The hepatitis C virus enigma

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Hepatitis C virus (HCV) has a high propensity to establish chronic infection with end-stage liver disease. The high turnover of virus particles and high transcription error rates due to lack of proof-reading function of the viral polymerase imply that HCV exists as quasispecies, thus enabling the virus to evade the host immune response. Clearance of the virus is characterized by a multispecific, vigorous and persistent T-cell response, whereas T-cell responses are weak, narrow and transient in patients who develop chronic infection. At present, standard treatment is a combination of pegylated interferon-α and ribavirin, with a sustained viral response rate of 40–80%, depending on genotype. The mechanisms for the observed synergistic effects of the two drugs are still not known in detail, but in addition to direct antiviral mechanisms, the immunomodulatory effects of both drugs seem to be important, with a shift from Th2- to Th1-cytokine profiles in successfully treated patients. This article describes virus–host relations in the natural course of HCV infection and during treatment.

Key words: Hepatitis; virus; variability; immunology.

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Since its identification in 1989 (1), hepatitis C virus (HCV) infection has been recognized as a major health problem worldwide. Approximately 170 million people are infected globally (2), and HCV infection is at present the most common cause of chronic hepatitis and cirrhosis in the United States and other western countries (3). The prevalence rate in Scandinavia is 0.2–0.5% (2, 4).

Contrary to the situation in hepatitis B virus (HBV) infection, the majority of hepatitis C cases develop chronic infection, and possibly around 50–80% of infected individuals fail to clear the virus and develop chronic infection (5). Once chronicity is established, there is no spontaneous resolution of the viremia.

HCV infection is characterized by a wide range of clinical manifestations, including asymptomatic chronic carriage, acute and chronic hepatitis, cirrhosis, hepatocellular carcinoma and extrahepatic manifestations. The latter are commonly observed and may represent the first sign of the disease. Although the major target for HCV is the hepatocyte, the virus also displays lymphotropicism, and HCV genome sequences have been detected in circulating lymphocytes (T and B cells) (6, 7) and antigen-presenting cells (8), as well as in other compartments such as the brain. Its wide cellular tropism may be explained by the ubiquitous expression of its putative cell receptor, CD81 (9).

THE VIRUS

HCV is a small, enveloped, positive single-stranded RNA virus that belongs to the genus Hepacivirus within the family of Flaviviridae (Fig. 1A). The genome has approximately 9600 nucleotides and contains one large open reading frame flanked by non-translated regions at the 5′ and 3′ ends (Fig. 1B). The polyprotein is cleaved by host-cell proteases and virus-encoded
proteases into structural (core, envelope 1 and 2) and non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B). NS5B encodes the viral RNA-dependent RNA polymerase that lacks a proof-reading function. Replication of the positive-stranded HCV genome is thus characterized by ongoing error rates of $10^{-4}$ and $10^{-5}$ nucleotide substitutions per base pair copied. Together with the high production of $10^{12}$ virions per day, with an average of 2.7 h half-life and a turn-over rate close to 99% (10), the calculated mutation rate is in the order of $1.5–2.0 \times 10^{-3}$ nucleotide substitutions per site and per year, and every possible mutation in every single position of the genome can theoretically be generated every day. This implies that HCV, like other RNA viruses, typically exists as quasispecies, which is a collection of related but not identical genomes. Based on phylogenetic analysis, HCV has been classified into six major genotypes. The genotypes differ from each other by 31–33% on the nucleotide level, and these genotypes can be further divided into multiple epidemiologically distinct subtypes that differ by 20–25% (11).

The origin of HCV has not yet been properly identified, but bovine viral diarrhoea virus has been suggested as a possible ancestral virus (12). However, the divergence of HCV genotypes, geographical distribution and presence of single types with numerous subtypes is compatible with a pattern that suggests long periods of endemic infection and existence for 500–2000 years. It has been suggested that various regions of the African continent are home for genotypes 1, 2, 4 and 5, whereas South East Asia is an endemic region for genotype 6. Of particular interest is the finding of more than one virus genotype, but each of them represented by only a few subtypes. This could indicate recent and limited introduction from endemic areas, exemplified by types 1a, 1b, 2a, 2b and 3a in Northern Europe and North America. For example, types 1a and 3a are found in young adults, often with intravenous drug use as a risk factor. The recent dissemination of these viruses is supported by more limited genetic diversity within these subtypes (13), a pattern also seen for spreading of human immunodeficiency virus type 1 (HIV-1), with restricted genetic variability in risk groups with rapid dissemination (14). In contrast, subtypes 2a, 2b and 2c from some African countries show extreme diversity in line with a longstanding infection. Epidemics linked to medical practice are the spreading of subtype 1b by contaminated anti-D immunoglobulin in
THE HEPATITIS C VIRUS ENIGMA

the 1970s in Ireland and former East Germany. The very high prevalence of subtype 4a in Egypt has been linked to cross-infection by mass treatment with anti-schistosomal agents. In earlier times, virus transmission may have been caused by variolation as a means of protection against smallpox, use of unsterilized needles and syringes after injection of arsphenamine for treatment of syphilis and association with scarification as part of culture-specific rites (13).

At present, the standard treatment of HCV-infection is a combination therapy with pegylated interferon-α (PEG-IFN) and ribavirin (15). Although their precise mode of action is not known in detail, both drugs have substantial antiviral and immunomodulatory effects. The response rate depends on the infecting genotype, which suggests that sequence differences between genotypes influence the susceptibility to the drugs.

The understanding of the HCV viral life cycle, its mode of pathogenesis and elaboration of antiviral drugs and vaccines, have all been hampered by the lack of a robust cell culture system for HCV replication and a small animal model. The chimpanzee is the only non-human species susceptible to HCV infection. Recently, however, mouse models with reconstituted human liver grafts have shown promising results (16, 17).

A break-through in HCV research came in 2005, when cell-culture systems were established that allowed production of infectious HCV particles from a cloned viral genome transfected into human hepatocellular carcinoma Huh-7-derived cells (18, 19). Also, a human hepatocyte cell line immortalized with human papilloma virus 18/E6E7 was susceptible to HCV infection (20). However, these cell lines were not susceptible to infection with primary HCV isolates from patients, and recent improvements have allowed the infection of normal hepatocytes by naturally occurring HCV genotypes. Primary hepatocytes were isolated and cultures were established from organ donors. After 5 days these cells were infected by addition of serum from chronically HCV-infected patients (21).

HCV infection and virus entry of a susceptible cell is a complex multistep process. The initial host-cell attachment may involve glycosaminoglycans and the low-density lipoprotein receptor. Then the particle interacts sequentially with the surface molecules SR-B1 (scavenger receptor), the tetraspannin CD81 and the tight-junction protein claudin-1 (CLDN1). The particle is then internalized by clathrin-mediated endocytosis and fusion, most likely occurring in early endosomes. However, more entry factors probably play a role in the infectious process, because some human cell lines expressing CD81, CLDN1 and SR-B1 still remain resistant to HCV (22).

HOST DEFENCE

Based on evolutionary and functional considerations, the molecular and cellular entities that make up the host response to HCV infection can be divided into innate and adaptive subcomponents. The innate components, including phagocytes and antigen-presenting cells, serve as a first line of defence. Upon infection, they recognize pathogen-associated molecular patterns through a variety of pattern-recognition receptors, including the Toll-like receptors (TLR). Recognition of microbial patterns or danger in turn triggers the whole cascade of effector mechanisms of the innate and adaptive immune systems (23). Acting through a restricted portal of four intracellular adapter molecules, a limited number of TLR are able to induce the transcriptional activation of hundreds of genes that code for systemic and localized defence factors. These include genes for proinflammatory cytokines, molecules that drive dendritic cell migration to the lymph nodes and MHC and costimulatory molecules.

The dispersed signals that emanate from the innate immune response trigger the components of the adaptive immune system within the secondary lymphoid organs, including the spleen and lymph nodes, where antigen-specific naïve T and B cells interact with antigen and antigen presenting cells (24). At this point, the extremely complex characteristics of the infectious agents are being met by a similarly complex response performed by the adaptive immune system. A major event at this early stage is the polarization of the T helper (Th) response into Th1 and Th2 cells (25). Whereas Th1 cells produce interleukin (IL) 2 and IFN-γ and activate macrophages and cytotoxic CD8+ T cells, Th2 cells produce IL-4, IL-5, IL-10 and IL-13, the secretion of which
leads to the activation and differentiation of B cells into antibody-producing plasma cells.

The diversification of the Th repertoire depends upon the microenvironment that is being generated at the contact surface between the T cell and the dendritic cell, within which signaling molecules of both cells become congregated. While immature dendritic cells energetically sample their external antigenic environment, the processed molecules are not expressed on their surface MHC molecules. However, upon activation the cells stop internalizing antigen and instead focus on generating complexes between peptides and MHC class II molecules for T-cell activation. Recognition of the MHC-antigen complex activates the T cell, which in turn further activates the dendritic cell to provide more stimulating signals (26).

But also the site in the body where infection or damage occurs is important for the ensuing polarization of the immune reaction. Different tissues mount different immune responses to the same antigenic stimulus. This is partly owing to the complex pattern of tissue-specific distribution of dendritic cells, but also because epithelial and stromal cells at the site of infection generate TLR-mediated signals that contribute to the activation of T cells (27). The liver has a unique capacity to induce antigen-specific tolerance, and it has been speculated as to whether this may be due to the tolerogenic potential of resident dendritic cells (28).

The adaptive immune response is influenced by properties of both the organism and the antigen. Organismal properties that may regulate the output include genetic makeup, previous encounters with similar infectious agents, and route of infection, while important properties of the antigen include its concentration and the timing and duration of antigen encounter. These considerations may be visualized as a lens metaphor (Fig. 2) in which both the evolutionary and the developmental aspects are taken into consideration. In this representation, evolutionary derived experiences (convex lens) serve to focus signals towards a species-specific norm of responses, while developmentally shaped experiences (concave lens) lead to diverging organism-specific responses (29). Accordingly, the various phenotypes that the immune response could take should emanate from the way the evolutionary selected genetic makeup of an organism intersects and maps onto its developmentally shaped adaptive systems.

**THE BALANCE**

Both pathogenesis and the eventual outcome of any viral infection are significantly influenced by the host immune response. As one of few RNA viruses able to cause persistent infection in man, HCV has evolved through the eons in an intimate relationship with its host. This adaptation has led to the evolution of several methods of evading or counteracting the host’s innate and adaptive antiviral defences. The mutability and replicative capacity of the virus also enables it to respond rapidly to new selection pressures, e.g. differences in B- and T-cell epitopes encountered in different individuals.

The genetic variability of HCV can be perceived at different levels. The main genotypes of the virus represent an obvious and substantial divergence often showing geographical or demographic (risk group) ranges. On another level
is the variability observed between strains or individual variants. Finally, there is the diversification of viruses within an infected individual over time (quasispecies). Taken together, this genetic variability linked with a large and rapidly replicating virus population facilitates the adaptation of HCV to new selection pressures such as immune responses and antiviral therapy.

HCV has a profound impact on the immune system of the host, not only through evasion and modification of the immune response, but also through a direct tropism for immune cells such as B lymphocytes. The virus is thought to both downregulate the type I IFN-α/β receptor and block type I IFN signalling pathways as well as to impair NK cell effector functions by interaction of the E2 protein with CD81 on the cell surface, thus counteracting viral clearance by the innate system (30–32).

Infection results in antibody production against various viral proteins, but the humoral immune response does not correlate with a favourable outcome of infection (33). Virus-specific antibodies can usually be detected within 50–60 days after HCV infection (34). To what extent antibodies neutralize HCV infectivity is not clear. HCV infectivity in chimpanzees has been neutralized by in vitro treatment of HCV pseudoparticles with antibodies (35), and polyclonal IgG from a chronically infected patient has recently been shown to convey sterilizing immunity towards the ancestral HCV strain in vivo (36). In addition, sequence changes in the hypervariable region 1 (HVR1) of the E2 protein, a major target for the immune response, has been shown to predict infection outcome in humans. These sequence changes coincide with seroconversion and probably represent escape mutations, implying that HCV adapts to immune selection pressure exerted by antibodies (37). In contrast to the ability of anti-HBs antibodies to prevent HBV reinfecion, anti-HCV antibodies do not seem to prevent HCV reinfecion in immune humans, and resolution of HCV infection has been reported to occur even in the absence of seroconversion (38). Taken together, these findings indicate that neutralizing antibodies (nAbs) are isolate specific, and raise concerns for the development of a broadly reactive vaccine against HCV.

There is strong evidence that virus-specific CD4⁺ and CD8⁺ T cells play a crucial role in both viral control and liver injury. Thus, the pathogenesis of liver damage associated with HCV infection is thought to be largely immunomediated, although a possible direct cytotoxic effect is suggested by histopathological features such as steatosis (39).

In both humans and chimpanzees, the clearance of acute infection is accompanied by a strong and multispecific CD4⁺ and CD8⁺ T-cell response (40, 41). CD4⁺ T cells exert a regulatory function by modulating antigen-specific B-cell activity (Th2 profile) through the recently described CXCR5⁺ T follicular helper cell subset (42), and the CD8⁺ T-cell responses (Th1 profile). Th1 cytokines, e.g. IL-2, IFN-γ and tumour necrosis factor (TNF-) α, activate several antiviral mechanisms, such as enhancing immune recognition by increasing the expression of HLA-molecules on infected cells or activating CD8⁺ T cells and NK cells. Several studies have shown a correlation between a multispecific and sustained CD4⁺ T-cell response directed against non-structural HCV proteins, often targeting immunodominant epitopes within the NS3-region, and viral clearance in acute HCV infection (43, 44). It seems that patients with acute HCV infection displaying a Th1 profile (IFN-γ and IL-2) when stimulated with HCV antigens are more likely to clear the virus than patients developing a Th2 phenotype response (IL-4 and IL-10) (45, 46). Indeed, even in chronically infected patients, a strong Th1 response seems to be associated with a more favourable and less inflammatory course of disease (47).

An interesting aspect of chronic HCV infection is the development of weak CD4⁺ and CD8⁺ T-cell responses. This phenomenon, which may be owing to the tolerogenic potential of the liver, may either be caused by a primary T-cell failure in which the dendritic cells fail to stimulate the antigen specific T cells, or by T-cell exhaustion in which virus-specific T cells become depleted owing to a continuous high viral load (48) (Fig. 3).

THE BATTLE

In the encounter between HCV and its human host there seems to be a ‘moment of truth’ during the first 12 weeks of infection (49). At this point, about 20–25% of patients with acute
Hepatitis C will have cleared the infection, whereas the majority becomes chronic carriers. However, if both HCV RNA-positive and -negative cases at the time of anti-HCV seroconversion are included, estimate of clearance has been found to be around 40%, indicating that the clearance rate may be underestimated (50). Indeed, several studies have shown that up to 53% of patients with acute HCV-infection show a self-limiting course of disease (49, 51, 52). This is in line with previous findings of presumed seroreversion cases among healthy blood donors (53). Accordingly, it may well be that the commonly assumed frequency of 80% chronic carriers is an overestimate, and that more patients actually clear the virus during the acute stage.

The characteristics of the immune response in cases of clearance have been studied extensively [for review, see (50)]. Several factors are associated with viral clearance, among them symptomatic hepatitis with icterus, female gender and the strength and pattern of HCV-specific CD4\(^+\) T-cell responses. In a systematic review of 31 longitudinal studies, Micallef et al. (50) found that female gender and a clinically acute hepatitis were independent predictors of spontaneous clearance. The reason for a better prognosis in females is currently not known, but it is a phenomenon also found in IFN response studies (54). One hypothesis is that clearance may be facilitated by oestrogen hormone.

A high rate of viral clearance among acute symptomatic hepatitis C patients, paralleling what is also observed in HBV infection with viral clearance, is consistent with the hypothesis of the importance of a vigorous broad initial immune response. Distinct patterns of host–virus interactions related to viral clearance or persistence have been identified. As previously mentioned, the antiviral T-cell response seems to be of paramount importance, and a lack of Th1 effector cells during the first few weeks of HCV-infection has been found to predict viral persistence (55). However, such immunologic testing has hitherto not been a part of the standard diagnostic procedures of acute hepatitis C. And while there is strong evidence to support the hypothesis of T-cell exhaustion accompanied by narrow specificity as determining factors for viral persistence, no testable hypothesis has so far been launched as to what factors will influence this. On the other hand, patients clearing the virus spontaneously can most often be identified by monitoring viral load during the first few weeks of infection. Accordingly, the strategy for treatment of acute hepatitis C should be to wait for 3 months before treating the persistently viremic patients (51).

**SHIFTING THE BALANCE – EFFECT OF TREATMENT**

**Effect of IFN-\(\alpha\)**

IFN-\(\alpha\), which belongs to a large group of closely related cytokines, is invariably produced in mammalian cells following virus infections. While plasmacytoid dendritic cells seem to be the main producers of IFN, just about any cell can produce IFN. The production is induced by...
virally derived pathogen-associated molecular patterns, including double- and single-stranded RNA, that bind to and activate corresponding molecules in host cells. Upon activation of such host cell pattern-recognition receptors, which include the TLR, intracellular signalling cascades become activated, leading to transcription of IFN genes and enhanced production and secretion of IFN. Once secreted, the IFN binds to IFN-receptors on the producer as well as neighbouring cells and initiates an intracellular signalling cascade, which leads to the upregulation of hundreds of IFN-responsive genes, many of which have antiviral effects.

The antiviral effects of IFN have led to its use in treatment of select viral diseases. A modified IFN molecule termed PEG-IFN has become the cornerstone for treatment of chronic HCV infection. In comparison with native IFN, PEG-IFN exhibits sustained exposure with once-weekly dosing, a better adverse effects profile and superior clinical efficacy. Recent data obtained from patients with chronic HCV infection indicate that the effects of PEG-IFN on viral clearance depend upon the baseline level of IFN stimulation in each patient (56). Paired liver biopsies obtained from patients before and 4 hours after administration of the first dose of PEG-IFN demonstrated that patients responding poorly to therapy expressed high levels of IFN-stimulated genes before therapy and had little additional effect on the same genes after PEG-IFN. In contrast, patients who responded well to therapy showed a strong upregulation of the IFN-stimulated genes following PEG-IFN administration. It is not known how IFN-stimulated gene preactivation is connected to treatment failure, but it may be due to some intricacies involved in the host–parasite interaction; like many other viruses HCV has evolved a great diversity of molecular mechanisms to evade the effects of IFN (57).

IFN is regarded as an important player in the innate immune response and therefore crucial in limiting the early replication and spread of infectious agents. But IFN is also important for indirect activation of the B and T lymphocytes of the adaptive immune system. This activity is mediated by the effects of IFN on dendritic cells, which are both producers and consumers of IFN; upon infection, dendritic cells are induced to produce large amounts of IFN, while produc-
transcription polymerase chain reaction (RT-PCR) does not distinguish between infectious and defective genomes. RNA rendered non-infectious by the mutagenic effect of the compound could be packaged and released in serum, and expression of defective antigens accompanied by reduced immune reaction may lead to reduced cellular damage and the observed fall in ALT levels (67). On the other hand, ribavirin has been shown to totally inhibit an exclusively Th2-mediated HBe-antigen specific immune response in transgenic mice, and such a suppressive effect may also partly explain the observed normalization of ALT-levels in HCV-infected patients in the absence of a decrease in viral load.

Ribavirin seems to affect humoral immune responses during chronic HCV infection, with transient decrease in both anti-HCV-core antibodies and anti-NS3 specific IgG (66). In any case, the simultaneous lack of effect on serum levels of HCV RNA suggests that the decrease in antibodies occurs independently of the virus load, at least as measured by RT-PCR.

The overall effect of ribavirin in vitro seems to be immunosuppressive. However, it does not have a generally immunosuppressive effect on B cells, but rather seems to act selectively. This is evidenced by its effect on shift in IgG subclasses in transgenic mice, where a dose-dependent decrease of IgG1 (negatively regulated by Th1-derived cytokines) and an increase in IgG2a (positively regulated by Th1-derived cytokines) has been shown (68). It would seem, therefore, that ribavirin influences antibody levels or subclass distribution through its effects on other immune cells, such as regulatory T cells. A shift towards a Th1-like immune response does not necessarily imply a reduction of humoral responses in a mixed Th1-/Th2-like polyclonal immune response, as both Th1- and Th2-like cytokines promote humoral responses. Nevertheless, the shift towards a Th1-response fits well with the observed responses in patients who clear the virus.

In conclusion, ribavirin may be viewed as an immunomodulating rather than a strictly antiviral compound in the treatment of chronic HCV-infection.

**IFN/ribavirin synergy**

When combining IFN and ribavirin, synergistic effects in clinical efficacy appear, exceeding that of the individual monotherapies (69, 70). Whereas PEG-IFN monotherapy is associated with an overall sustained viral response (SVR) rate (i.e. no detectable virus 6 months after cessation of treatment) in 30–39% of treated patients (71, 72), and ribavirin alone has virtually no impact on viral clearance, the combination therapy results in SVR rates of 42–80% (73, 74). This may be due to the effect of ribavirin in determining the adaptive immune response bias towards a Th1 cytokine profile, and this effect acting synergistically with the effect of IFN-α. It may also partly be explained by the multistep antiviral mechanisms of ribavirin, especially the mutagenic effect. Ribavirin may slow down the HCV replication and impair its infectivity, while the accompanying IFN-α antiviral effects may be needed for clearance of the virus. Whatever the mechanisms, adding ribavirin with PEG-IFN is the key to success in the treatment of chronic HCV.

**FUTURE PERSPECTIVES**

**New antiviral drug designs**

With an SVR rate of 40–80% for the susceptible genotypes, there is an urgent need for other treatment strategies. The access to culture systems for primary HCV isolates (21) and chimeric mice with ‘human livers’ (17) for evaluation of drug metabolism (human cytochrome P450), pharmacokinetics and toxicity has dramatically improved the design of new specific anti-HCV drugs (75, 76). Several companies are currently developing specific, small-molecular antiviral HCV drugs, such as inhibitors of HCV protease, polymerase and NS5A. One example is the protease inhibitor boceprevir that has advanced into clinical phase II trials (77). However, the efficiency of monotherapeutic strategies is questionable. Lessons learned from the antiviral therapy of HIV-1 infection are that combinations of non-cross-resistant classes of drugs are key to successful antiviral therapy (78).

**Perspectives for development of a vaccine**

There is evidence that chimpanzees that have cleared a primary infection can be protected against re-exposure to the same virus, and that protection is associated with a rapid, multi-antigen
memory T-cell response (79). Alternatively, a new infection leads to rapid control (80). Moreover, chimpanzees that recovered from a genotype 1 infection were protected from challenges with mixtures of four genotypes and complex inocula exhibiting up to 30% amino acid divergence (81). The rapid clearance of the challenge virus was associated with demonstrable increases in intrahepatic interferon stimulating gene transcripts in liver biopsies. However, another study showed that the protection may not resist repeated challenges. After five homologous (genotype 1a) and six heterologous (genotypes 1b or 2a) rechallenges the chimpanzee finally became persistently infected by the original virus (82).

With respect to HCV infections in injecting drug users, there are contradicting reports. Some studies find that drug users who had cleared initial HCV infection remained uninfected despite ongoing exposure, or if reinfected the magnitude of viremia and frequency of viral persistence was significantly lower than in controls (83). Other studies show a high incidence of HCV reinfec tion in injecting drug users, which would indicate no increased immunity against further infections (84).

Major hurdles in vaccine studies have been the lack of small animal models and the inability to grow HCV in vitro. These difficulties have partly been overcome by use of mouse models reconstituted with human liver cells (16, 85), tissue culture systems allowing replication of primary HCV isolates (21) and testing for neutralization. Remaining difficulties are associated with the great genetic variability and mutation rate of HCV. Many linear and conformational epitopes targeted by nAbs have been identified in the E1 and E2 glycoproteins near the HVR1 (86). In a very elegant study, the impact of nAbs on the HVR1 was shown in serum samples collected from one infected individual over 26 years. It turns out that nAb responses always lag behind the rapidly evolving quasispecies population (87). In spite of this, there is a growing number of vaccine candidates under development [reviewed in (88, 89)]. There are three approaches for HCV vaccine design: (1) to prevent initial infection (sterilizing immunity), (2) to prevent viral persistence, and (3) to improve virologic response rates in chronic infection (therapeutic vaccines). Of particular interest is the use of nAbs as therapeutic vaccines and antiviral drugs for potential treatment of liver transplant patients to prevent HCV from reinfecting the transplant (90–92). One of these broadly reacting nAbs competes directly with binding to the cellular receptor CD81 (93).

**CONCLUSION**

The partnership between HCV and its human host has evolved over millennia, whereas we have only known the virus for a couple of decades. The virus displays numerous mechanisms to evade the host defence, and there is still much to be learned about the regulatory and effector mechanisms of the host immune response. An efficient, multispecific and vigorous T-cell response at the early stage of infection is critical to clear the virus. The vaccine issue is complex and at present the outlook is not very heartening owing to the extreme adaptability of the virus. Nevertheless, rapidly increasing knowledge of viral mechanisms and strategies and accompanying progress in therapeutic measures hold promise that man in the foreseeable future will equalize the millenial lead of the virus.

**REFERENCES**


