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EDITORIAL

The iron homeostasis network and hepatitis C virus – a new challenge in the era of directly acting antivirals

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Hepatitis C virus (HCV) is a small, enveloped, positive strand RNA virus belonging to genus Hepacivirus, family Flaviridae. It is one of the most common etiologic agents of progressive liver disease leading to liver cirrhosis and hepatocellular carcinoma. As a consequence it remains a major indication for liver transplantation in developed countries. Still the number of HCV-related deaths is estimated to be 700,000 per year.[1-3]

Moreover, a wide spectrum of extrahepatic manifestations induced by HCV infection is responsible for a large number of significant health complications. These manifestations affect even up to 74% of patients and include endocrine, renal, lymphoproliferative, cardiovascular, metabolic, and central nervous system comorbidities, which significantly contribute to HCV-related mortality.[4]

It is estimated that chronic infection with HCV affects 130–170 million people worldwide. Rapid evolution of therapeutic strategies with approval of promising new highly effective and safe directly acting antivirals (DAA) is changing the landscape of HCV-related health burden. Total cure, defined as sustained viral response (undetectable HCV RNA in serum), may be expected in more than 90% of chronically HCV-infected patients.[1,5]

However, despite remarkable advances in HCV-treatment, it cannot be excluded that the number of newly acquired infections will be increasing due to widespread risky behaviors including injecting drug use and sexual practices.[6] Efficient active or passive specific prophylaxis is not available which additionally makes it difficult to control the HCV epidemic in all populations of the world. Re-infection after a successful cure, observed in special risk groups, sometimes caused by distinct strains of HCV, demonstrates a lack of long-lasting, protective immune response.[7]

More than 70% of patients are not able to clear the virus during an acute infection. Also not all treated patients respond to new forms of treatment. Relapses of HCV replication are confirmed, mainly as early events that occur within 1 – 4 weeks after the end of antiviral treatment. Late relapses, rarely described, may associate with the possibility of reactivation of occult hepatitis C (OCI) and they refer to an issue of persistent HCV replication not only in hepatocytes but also peripheral blood mononuclear cells (PBMCs). The innate immune system plays a crucial role as a first line of defense against HCV in an acute infection. The interaction between innate and adaptive immunity responses in HCV infection is not fully explained. Altered immune host response in combination with high replication rates and escape mechanisms of HCV are responsible for persistency of the infection.[8]

In this issue of *Virulence*, Foka *et al.* describe a study which brings new insight on the interplay between regulation of iron homeostasis and propagation of HCV infection. Main findings of this research are focused on the impact of HCV on the upregulation of hepcidin expression and the following changes in synthesis of ferritin and ferroportin. The study was performed using human hepatoma cell lines (Huh7.5) and THP-1 macrophages as well as HCV JFH-1 infectious clone and HCV replicons in order to analyze the course of an early phase of infection. Authors observed that increased hepcidin expression and changes in intracellular iron content associated with an enhanced viral translation and replication in Huh7.5 cells. Compared to hepatoma monoculture, in co-cultures of Huh7.5 with THP-1 macrophages increase in the levels of hepcidin was significantly higher. HCV NS3 protein also was elevated faster in co-cultures. Moreover iron loading

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of macrophages, caused by hepcidin overexpression, resulted in induction of viral transmission to naïve hepatoma cells. Authors concluded that HCV-related alterations of iron content in macrophages may be involved in the propagation of chronic HCV replication. On the basis of these results they also suggest that macrophages might serve as a reservoir of persistent HCV infection in conditions of excessive iron accumulation.[9]

Iron homeostasis, the life cycle of the virus and the efficacy of antiviral drugs, which act through inhibition of viral replication and modulation of the immune system (interferons), are linked with each other, but these relationships have not yet been fully understood. This issue has been intensively discussed following the conflicting and contradictory published results of in vitro and in vivo studies. Enhancement of HCV translation was reported as well as promotion or inhibition of HCV replication, all of them induced by intracellular iron.[10,11] Based on experimental studies iron loading was even proposed to be a part of antiviral defense leading to limitation of HCV multiplication in chronic hepatitis C (CHC).[11] However, from the clinical point of view this argument does not find convincing evidence. More than 40% of patients with advanced CHC present symptoms of iron overload which associate with a higher rate of liver damage, exacerbated inflammatory activity, failure of antiviral treatment with interferon, and a significant risk of hepatocarcinogenesis.[12,13]

The reason for the excessive accumulation of iron in CHC was not clearly identified. Basing on results of both studies in experimental cell and animal models of HCV infection and observations of patients with CHC, disturbances of iron metabolism were linked to inhibition of hepcidin expression.[14,15] Hepcidin is the primary regulator of iron homeostasis as a main controller of iron content in the extracellular space. It acts through direct binding to ferroportin—its membrane receptor and stops export of iron out of the cells. Hepcidin is induced by increased serum iron concentration and the inflammatory response and inhibited by hypoxia, iron deficiency, and stimulation of erythropoiesis.[16] HCV induced oxidative stress was shown to decrease hepcidin expression.[14,15] However, some discrepancies in relation to the role of hepcidin in HCV-induced iron overload were confirmed in clinical studies with CHC patients. Positive correlation of hepcidin expression with liver iron stores or serum iron concentration was observed and that corresponded to the physiological mechanisms of iron homeostasis regulation.[17-19] It could not explain causal relationship between iron overload and hepcidin inhibition in CHC. Changes in hepcidin synthesis, including lower serum levels in CHC patients compared to patients with other liver diseases, indicated rather a need to understand the role of this "iron regulator" in the context of disorders of the innate immune response in HCV infection.[19,20] This thesis partially may be explained by results of studies which reported inhibition of HCV replication caused by HAMP silencing in HCV replicon models.[21,22] On the contrary a direct antiviral activity of hepcidin against HCV replication in cell culture was also proved.[23]

Foka *et al.* attempt to clarify these mutual interactions between HCV, hepcidin and iron. Their results bring new light on the impact of hepcidin and iron on the promotion of HCV infection in its early phase.[9]

Their results underscore the importance of the changes in the regulation of hepcidin in chronic HCV infection. Decreased hepcidin in CHC patients was confirmed but in fact it is significantly differentiated in different groups of CHC patients. Recently, we have confirmed an interesting link between favorable, prognostic immune profile associated with single nucleotide polymorphism (SNP) encoding interferon lambda 3 (rs12979860 CC) with lower serum iron and ferritin, and decreased hepatic expression of hepcidin and some interferon stimulated genes in CHC patients.[24] This SNP associates with a better response to treatment with interferon and a higher chance for spontaneous HCV elimination. These observations in vivo are compatible with the results by Foka et al. They may serve for better understanding of host-virus interactions and the links between virulence of HCV, iron metabolism and immune response in HCV-related disease. It may appear especially interesting to attempt to control iron homeostasis in relation to long-term effects of treatment with new DAA patients in advanced phase of liver disease, with high risk of hepatocarcinogenesis and significant extrahepatic HCV-induced comorbidities.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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