



Editorials

Where is the focus on hepatitis C research after the introduction of DAAs: To Understand, knowledge, prevent or cure hepatitis C?



The interests and approaches in science are very changing, and it is not uncommon to obey economic and political purposes of pharmaceutical companies and governments in turn. Perhaps due to the lack of sufficient public resources, in several countries such as our, priority funding in science and technology is articulated for research programs that allow finding interdisciplinary and transversal solutions to the great national problems, thus establishing National Strategic Programs.¹ These types of initiatives are adequate; however, the generation of basic science is lagging behind, which also generates knowledge applicable in the longer term. The interests in generating frontier science have changed dramatically in recent years, which have greatly modified the approach and the different routes in the understanding of human diseases. In the area of hepatology, the generation of scientific knowledge is an incubation process that must be taken care of from a long-term perspective, starting from the understanding of molecular processes to design new drugs that improve or restore liver function.^{2,3} In this editorial, we highlight the need to continue supporting the generation of basic scientific knowledge in hepatology, that later on in conjunction with clinical research, will allow us to establish translational medicine to create preventive strategies, new treatments, vaccines and new antivirals to combat viral hepatitis and demonstrate how basic scientific knowledge is applied to patient care.

In recent years, our knowledge about the hepatitis C virus (HCV) has expanded. Numerous aspects of the virus replication cycle have been published, as well as abundant knowledge generated about the molecular mechanisms of pathogenicity of this virus. All this avalanche of knowledge has allowed the development of currently, effective antiviral treatments. Particularly, in the case of hepatitis C, since the launch in 2011 of the first specific direct-acting antiviral agents (DAAs) that demonstrated to reduce viral load (reaching an SVR in more than 90% or 95% of the patients who received treatment) directly affecting a viral target, the investigation in hepatitis C has dramatically turned in this direction towards the search for new specific antivirals, as well as the corresponding clinical trial with all its preclinical and clinical stages. Nowadays, there are several options accessible for HCV treatment, such as DAAs, including HCV protease inhibitors, polymerase inhibitors, and NS5A inhibitors. As spectators of the field, it seems that the search for a vaccine against this virus that allows prophylactically combating the spread of this disease has been left aside in an important way. Likewise, it seems that the same thing happens in the processes or

regulations to combat the transmission of the disease through one of its main old routes, such as blood transfusion and blood products. Under this same wording it is important to highlight that in many blood banks, the identification of blood donors infected with the hepatitis C virus is only carried out by ELISA and western blot tests, and the use of nucleic acid tests (NAT) has not been generalized in order to establish a more accurate and reliable diagnosis and prevent transmission during the immunological window period.

Nowadays the funding for basic research started to be considered of little relevance in our country, and it is actually imperative that HCV research needs to be evaluated in order to establish priorities to fulfill the goal of eradication in the upcoming years. We need to focus in the detection of those clinically silent HCV infections, developing cheaper drugs and therapies for those who do not have access to the current DAAs, new vaccine development technologies, face antiviral resistance, and the risk of developing hepatocellular carcinoma (HCC) after antiviral treatment and viral clearance. It is important to highlight that recently it has been reported that CHC appears shortly after HCV clearance with antivirals, that is, less than 10 years, especially in patients with advanced fibrosis or cirrhosis and it seems to be more common in genotypes other than the common ones, so it should be investigated.^{4–6} In addition, nowadays the gap between basic and clinical research has been reduced with the raise of translational science funds, which facilitates the interaction among clinicians, scientists, academia, industry and governments. In this regard, an example of this is in genomic medicine research which looks for strategies to prevent liver disease progression.⁷

We know that HCV is capable of evade the immune system response and one of the barriers in the development of a vaccine is the lack of an immune-competent model where the virus could replicate and the immune response could be evaluated. With the DAAs based therapy, the possibility to study the immune reconstitution in patients undergoing DAA-based therapy and eliminating the virus is an opportunity to starting to cover the lack of information in this regard. The Norway rat hepacivirus, recently discovered, can be propagated in lab strains of mice and it seems to have some of the immunological features that HCV has, and that is important to promote the vaccine development.^{8,9}

Regarding research priorities in this field, much remains to be understood about the molecular mechanisms of HCV pathogenicity. This will allow us not only to design new antiviral drugs, but also to look for new ways that facilitate the regression of damage and

restoration of functionality in the infected and cleared HCV liver. One of the most important areas to continue generating knowledge that allows not only eradicating the virus but also recovering liver function is to understand the mechanisms involved in liver damage resolution upon hepatitis C virus clearance. Once the virus is eliminated patients should try to re-establish their metabolic functions efficiently from an environment where there was great cellular destruction. Once the causative agent of damage is removed, the progression of liver disease is attenuated.

However, if the patient has an advanced state of fibrosis or cirrhosis, hepatic regeneration becomes a challenge where numerous known and unknown cellular mechanisms are involved. Fortunately, there are drugs that facilitate this process of reversion; however, it is still not clear what conditions favor the success of this regression. From this perspective, the participation of several subcellular compartments in the cytoplasm has taken great importance, such as the endoplasmic reticulum and mitochondria. The endoplasmic reticulum (ER) is the major cell site to achieve protein folding and calcium storage. In addition ER regulates cholesterol production and lipid-membrane biosynthesis as well as major surviving and cell death pathways. Alteration of ER function induces adverse effects in liver function, as reported in fibrosis, cirrhosis and hepatocellular carcinoma. On the other hand, this organelle is intimately linked to the function of the mitochondria. Mitochondria has a critical role in generation of cellular energy (as ATP), calcium and redox homeostasis, surviving cellular signaling and cell death. ER and mitochondria share the protective mechanisms to restore their damaged function by known intrinsic and extrinsic stresses, but their chronic dysfunctions are associated with viral pathogenesis.

Our research during the past 25 years has focused in the molecular mechanisms of HCV pathogenicity, and more recently about the study of antioxidant molecules with promising antiviral action. Such is the case of acetyl salicylic acid and gallic acid, both with antioxidant capacities and with prominent antiviral effect against HCV.^{10,11}

Studies of the HCV replication cycle and virus-host interaction have provided important insights that helped to develop the direct antiviral therapy available nowadays. For example, HCV-related studies have directed research on interferon lambda, an important antiviral cytokine discovered only more recently.¹² Additionally, we recently reported the role of s-adenosyl methionine (SAM) in HCV downregulation.¹³ SAM is the main precursor of glutathione synthesis and also is considered the principal methyl donor.¹⁴ We reported that this molecule regulates the expression of interferon gamma mRNA, which is related to antiviral effect against HCV. Recently there has been reported that APOE $\epsilon 4$ allele and LDL-cholesterol level confer a protective effect in the course of the HCV infection in the context of high BMI, this suggests that host's, environmental and metabolic factors should be taken into account to give a personalized therapy and also these factors could be used to early detection of chronicity in HCV-infected patients.¹⁵

Understanding how HCV modulates cell signaling pathways will allow us better therapeutic approaches to once the virus has been eradicated; start new therapies that facilitate the improvement of liver function. As a last point to reflect, worldwide the disposition of antivirals does not reach us all equally. Mexico is far from reaching the eradication of viral hepatitis. Antivirals are still

expensive and therefore more accessible treatment strategies must be established for the Mexican and Latin American patient. All these elements together must be considered to comprehensively address the understanding, prevention, cure and restoration of liver function after HCV infection.

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Received 13 February 2020

Accepted 14 February 2020