36): 1305-1314 titled "Molecular basis of hepatocellular carcinoma (HCC) induced by hepatitis C virus infection"[1].

Among all human cancers, the hepatocellular carcinoma (HCC) is one of the most frequent[2-6]. There are several causes of HCC (asian males > 40 years, asian females > 50 years, africans, family history of HCC, hepatitis B chronic infection, non-alcoholic steatohepatitis, occupational exposure to chemicals), but certainly the hepatitis C virus (HCV) is one of the most common[7,8].

In recent years, many efforts have been made to obtain an early diagnosis of HCC, through: (1) the use of serum HCC biomarkers, such as: Alpha fetoprotein (AFP), Lens culinaris agglutinin-reactive AFP (AFP-L3), des-gamma-carboxyl prothrombin (DCP), glypican-3 (GPC-3), osteopontin (OPN), squamous cell carcinoma antigen-immunoglobulin M complex (SCCA-IgM), alpha-1-fucosidase (AFU), chromogranin A (CgA), human hepatocytes growth factor (HGF), insulin-like growth factor (IGF); (2) through the computerized axial tomography (CT); and (3) the nuclear magnetic resonance with hepatospecific contrast agent (MR). The use of these tools, often in combination, allows an early diagnosis of HCC especially in the context of close follow-up protocols[9-11].

However, there remains the great problem of understanding the mechanisms that determine the development of HCC in subjects with chronic HCV infection[12,13]. Moreover, even if an exact diagnosis of image and histology of HCC is often obtained, a molecular typing of the alterations that determine HCC is not routinely carried out, also because these are not yet fully known[6].

Irshad *et al*[1], in a very clear and precise way, show that chronic HCV infection is able to determine a progressive fibrosis with transition to cirrhosis, through the mechanisms of inflammation, the activation of stellate cells and the proliferation of hepatocytes. Hepatic cirrhosis and cell proliferation are risk factors for HCC.

Nevertheless, we should also take into account the alteration of the hepatic microenvironment in a pro-oncogenic sense and of the intestinal microbiome. The HCV also determine insulin resistance, hepatic steatosis, oxidative stress and all these events are associated with genetic instability[13-15].

Furthermore, the HCV, which is an RNA virus and does not integrate into the host genome, also has a direct role in the development of HCC, through the interaction of its proteins (HCV core, E1, E2, NS3 and NS5A) with various cell pathways that produce different effects as preconditions for the induction of HCC[16-18].

The data provided by the manuscript of Irshad *et al*[1] are very interesting because they set up a new panorama in chronic HCV infection, underline the role of HCV in the development of HCC and arouse some considerations.

Since the HCV is able to contribute, both directly and indirectly, to the development of HCC, it is now absolutely a priority to treat all subjects with chronic HCV infection, regardless of the degree of liver disease and the presence or absence of any co-morbidities[8,19].

Nowadays, the therapy is based on the use of direct antiviral agents (DAAs) that guarantee the disappearance of the infection, intended as Sustained Virologic Response (SVR), in over 95% of cases, with no significant side effects, which are instead reported during interferon and ribavirin therapy[20-23].

In the scientific community, the paper by Reig *et al*[24] published in *Journal of Hepatology* 2016; 65: 719-726, has provoked great concern because the authors concluded that an unexpected and high percentage of HCC recurrence had occurred in their patients after obtaining the clearance of HCV with DAAs therapy. Fortunately, this statement was "reshaped" by subsequent research that demonstrated, in a large cohort of subjects treated with DAAs, the risk of early recurrence from HCC was comparable and not higher than that observed in patients not treated with DAAs. On the other hand, we must not forget that the rate of early recurrence of HCC remains elevated in patients with advanced liver disease despite the HCV clearance, since liver cirrhosis is a itself risk factor for the development and recurrence of HCC[25].

The research by Ikeda *et al*[26] in *Digestive Diseases and Sciences* 2017 Oct; 62(10), by Kanwal *et al*[27] in *Gastroenterology* 2017 Oct; 153(4) and of Petta *et al*[28] in *Alimentary Pharmacology and Therapeutics* 2017 Jan; 45(1), have clearly shown that Direct-Acting Antivirals therapy reduces the frequency of HCC relapse when performed after initial HCC therapy and that obtaining

SVR is associated with the reduction of HCC. However, in patients with cirrhosis, even if SVR is obtained, the risk of HCC remains present. In fact, these subjects require continuous surveillance[26-28].

Determining early HCV clearance before an advanced liver disease develops, is absolutely necessary as this prevents the initiation of the cascade of events induced by HCV which may result in the development of HCC.

The emphasis made by Irshad *et al*[1] on the prominent role of HCV in hepatic tumorigenesis is very important, both in order to intercept possible new pathways of HCC development that could be used for the development of drugs against specific molecular targets of HCC, both because it reinforces our idea, shared by other researchers, that the early treatment of the infection and the clearance of HCV represents today, in the age of the DAAs, an extraordinary opportunity for true prevention of the development of HCV-related HCC.

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