

## Editorial

# Hepatitis C: virus, host, disease

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Worldwide, Hepatitis C virus (HCV) infection continues to represent a relevant public health problem. The World Health Organization has estimated that 3% of the world's population, approximately 170–200 million people, are infected with HCV, as a result of unsuspected infection from contaminated blood and blood products prior to the introduction of routine blood screening in the early 90s, nosocomial or occupational exposure, and/or intravenous drug use.

Chronic hepatitis C continues to greatly affect individuals both in Italy and internationally. In fact, in Italy at least 3–4% (1.7–2.25 million) of adults have detectable anti-HCV antibody, and 75% of these are viremic with detectable serum HCV RNA. Data from population-based studies demonstrate that chronic HCV infection accounts for 40% of chronic liver disease. Most probably less than 20% of all infected individuals have been identified, leaving a large undiagnosed reservoir of predominantly adult-aged persons. Progression to cirrhosis occurs in 20% or more cases within two decades of infection, and hepatocellular carcinoma (HCC) starts developing after the second decade, once cirrhosis is present, at a rate of 2–5% per year. Chronic HCV infection are thus on the Western world the leading and increasing cause of cirrhosis, end-stage liver disease, liver cancer, and is the most common cause of need for liver transplantation. Recently, the accessibility to blood screening tests in western countries, as well as compliance with universal precautions, and the use of disposable medical devices have revealed a decline in the number of new infections.

In less than two decades impressive advances in the understanding of the etiology, pathogenesis, natural history and the treatment of the formerly nonA-non B viral hepatitis has become more readily available. The identification of HCV in 1989 launched an impressive growth of knowledge regarding the biological and molecular basis of HCV infection and in diagnostic and therapeutic possibilities. Molecular tests have been developed to detect and quantify HCV and to determine viral genotypes that are more susceptible to therapy.

The clinical behavior of hepatitis C is different from hepatitis B. The two infections have markedly different

outcomes after primary infection. In spite of the significant progress in understanding the mechanisms of HCV pathogenesis in the last decade, experimental evidence to explain the two major features of the natural history of this viral infection (viral persistence and hepatic damage) is still lacking.

Immune responses to HCV may play an important role at various stages of infection. In fact, from an immunological point of view the liver is a unique organ. This is primarily due to the fact that the liver is exposed to a large amount of antigenic stimulation and develops a specific yet still undefined pattern of response and is the site of programmed cell death of activated lymphocytes.

There is emerging evidence that during acute infection, cellular immune responses are imperative for the initial control of viral replication in those patients who subsequently control infection. In the chronic phase of infection, immune responses potentially determine the rate of progression of diseases both by limiting viral replication and by contributing to immunopathology. Finally, during combination therapy, cellular immune responses may contribute to the success or failure of treatment.

Recently combination therapy has created new challenges and benefits, while researchers attempt to find vaccines and other biological approaches to prevent further dissemination of infection and/or reduce side effects or the negative impact of infection. Clinical trials are providing persuasive evidence that treating HCV with a combination of pegylated interferon and ribavirin produces a considerably better sustained viral response (SVR) than monotherapy alone or standard interferon-ribavirin combination. Unfortunately, patients with genotype 1 HCV, who account for 70–75% of infected persons, require a longer duration of therapy and have a lower SVR. Although SVR has not yet been correlated with improved survival because of the need for long-term follow-up, the absence of detectable HCV provides a significant benefit in terms of the resolution of liver injury, reduction of liver fibrosis, and a lower likelihood of HCV re-infection. Optimum treatments are less clear for non-responders and relapsers.

The goal of this supplement is to provide helpful reviews and commentaries in some of the areas where major progress has or is being made. Some of the challenges that we still face include gaining a better understanding of the replicative biology of HCV and the molecular details of viral pathogenesis, as well as the mechanisms by which the virus persists even under the pressure of powerful antivirals and is able to induce fibrosis and in the long run cirrhosis and hepatocellular carcinoma.

The articles contained in this issue are divided into five sections: virology, models (animal, biological, mathematical), apoptosis, immunology and immunopathology, fibrosis and co-infections.

Viral pathogenetic mechanisms based on the interaction of HCV proteins with host cellular signal transduction are discussed by Giannini *et al.*<sup>1</sup>. Capobianchi *et al.*<sup>2</sup> summarize some viral strategies to evade innate defense and the role of the interferon system in the innate mechanism of defense. Falasca *et al.*<sup>3</sup> report viral particles identified in liver biopsies of HCV infected patients using electronic microscopy.

Animal and mathematical models could provide a powerful tool in the understanding of this complex biological phenomenon. Herrmann *et al.*<sup>4</sup> present viral kinetic mathematical models of HCV that provide insight into the dynamics of viral kinetics and calculate turnover rates of infected hepatocytes and free viruses. Fimia *et al.*<sup>5</sup> summarize the results of transgenic mouse models, which do not allow as yet unequivocal conclusions. Columbano *et al.*<sup>6</sup> present a model based on mitogenesis by ligand of nuclear receptors for the study of the molecular mechanisms implicated in liver growth, including hepatic carcinogenesis.

Liver cell damage in chronic HCV infection is mediated by the induction of apoptosis that plays a critical role in influencing the outcome of HCV-induced liver disease; three different papers, by Ameisen *et al.*<sup>7</sup>, Bantel *et al.*<sup>8</sup> and Piacentini *et al.*<sup>9</sup> analyze the host-parasite interaction and apoptotic mechanisms to evaluate new possible therapeutics, also describing the mechanisms involved in liver damage and long viral persistence associated with an increased risk of the development of hepatocellular carcinoma. Majano *et al.*<sup>10</sup> report the results of studies to define if and how nitric oxide plays a role in HCV pathogenesis.

Two papers, by Poccia *et al.*<sup>11</sup> and Willberg *et al.*<sup>12</sup> summarize current knowledge on the immunology, immunopathology and immunopathogenesis of HCV infection, including aspects related to the intrahepatic non-specific immunity and HCV.

Liver fibrosis is the cause of the negative outcome of HCV infection; Schuppan *et al.*<sup>13</sup> summarize the mechanisms of fibrosis in HCV infection and Antonucci *et al.*<sup>14</sup> describe HIV-HCV co-infection and evaluate the biological mechanisms involved.

We hope that the contents of this volume will spark new and innovative approaches to HCV research by bringing together information and interested researchers from different disciplines. Finally we would like to thank the colleagues who made this special issue possible and who took time from their research work to write papers for this supplement.

1. Giannini *et al.* (2003) Cell. Death. Differ. 10: this issue
2. Capobianchi *et al.* (2003) Cell. Death. Differ. 10: this issue
3. Falasca *et al.* (2003) Cell. Death. Differ. 10: this issue
4. Herrmann *et al.* (2003) Cell. Death. Differ. 10: this issue
5. Fimia *et al.* (2003) Cell. Death. Differ. 10: this issue
6. Columbano *et al.* (2003) Cell. Death. Differ. 10: this issue
7. Ameisen *et al.* (2003) Cell. Death. Differ. 10: this issue
8. Bantel *et al.* (2003) Cell. Death. Differ. 10: this issue
9. Piacentini *et al.* (2003) Cell. Death. Differ. 10: this issue
10. Majano *et al.* (2003) Cell. Death. Differ. 10: this issue
11. Poccia *et al.* (2003) Cell. Death. Differ. 10: this issue
12. Willberg *et al.* (2003) Cell. Death. Differ. 10: this issue
13. Schuppan *et al.* (2003) Cell. Death. Differ. 10: this issue
14. Antonucci *et al.* (2003) Cell. Death. Differ. 10: this issue