Available online at www.sciencedirect.com
SCIENCE DIRECT®
Antiviral Research 60 (2003) 111–115
Antiviral Research
www.elsevier.com/locate/antiviral

Multifaceted functions of B cells in chronic hepatitis C virus infection

Mario U. Mondelli*

Research Laboratories, Department of Infectious Diseases, IRCCS Policlinico San Matteo and University of Pavia, Via Taramelli, 5, 27100 Pavia, Italy

Abstract

Hepatitis C virus (HCV) elicits T- and B-cell responses which are believed to play an important role in infection control. B cells have generally been neglected because they do not seem to significantly influence the course of HCV infection. In this review, B lymphocytes are viewed both as classical antibody producing cells, with the hypervariable region 1 being a biologically relevant target protein and as a model of virus–host interaction in lymphoproliferative disorders characteristic of persistent microbial infections.

Keywords: HCV; HVR1; B lymphocytes

Hepatitis C virus (HCV) infection is characterised by a disturbingly high propensity to persist in the host for an indefinite period of time leading to chronic liver disease which may evolve into cirrhosis and hepatocellular carcinoma (Alberti et al., 1999). Several studies have pointed to the importance of T-cell-mediated immune responses in controlling HCV infection (Bertoletti and Ferrari, 2003). However, little is known on the role of B-cell responses in this setting. The purpose of this review is to examine the role of B cells in the evolution of HCV infection as well as their interaction with viral proteins, which is thought to be the basis for B-cell clonal expansion in lymphoproliferative disorders.

1. Role of antibody responses to HCV with particular emphasis on the hypervariable region 1 (HVR1)

In contrast with hepatitis B virus infection in which envelope-specific neutralizing antibodies (Ab) closely correlate with clinical recovery, patients chronically infected with HCV invariably have envelope-specific Ab detectable in their serum, indicating an ongoing B-cell response (Cerino et al., 1997). The significance and utility of such circulating Ab are currently uncertain, since re-challenge of experimentally infected chimpanzees with high levels of circulating anti-HCV immunoglobulin still results in the reappearance of viraemia (Farci et al., 1992). Our current understanding of the possible functions of B-cell responses in HCV infection as well as the role of the virus in causing B-cell clonal expansion is depicted in Fig. 1.

Over the past several years, attempts were made to identify reproducible patterns of B-cell responses that correlated with specific clinical outcomes without success. However, one particular region the hypervariable region 1 (HVR1) has attracted the attention of many investigators because it was generally believed to play an important role in the pathogenesis of HCV infection. In a previous study, we prospectively followed serological responses to synthetic oligopeptides derived from HVR1 sequences of patients with acute and chronic HCV infection obtained at baseline and after a defined follow-up period (Mondelli et al., 1999). Extensive serological cross-reactivity for unrelated HVR1 peptides was observed in the majority of the patients. Ab responses were restricted to the IgG1 subclass and were focused on the carboxy-terminal end of the HVR1 region. Cross-reactive Ab could also be readily elicited following immunization of mice with multiple antigenic peptides carrying HVR1 sequences derived from our patients.

To investigate further the molecular basis for Ab cross-reactivity for unrelated HVR1 sequences we generated a panel of murine monoclonal antibodies (mAb) from mice immunized with HVR1 surrogate peptides (mimotopes), affinity-selected with sera from HCV-infected patients from a phage-display library (Puntoriero et al., 1998). A significant number of antigen-specific hybridomas was obtained after immunization with a pool of 9 mimotopes. The mAbs were shown to recognize a number of 16- and 27-mer peptides derived from natural HVR1 sequences isolated from patients with acute and chronic HCV infection and a major binding site could be mapped at amino acid

* Tel.: +39-0382-502636/502639; fax: +39-0382-526450.
E-mail address: m.mondelli@smatteo.pv.it (M.U. Mondelli).

0166-3542/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.antiviral.2003.08.004

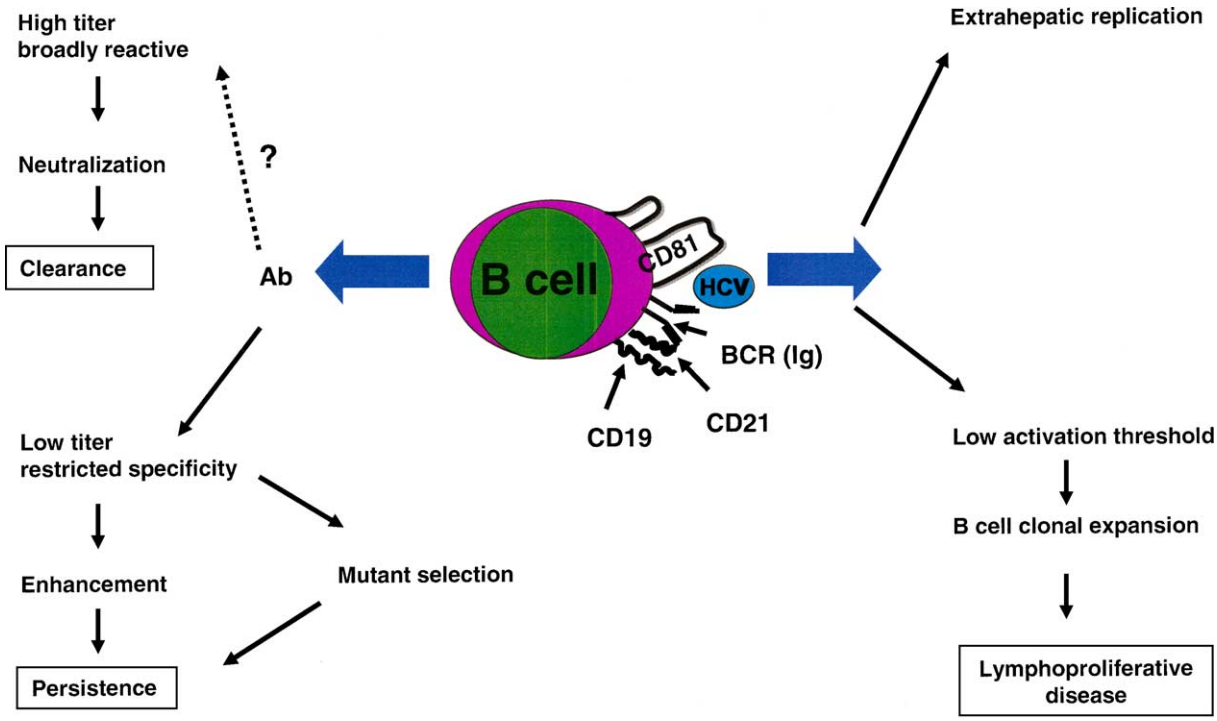

Fig. 1. Proposed functions of B cells in HCV infection. Production of highly efficient neutralizing antibodies to HCV is currently uncertain although it is likely to occur only in certain circumstances. Such antibodies should be produced at high concentration and possibly have broad specificity, though this is currently unknown. However, in most circumstances neutralizing antibodies would be produced at low concentrations and with restricted specificity; this would on the one hand favour selection of viral mutants and on the other hand it could generate an enhancement mechanism which would increase the spread of the infection to other susceptible cells. In addition to classical antibody production, B cells may undergo aberrant proliferation and rheumatoid factor production, as seen in extrahepatic disease, such as cryoglobulinaemia. To this end, HCV polypeptides such as the E2 glycoprotein and, possibly, NS3 may lower the physiological activation threshold of B cells by interacting with CD81 and the B-cell receptor complex, inducing clonal expansion and, eventually, malignant proliferation as in B-NHL.

position 390–405, akin to our previous findings using human sera (Cerino et al., 2001). HVR1 mimotope-specific mAb were also able to efficiently compete with sera from HCV-infected patients for binding to peptides derived from natural HVR1 sequences, thus confirming previous data obtained with polyclonal Ab showing that HVR1 peptide mimotopes are efficient antigenic and immunogenic mimics of naturally occurring HCV variants.

A plausible explanation accounting for the promiscuous binding characteristics of HVR1-specific antibodies comes from a recent theoretical study on the structural conformation of HVR1 which showed either a broad amino acid repertoire at each position in spite of a remarkable residue conservation in specific sites or replacements with amino acids with similar physicochemical properties, usually positively charged basic residues, in the most variable segments (Penin et al., 2001). The very similar hydropathy and antigenicity profiles of HVR1 variants revealed a substantial conformational conservation, thus providing a plausible explanation for the extensive cross-reactivity demonstrated by Ab and confirming the existence of an active selection process. Interestingly, two sites with a high antigenicity score were identified at positions 1–13 and 19–24, a pattern which is predicted also with phylogenetically distant variants (Penin et al., 2001). The latter site contains the immunodominant B-cell epitope(s) described previously (Scarselli et al., 1995; Mondelli et al., 1999) and is compatible with B-cell epitope mapping data (Zibert et al., 1997; Mondelli et al., 1999).

The possibility to generate broadly reactive antibodies may represent a useful approach to overcome the natural diversity of a virus such as HCV, suggesting that mimotope-based vaccines can be used as potentially effective HCV immunogens. This assumption is based on evidence indicating that antibodies to HVR1 can prevent HCV infection in the chimpanzee model by both in vitro and in vivo neutralization of a pedigreed virus inoculum of HCV strain H (Farci et al., 1994, 1996). However, exposure of HVR1 on complete viral particles has not been formally proven and, in principle, the role of this sequence in binding neutralizing antibodies is far from being established. A recent preliminary study suggested that mAb obtained by immunization with peptides derived from natural HVR1 isolates were able to capture bona fide viral particles only from homologous HCV isolates and could also prevent infection of an allegedly susceptible cell line in vitro (Zhou et al., 2000). These findings are in partial agreement with our data in that one of our mAbs was also able to capture bona fide and recombinant viral particles, although there

was no apparent genotype or isolate-specific recognition (Cerino et al., 2001). Similar findings were reported by Li et al. (2001), who were able to show that mAbs generated by immunization with HVR1 peptides, specific for conserved motifs, could capture HCV RNA from patients' plasmas and were also able to block HCV binding to Molt-4 cells which, in previous experiments (Hamaia et al., 2001), were shown to efficiently bind HCV. These observations fit with the idea of a significant structural conservation of HVR1 as discussed above.

It may be argued that mAb raised against HVR1 peptides are unable to recognize the same sequence when expressed in the context of a correctly-folded complete E2 glycoprotein which included HVR1. However, our mAb were shown to recognize correctly-folded E2 polypeptides expressing the same HVR1 sequences synthesized as linear peptide, providing additional evidence supporting the existence of immunodominant, conformation-independent epitope(s) in the C-terminal sub-region which, under certain circumstances, may be exposed on integral viral particles.

The role, if any, played by HVR1 in host–virus interactions at the protein level is still unknown. Recently, a novel HCV candidate receptor, in addition to CD81 (Pileri et al., 1998) has been identified on human hepatocellular carcinoma cell lines. Such putative receptor, the scavenger receptor class B type I (SRBI), binds E2 via HVR1 and is species-specific (Scarselli et al., 2002). Thus, high-affinity anti-HVR1 Ab elicited by immunization could modulate HCV infection by inhibiting binding of viral particles to SRBI. This approach may have important implications for immunotherapy or prophylaxis of HCV infection.

2. What is the biological basis for B-cell clonal expansion in chronic HCV infection?

In addition to causing liver pathology, HCV infection is frequently associated with extrahepatic manifestations such as mixed cryoglobulinaemia and non-Hodgkin's B-cell lymphoma, which are characterised by B-cell proliferation and clonal expansion (Ferri et al., 1994; Haddah et al., 1992; Mariette et al., 1993; Selva-O'Callaghan et al., 1999; Zuckerman et al., 1997). It is currently believed that more than 50% of the patients with chronic HCV infection have asymptomatic cryoglobulinaemia (Lunel et al., 1994; Mondelli et al., 1998). A form frequently detected in chronically infected patients is type II cryoglobulinaemia which is characterised by the presence of cryoprecipitable immune complexes formed by a polyreactive monoclonal IgMκ with rheumatoid factor activity (Gorevic and Frangione, 1991) binding to oligo- or polyclonal IgG (Mondelli et al., 1998) and a non-neoplastic expansion of a B-cell clone producing this IgM (Monteverde et al., 1995). It is conceivable that the non-neoplastic monoclonal expansion characteristic of type II cryoglobulinaemia and that observed in some HCV related lymphomas such as B-cell non-Hodgkin lymphoma (B-NHL) are a consequence of protracted antigenic stimulation (Quinn et al., 2001). To this end, a direct demonstration of HCV antigen-dependent stimulation in NHL associated with HCV is supported by recent observations (Casato et al., 2002; Hermine et al., 2002) showing complete remission of splenic lymphomas following eradication of HCV infection. The mechanisms through which HCV infection promotes a potent and selective B-cell clonal expansion are currently unknown, but it is likely that this is a multistep process during which specific genetic anomalies accumulate, similarly to what is thought to occur in lymphomas associated with chronic *Helicobacter. pylori* infection (Zucca et al., 2000). The established ability of HCV to directly stimulate B cells by lowering the B-cell activation threshold via engagement of CD81 (Rosa et al., 2001), a tetraspanin that has been shown to specifically bind the E2 envelope glycoprotein (Pileri et al., 1998), suggests that HCV is an additional prototypic agent capable of performing functions that go well beyond that causing persistent infection. Indeed, the mere presence of replicating HCV can result in clonal expansion of B cells expressing immunoglobulin variable region genes that are commonly expressed during HCV-associated B-cell lymphoproliferative disorders. Why this occurs is still largely a matter of speculation.

The clonally expanded B cells in type II cryoglobulinaemia are similar to murine B-1 cells (Clarke and Arnold, 1998; Berland and Wortis, 2002). These cells, which account for approximately 5% of total B cells in mice and humans, arise during foetal development, show a restricted receptor repertoire, express CD5 and have high levels of surface IgM with little surface IgD. They are of interest to clinicians as they are the origin of chronic lymphocytic leukaemia. The restricted receptor repertoire resembles that of γ:δ T cells. Indeed, B-l cells hardly undergo somatic hypermutation, and their V gene segments that are commonly used to encode their receptor seem to have evolved to recognize common bacterial and self antigens, thus allowing them on the one hand to contribute to the early, non-adaptive (innate) phase of the immune response and on the other hand to be maintained partially activated as they are selected for self-renewal by ubiquitous self and foreign antigens. This is further supported by their ability to produce polyreactive IgM with features of natural (auto)antibodies and to clonally expand (Le Maoult et al., 1999). Recently, Curry and co-workers have shown specific expansion of CD5+ B cells in the peripheral blood (Curry et al., 2000) and in the liver (Curry et al., 2003) of patients with chronic HCV infection. Expression of CD81, was significantly increased in CD5+ B cells compared with conventional B cells, and this appeared to correlate with the presence of HCV RNA, suggesting a close relationship between HCV replication and CD5+ B-cell clonal expansion (Curry et al., 2003). The demonstration that this B-cell subset expresses sizeable amounts of CD81 provides strong evidence in support of the hypothesis that B-cell clonal expansion results from direct viral protein stimulation via CD81, which is now

currently regarded more as a signalling molecule rather than a virus-internalising receptor (Crotta et al., 2002). Moreover, the demonstration that CD5+ B cells produce IgM monoclonal rheumatoid factor (Kipps, 1989) would establish a plausible pathogenetic basis for type II cryoglobulinaemia in this setting. However, the finding of CD5+ B-cell expansion in the peripheral blood has not been confirmed in a recent study (Ni et al., 2003), in which the proportion of CD5+ B cells was found to be normal or reduced in patients with chronic HCV infection and this was accompanied by an accumulation of B cells characterised by a naïve phenotype.

Although it seems that there is sufficient evidence in favour of a role of viral gene products in generating clonal expansion of B cells, only little information is available on the ability of HCV to infect cells other than hepatocytes. Controversial data have been reported on the detection of HCV RNA positive and negative strands in peripheral blood B lymphocytes of some patients with chronic hepatitis C (Lanford et al., 1995; Laskus et al., 2000; Zignego and Brechot, 1999). However, until recently, the virus has never been directly demonstrated and isolated ex vivo or in tissue culture. Sung et al. (2003) now provide convincing and reproducible evidence that HCV can replicate in B-cell lines obtained from the spleen of a patient with B-NHL chronically-infected with HCV or following immortalization of peripheral blood B cells of HCV-infected patients with Epstein–Barr virus. These cell lines were persistently infected for several months in culture, expressed the viral NS3 protein and produced HCV particles that were capable of infecting primary human hepatocytes and other B cells in culture. Unfortunately, we do not know whether they also expressed CD5, although preliminary evidence would suggest that the B-NHL derived cell line produces a monoclonal IgM with an apparent anti-NS3 specificity. However, infection of B lymphocytes with HCV would probably be contributory, but not strictly necessary, to perpetuate antigen-dependent growth and eventually expansion of pre-malignant B cells.

3. Conclusions

HCV may develop several strategies to avoid immune clearance and establish persistent infection. The high rate of virus production early during infection may result in immune exhaustion or, rather, be caused by a failure of the innate immune response to control virus replication (Crotta et al., 2002; Tseng and Klimpel, 2001). The intrinsic variability of HCV, most likely induced by the host's immune pressure on certain viral regions (Mondelli et al., 1999) may select cytotoxic T-cell escape mutants (Chang et al., 1997; Erickson et al., 2001). Several lines of evidence also suggest that the viral core protein (Large et al., 1999; Yao et al., 2001; Francavilla et al., 2003) may inhibit T-cell effector function. However, the teleological significance of HCV-B lymphocyte interaction remains largely unexplained.

References

Alberti, A., Chemello, L., Benvegnù, L., 1999. Natural history of hepatitis C. J. Hepatol. 31S, 17–24.

Berland, R., Wortis, H.H., 2002. Origins and functions of B-1 cells with notes on the role of CD5. Annu. Rev. Immunol. 20, 253–300.

Bertoletti, A., Ferrari, C., 2003. Kinetics of the immune response during HBV and HCV infections. Hepatology 38, 4–13.

Casato, M., Meccucci, C., Agnello, V., Fiorilli, M., Knight, G.B., Matteucci, C., Gao, L., Kay, J., 2002. Regression of lymphoproliferative disorder after treatment for hepatitis C virus infection in a patient with partial trisomy 3, Bcl-2 overexpression, and type II cryoglobulinemia. Blood 99, 2259–2261.

Cerino, A., Bissolati, M., Cividini, A., Nicosia, A., Esumi, M., Hayashi, N., Mizuno, K., Slobbe, R., Oudshoorn, P., Silini, E., Asti, M., Mondelli, M.U., 1997. Antibody responses to the hepatitis C virus (HCV) E2 protein: relationship to viraemia and prevalence in anti-HCV seronegative subjects. J. Med. Virol. 51, 1–5.

Cerino, A., Meola, A., Segagni, L., Furione, M., Marciano, S., Triyatni, M., Liang, T.J., Nicosia, A., Mondelli, M.U., 2001. Monoclonal antibodies with broad specificity for hepatitis C virus hypervariable region 1 variants can recognize viral particles. J. Immunol. 167, 3878–3886.

Chang, K.M., Rehermann, B., McHutchison, J.G., Pasquinelli, C., Southwood, S., Sette, A., Chisari, F.V., 1997. Immunological significance of cytotoxic T lymphocyte epitope variants in patients chronically infected by the hepatitis C virus. J. Clin. Invest. 100, 2376–2385.

Clarke, S.H., Arnold, L.W., 1998. B-1 cell development: evidence for an uncommitted immunoglobulin IgM+ B cell precursor in B-1 cell differentiation. J. Exp. Med. 187, 1325–1334.

Crotta, S., Stilla, A., Wack, A., D'Andrea, A., Nuti, S., D'Oro, U., Mosca, M., Filipponi, F., Brunetto, R.M., Bonino, F., Abrignani, S., Valiante, N.M., 2002. Inhibition of natural killer cells through engagement of CD81 by the major hepatitis C virus envelope protein. J. Exp. Med. 195, 35–41.

Curry, M.P., Golden-Mason, L., Nolan, N., Parfrey, N.A., Hegarty, J.E., O'Farrelly, C., 2000. Expansion of peripheral blood CD5+ B cells is associated with mild disease in chronic hepatitis C virus infection. J. Hepatol. 32, 121–125.

Curry, M.P., Golden-Mason, L., Doherty, D.G., Deignan, T., Norris, S., Dufiy, M., Nolan, N., Hall, W., Hegarty, J.E., O'Farrelly, C., 2003. Expansion of innate CD5(pos) B cells expressing high levels of CD81 in hepatitis C virus infected liver. J. Hepatol. 38, 642–650.

Erickson, A.L., Kimura, Y., Igarashi, S., Eichelberger, J., Houghton, M., Sidney, J., McKinney, D., Sette, A., Hughes, A.L., Walker, C.M., 2001. The outcome of hepatitis C virus infection is predicted by escape mutations in epitopes targeted by cytotoxic T lymphocytes. Immunity 15, 883–895.

Farci, P., Alter, H.J., Govindarajan, S., Wang, D.C., Engle, R., Lesniewski, R.R., Mushahwar, I.K., Desai, S.M., Miller, R.H., Ogata, N., Purcell, R.H., 1992. Lack of protective immunity against reinfection with hepatitis C virus. Science 258, 135–140.

Farci, P., Alter, H.J., Wong, D.C., Miller, R.H., Govindarajan, S., Engle, R., Shapiro, M., Purcell, R.H., 1994. Prevention of hepatitis C virus infection in chimpanzees after antibody-mediated in vitro neutralization. Proc. Natl. Acad. Sci. U.S.A. 91, 7792–7796.

Ferri, C., Caracciolo, F., Zignego, A.L., 1994. Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. Br. J. Haematol. 88, 392–394.

Farci, P., Shimoda, A., Wong, D., Cabezon, T., De Gioannis, D., Strazzera, A., Shimizu, Y., Shapiro, M., Alter, H.J., Purcell, R.H., 1996. Prevention of hepatitis C virus infection in chimpanzees by hyperimmune serum against the hypervariable region 1 of the envelope 2 protein. Proc. Natl. Acad. Sci. U.S.A. 93, 15394–15399.

Francavilla, V., Accapezzato, D., De Salvo, M., Finocchi, L., D'Amico, F., Rawson, P., Lipp, M., Cerino, A., Cividini, A., Mondelli, M.U.,

Barnaba, V., 2003. Viral subversion of effector CD8+ T cell differentiation in acute hepatitis C virus infection. Submitted for publication.
Gorevic, P.D., Frangione, B., 1991. Mixed cryoglobulinemia cross-reactive idiotypes: implications for the relationship of MC to rheumatic and lymphoproliferative diseases. Semin. Hematol. 28, 79–94.
Haddah, J., Deny, P., Munz-Gotheil, C., Ambrosini, J.C., Trinchet, J.C., Pateron, D., Mal, F., Callard, P., Beaugrand, M., 1992. Lymphocytic sialadenitis of Sjögren's syndrome associated with chronic hepatitis C virus liver disease. Lancet 339, 321–323.
Hamaia, S., Li, C., Allain, J.-P., 2001. The dynamics of hepatitis C virus binding to platelets and 2 mononuclear cell lines. Blood 98, 2293–2300.
Hermine, O., Lefrere, F., Bronowicki, J.P., Mariette, X., Jondeau, K., Fclache-Saudreau, V., Delmas, B., Valensi, F., Brechot, C., Varet, B., Troussard, X., 2002. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N. Engl. J. Med. 347, 89–94.
Kipps, T.J., 1989. The CD5 B cell. Adv. Immunol. 47, 117–185.
Lanford, R.E., Chavez, D., Chisari, F.V., Sureau, C., 1995. Lack of detection of negative-strand hepatitis C virus RNA in peripheral blood mononuclear cells and other extrahepatic tissues by the highly-strand specific rTth reverse transcriptase PCR. J. Virol. 69, 8079–8083.
Large, M.K., Kittlesen, D.J., Hahn, Y.S., 1999. Suppression of host immune response by the core protein of hepatitis C virus: possible implications for hepatitis C virus persistence. J. Immunol. 162, 931–938.
Laskus, T., Radkowski, M., Wang, L.F., Nowicki, M., Rakela, J., 2000. Uneven distribution of hepatitis C virus quasispecies in tissues from subjects with end-stage liver disease: confounding effect of viral adsorption and mounting evidence for the presence of low-level extrahepatic replication. J. Virol. 74, 1014–1017.
Le Maoult, J., Manavalan, J.S., Dyall, R., Szabo, P., Nikolic-Zugic, J., Weksler, M.E., 1999. Cellular basis of B cell clonal populations in old mice. Immunology 162, 6384–6391.
Li, C., Candotti, D., Allain, J.-P., 2001. Production and characterization of monoclonal antibodies specific for a conserved epitope within hepatitis C virus hypervariable region 1. J. Virol. 75, 12412–12420.
Lunel, F., Musset, L., Cacoub, P., Frangeul, L., Cresta, P., Perrin, M., Grippon, P., Hoang, C., Piette, J.C., Huraux, J.-M., Opolon, P., 1994. Cryoglobulinemia in chronic liver diseases: role of hepatitis C virus and liver damage. Gastroenterology 106, 1291–1300.
Mariette, X., Zerbib, M., Jaccard, A., Schenmetzler, C., Danon, F., Clauvel, J.P., 1993. Hepatitis C virus and Sjögren's syndrome. Arthritis Rheum. 36, 280–281.
Monteverde, A., Sabattini, F., Poggi, S., Ballare, M., Bertoncelli, M.C., De Vivo, A., Briskomatis, A., Roncador, G., Falini, B., Pileri, S.A., 1995. Bone marrow findings further support the hypothesis that essential mixed cryglobulinemia type II is characterized by a monoclonal B-cell proliferation. Leuk. Lymphoma 20, 119–124.
Mondelli, M.U., Zorzoli, I., Cerino, A., Cividini, A., Bissolati, M., Segagni, L., Perfetti, V., Anesi, F., Garini, P., Merlini, G.P., 1998. Clonatily and specificity of cryoglobulins associated with HCV: pathophysiological implications. J. Hepatol. 29, 879–886.
Mondelli, M.U., Cerino, A., Lisa, A., Brambilla, S., Segagni, L., Cividini, A., Bissolati, M., Missale, G., Bellati, G., Meola, A., Bruniercole, B., Nicosia, A., Galfrè, G., Silini, F., 1999. Antibody responses to hepatitis C virus hypervariable region 1: evidence for cross-reactivity and immune-mediated sequence variation. Hepatology 30, 537–545.
Ni, J., Hembrador, F., Di Bisceglie, A.M., Jacobson, I.M., Talal, A.H., Butera, D., Rice, C.M., Chambers, T.J., Dustin, L.B., 2003. Accumulation of B lymphocytes with a naive, resting phenotype in a subset of hepatitis C patients. J. Immunol. 170, 3429–3439.
Penin, F., Combet, C., Germanidis, G., Frainais, P.O., Deléage, G., Pawlotsky, J.-M., 2001. Conservation of the conformation and positive charges of hepatitis C virus E2 glycoprotein hypervariable region 1 points to a role in cell attachment. J. Virol. 75, 5703–5710.
Pileri, P., Uematsu, Y., Campagnoli, S., Galli, G., Falugi, F., Petracca, R., Weiner, A.J., Houghton, M., Rosa, D., Grandi, G., Abrignani, S., 1998. Binding of hepatitis C virus to CD81. Science 282, 938–941.
Puntoriero, G., Meola, A., Lahm, A., Zucchelli, S., Bruno, B., Tafi, R., Pezzanera, M., Mondelli, M.U., Cortese, R., Tramontano, A., Galfrè, G., Nicosia, A., 1998. Towards a solution for hepatitis C virus hypervariability: mimotopes of the hypervariable region 1 can induce antibodies cross-reacting with a large number of viral variants. EMBO J. 17, 3521–3533.
Quinn, F.R., Chan, C.H., Hadlock, K.G., Foung, S.K., Flint, M., Levy, S., 2001. The B-cell receptor of a hepatitis C virus (HCV)-associated non-Hodgkin lymphoma binds the viral E2 envelope protein, implicating HCV in lymphomagenesis. Blood 98, 3745–3749.
Rosa, D., Salefti, G., Pozzato, G., Abrignani, S., 2001. HCV can activate B cells via CD81 engagement: a molecular mechanism for B cell autoreactivity and cryoglobulinemia in HCV infection. Hepatology 34, 252A.
Scarselli, E., Cerino, A., Esposito, G., Silini, E., Mondelli, M.U., Traboni, C., 1995. Occurrence of antibodies reactive with more than one variant of the putative envelope glycoprotein (E2; gp70) hypervariable region 1 in hepatitis C viremic patients. J. Virol. 69, 4407–4412.
Scarselli, E., Ansuini, H., Cerino, R., Roccasecca, R.M., Acali, S., Filocamo, G., Traboni, C., Nicosia, A., Cortese, R., Vitelli, A., 2002. The human scavenger receptor class B type I is a novel candidate receptor for the hepatitis C virus. EMBO J. 21, 5017–5025.
Selva-O'Callaghan, A., Rodriguez-Pardo, D., Sanchez-Sitjes, L., Matas-Pericas, L., Solans-Laque, R., Bosch-Gil, J.A., Vilardell-Tarres, M., 1999. Hepatitis C virus infection, Sjögren's syndrome, and non-Hodgkin's lymphoma. Arthritis Rheum. 42, 2489–2490.
Sung, V.M., Shimodaira, S., Doughty, A.L., Picchio, G.R., Can, H., Yen, T.S., Lindsay, K.L., Levine, A.M., Lai, M.M., 2003. Establishment of B-cell lymphoma cell lines persistently infected with hepatitis C virus in vivo and in vitro: the apoptotic effects of virus infection. J. Virol. 77, 2134–2146.
Tseng, C.T.K., Klimpel, G.R., 2001. Binding of the hepatitis C virus envelope protein E2 to CD81 inhibits natural killer cell functions. J. Exp. Med. 195, 43–50.
Yao, Z.Q., Nguyen, D.T., Hiotellis, A.I., Hahn, Y.S., 2001. Hepatitis C virus core protein inhibits human T lymphocytes responses by a complement-dependent regulatory pathway. J. Immunol. 167, 5264–5272.
Zhou, Y.H., Shimizu, Y.K., Esumi, M., 2000. Monoclonal antibodies to the hypervariable region 1 of hepatitis C virus capture virus and inhibit virus adsorption to susceptible cells in vitro. Virology 269, 276–283.
Zibert, A., Kraas, W., Meisel, H., Jung, G., Roggendorf, M., 1997. Epitope mapping of antibodies directed against hypervariable region 1 in acute self-limiting and chronic infections due to hepatitis C virus. J. Virol. 71, 4123–4127.
Zignego, A.L., Brechot, C., 1999. Extrahepatic manifestations of HCV infection: facts and controversies. J. Hepatol. 31, 369–376.
Zucca, E., Bertoni, F., Roggero, F., Cavalli, F., 2000. The gastric marginal zone B-cell lymphoma of MALT type. Blood 96, 410–419.
Zuckerman, F., Zuckerman, T., Levine, A.M., Douer, D., Gutekunst, K., Qian, D.G., Velankar, M., Nathwani, B.N., Fong, T.L., 1997. Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. Ann. Intern. Med. 127, 423–428.