ELSEVIER

Antiviral Research 52 (2001) 113–116

Antiviral Research

www.elsevier.com/locate/antiviral

Genetic susceptibility in chronic viral hepatitis

Mark Thursz *

Imperial College School of Medicine, St. Mary's Hospital, Norfolk Place, London W 2 1NY, UK

Abstract

Infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) may result in a number of different clinical outcomes. There is strong evidence in HBV infection that host genetic factors play a major role in determining the outcome of infection. A number of approaches may be used to determine the specific genetic factors involved but the principal method which has been used to date is the disease association study. Disease association studies have a number of drawbacks but trials with well-constructed designs and large numbers of cases have recently produced compelling and reproducible results. In particular alleles in the MHC class II loci and interleukin 10 promoter have been demonstrated to influence the outcome of these infections. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Hepatitis B virus; Hepatitis C virus; Hepatitis B surface antigen

1. Introduction

The outcome of hepatitis B and hepatitis C virus (HBV and HCV) infections is highly variable, ranging from asymptomatic disease culminating in the spontaneous elimination of infection to persistent infection that can lead to cirrhosis, liver failure or hepatocellular carcinoma. The factors which determine the outcome in an individual patient are poorly understood but may be classified into three categories: environmental, viral and host factors. Fundamental to the host's response to infection is their genetic makeup. The focus of this article is to review the evidence that identifies host genes, which influence the outcome of HBV and HCV infection. In many respects, HBV and HCV infection are ideal examples for the study of host genetic factors because it is easy to define a clearly dichotomous outcome: persistent infection versus spontaneous elimination of virus.

2. Do genetic factors influence the outcome of infection?

Before undertaking a study of specific host factors, which may influence the outcome of HBV or HCV infection, it is crucial to study the evidence suggesting that genetic factors influence disease outcome. Initial studies by London and Blumberg found that persistent HBV segregated within families in a manner suggestive of an autosomal recessive trait (Blumberg et al., 1969). Since that time, knowledge of the outcome of vertical transmission has complicated this sort of analysis. More robust evidence in support of genetic fac-

* Tel.: +44-20-7594-3851.
E-mail address: m.thursz@ic.ac.uk (M. Thursz).

PII: S0166-3542(01)00175-9

tors arises from twin studies conducted in Taiwan (Lin et al., 1989). In these studies, it was demonstrated that the degree of concordance for hepatitis B surface antigen (HBsAg) status was significantly higher in monozygotic twins than in dizygotic twins. In HCV infection, the evidence for genetic factors is more circumstantial. No twin studies have been published nor can we expect these studies to be conducted as the rate of intrafamilial transmission of the virus is very low. Genetic factors are implicated in the outcome of HCV by analogy to other infectious diseases, to the establishment of clear-cut disease associations with polymorphic host genes and to variations in the outcome of other flavivirus infections observed in inbred strains of mice (Urosevic et al., 1995).

3. Strategies for identifying disease susceptibility genes

Having accepted the assumption that the outcomes of both HBV and HCV are influenced by environment and/or viral and host genetic variables with no clear pattern of inheritance, the geneticist will view these conditions as complex traits. A number of strategies have been developed to identify host genetic factors in complex traits (reviewed by Lander and Schork, 1994). These include genome-based scans of affected sibling pairs, genome-based scans of rodent models of infection, and disease association studies.

Affected sibling pair studies have become popular over the last decade due to advances in genotyping technology and capacity. Based on Mendelian inheritance, a genetic marker would be transmitted from a parent to neither sibling 25% of the time, one of the two siblings 50% of the time, and both siblings 25% of the time. However, if the marker is in linkage disequilibrium to a disease susceptibility gene, and the two siblings both have that disease, then the Mendelian pattern of inheritance will be skewed. Therefore, in a large group of sibling pairs with the disease, a much higher proportion of siblings will share the marker. These studies have been used to investigate the genetic factors in hypertension, asthma, diabetes and inflammatory bowel disease (Malerba et al., 1999; Wu et al., 1996; Satsangi et al., 1996). The proposed benefit of these studies is that novel genes and potentially novel biological pathways may be identified. This represents a significant advantage compared to disease association studies. However, the negative side of these studies is that, few novel genes have been identified and where multiple genome scans have been conducted, discrepant results have been observed. This may reflect an inherent problem with the technique which is its lack of statistical power (Lander and Schork, 1994). We are currently conducting a genome scan in families from Europe and West Africa where there are at least two siblings carrying HBsAg. No other groups have reported results using this technique in HBV infection to date.

In some infectious diseases, there are well-characterised animal models in which the outcome of infection is determined by the genetic strain of the animal. Where this is the case, crosses between strains with divergent outcomes can be used to identify genetic factors using genome scanning techniques. Unfortunately, no suitable rodent model exists for HBV infection; therefore, this technique is not applicable. HCV is a member of the flavivirus family and, although there is no animal model for HCV infection, there are good animal models for other flavivirus infections. Using West Nile virus a group in Adelaide have identified a locus on mouse chromosome 5 which confers resistance to infection (Urosevic et al., 1995). Mice possessing the resistance allele are capable of rapidly controlling viral replication. In this regard, there is evidence to suggest that the replication complex of viral and host proteins with the negative strand viral RNA is less stable in resistant than in susceptible mice (Shi et al., 1996). Once the gene responsible for flavivirus resistance is identified, it will be import to identify the human homologue and determine its role in HCV infection. This strategy has previously been used successfully to establish the role of NRAMP1 in determining susceptibility to tuberculosis (Bellamy et al., 1998).

4. Disease association studies

At this juncture, the influence of specific genes on the outcome of HBV and HCV infections has only been established using disease association studies. This is a simple technique which compares the allele frequency of a polymorphic gene between a group of subjects with the condition (cases) and a suitably selected control group. The most appropriate case and control groups are the phenotypically extreme outcomes of infection. Therefore, subjects who spontaneously eliminate HBV or HCV infection are compared to those who develop a persistent infection.

The selection of candidate genes in disease association studies has to be carefully considered. The analysis of allele frequency data uses a simple χ^2 test. If P value of 0.05 is accepted as confirmation of statistical significance, then one in 20 studies can be expected to give a positive result purely by chance. Careful selection of candidate genes and building a suitable hypothesis before undertaking the disease association study minimises the chance of producing erroneous results. Furthermore, reproducing a positive result in second population provides the required confirmation for an association.

In HBV, infection a number of studies have examined the role of MHC class II polymorphisms with the outcome of infection. In The Gambia, we found that the allele HLA-DRB1*1302 was associated with spontaneous elimination of infection and this was subsequently replicated in a European population (Thursz et al., 1995; Hohler et al., 1997a). In HCV, infection a number of studies have compared patients who cleared this infection with those who have persistent infection. This has identified one of the most robust disease associations in this field: the alleles DRB1*1101 and DQB1*0301 are consistently associated with spontaneous elimination of HCV (Minton et al., 1998; Alric et al., 1997; Thursz et al., 1999). In contrast, a number of studies have compared allele frequencies between subjects with persistent HCV infection and healthy population controls (Hohler et al., 1997b). These studies have produced inconsistent results suggesting that there is a flaw in the study design.

There are a number of polymorphisms in the promoter region of the tumour necrosis factor alpha (TNFα) gene that appear to influence the transcriptional efficiency of this gene. It has been established that TNFα is an important cytokine in the immune pathogenesis of both HBV and HCV infection particularly with regard to the noncytolytic control of viral replication. Initial studies in The Gambian population suggested that a point nucleotide substitution at position -308 (with respect to the transcription initiation site) was accompanied by an adverse outcome of HBV infection in which an allele associated with raised TNFα secretion correlated with persistent infection (Thursz et al., 1996; Tibbs et al., 1996). In a European population a second polymorphism at position -238 in the promoter region was associated with outcome although in this study, higher TNFα secretion correlated with clearance of infection (Hohler et al., 1998a). This second polymorphism and the allele associated with higher levels of TNFα secretion also have been associated with spontaneous elimination of HCV infection (Hohler et al., 1998b).

The interleukin 10 (IL10) gene, like the TNFα gene has a number of polymorphisms in the promoter region which influence the level of cytokine secretion. We found that an allele associated with high levels of IL10 secretion was associated with spontaneous elimination of HBV infection though it apparently had no effect on the outcome of HCV infection (Zhang, unpublished research). The association of high IL10 secretion with viral elimination appears to be counter-intuitive, but the association has been replicated in a second population. These data suggest that the role of IL10 in viral immunology is more complex than was initially believed and will need further elucidation.

The vitamin D receptor is expressed on monocytes and lymphocytes and stimulation of this receptor is thought to influence the immune response. There are a number of polymorphisms in the vitamin D receptor some of which appear to influence transcription efficiency of this gene. An allele of the vitamin D receptor that increases transcriptional efficiency has been associated with control of viral replication in HBV infection (Bellamy et al., 1999).

5. Summary

The process of dissecting the genetic contribution to the outcome of HBV and HCV infection has just begun and it appears that a number of genes may be involved in each infection. Identification of MHC class II associations is now being used to direct the identification of immunodominant epitopes using reverse immunogenetic approaches. The association an IL10 allele producing high levels of IL10 to the control of viral replication in hepatitis B has challenged our view of the role of this cytokine and is guiding further studies on the immune pathogenesis. One aim of this type of research is to provide prognostic markers for the outcome of these infections, but we are still a long way from accomplishing this objective.

References

Alric, L., Fort, M., Izopet, J., Vinel, J.P., Charlet, J.P., Selves, J., Puel, J., Pascal, J.P., Duffaut, M., Abbal, M., 1997. Genes of the major histocompatibility complex class II influence the outcome of hepatitis C virus infection. Gastroenterology 113, 1675–1681.

Bellamy, R., Ruwende, C., Corrah, T., McAdam, K.P., Whittle, H.C., Hill, A.V., 1998. Variations in the NRAMP1 gene and susceptibility to tuberculosis in West Africans. New Engl. J. Med. 338, 640–644.

Bellamy, R., Ruwende, C., Corrah, T., McAdam, K.P., Thursz, M., Whittle, H.C., Hill, A.V., 1999. Tuberculosis and chronic hepatitis B virus infection in Africans and variation in the vitamin D receptor gene. J. Infect. Dis. 179, 721–724.

Blumberg, B.S., Friedlaender, J.S., Woodside, A., Sutnick, A.I., London, W.T., 1969. Hepatitis and Australia antigen: autosomal recessive inheritance of susceptibility to infection in humans. Proc. Natl. Acad. Sci. USA 62, 1108–1115.

Hohler, T., Gerken, G., Notghi, A., Lubjuhn, R., Taheri, H., Protzer, U., Lohr, H.F., Schneider, P.M., Meyer zum Buschenfelde, K.H., Rittner, C., 1997a. HLA-DRBI*1301 and *1302 protect against chronic hepatitis B. J. Hepatol. 26, 503–507.

Hohler, T., Gerken, G., Notghi, A., Knolle, P., Lubjuhn, R., Taheri, H., Schneider, P.M., Meyer zum Buschenfelde, K.H., Rittner, C., 1997b. MHC class II genes influence the susceptibility to chronic active hepatitis C. J. Hepatol. 27, 259–264.

Hohler, T., Kruger, A., Gerken, G., Schneider, P.M., Meyer zum Buschenefelde, K.H., Rittner, C., 1998a. A tumor necrosis factor-alpha (TNF-alpha) promoter polymorphism is associated with chronic hepatitis B infection. Clin. Exp. Immunol. 111, 579–582.

Hohler, T., Kruger, A., Gerken, G., Schneider, P.M., Meyer zum Buschenfelde, K.H., Rittner, C., 1998b. Tumor necrosis factor alpha promoter polymorphism at position −238 is associated with chronic active hepatitis C infection. J. Med. Virol. 54, 173–177.

Lander, E.S., Schork, N.J., 1994. Genetic dissection of complex traits. Science 265, 2037–2048.

Lin, T.M., Chen, C.J., Wu, M.M., Yang, C.S., Chen, J.S., Lin, C.C., Kwang, T.Y., Hsu, S.T., Lin, S.Y., Hsu, L.C., 1989. Hepatitis B virus markers in Chinese twins. Anticancer Res. 9, 737.

Malerba, G., Trabetti, E., Patuzzo, C., Lauciello, M.C., Galavotti, R., Pescollderungg, L., Boner, A.L., Pignatti, P.F., 1999. Candidate genes and a genome-wide search in Italian families with atopic asthmatic children. Clin. Exp. Allergy 29 (Suppl. 4), 27–30.

Minton, E.J., Smillie, D., Neal, K.R., Irving, W.L., Underwood, J.C., James, V., 1998. Association between MHC class II alleles and clearance of circulating hepatitis C virus. Members of the Trent Hepatitis C Virus Study Group. J. Infect. Dis. 178, 39–44.

Satsangi, J., Parkes, M., Louis, E., Hashimoto, L., Kato, N., Welsh, K., Terwilliger, J.D., Lathrop, G.M., Bell, J.I., Jewell, D.P., 1996. Two stage genome-wide search in inflammatory bowel disease provides evidence for susceptibility loci on chromosomes 3, 7 and 12. Nat. Genet. 14, 199–202.

Shi, P.Y., Li, W., Brinton, M.A., 1996. Cell proteins bind specifically to West Nile virus minus-strand 3′ stem-loop RNA. J. Virol. 70, 6278–6287.

Thursz, M.R., Kwiatkowski, D., Allsopp, C.E.M., Greenwood, B.M., Thomas, H.C., Hill, A.V.S., 1995. Association between an MHC class II allele and clearance of hepatitis B virus in The Gambia. New Engl. J. Med. 332, 1065.

Thursz, M.R., Kwiatkowski, D., McGuire, W., Hill, A.V.S., Thomas, H.C., 1996. TNF promoter polymorphism and the outcome of hepatitis B virus infection. Gut 39 (Suppl. 1), A19.

Thursz, M.R., Yallop, R., Goldin, R., Trepo, C., Thomas, H.C., 1999. Influence of MHC class II genotype on outcome of infection with hepatitis C virus. Lancet 354, 2119–2124.

Tibbs, C., Donaldson, P., Underhill, J., Thomson, L., Manabe, K., Williams, R., 1996. Evidence that the HLA DQA1*03 allele confers protection from chronic HCV-infection in Northern European Caucasoids. Hepatology 24, 1342–1345.

Urosevic, N., Mansfield, J.P., Mackenzie, J.S., Shellam, G.R., 1995. Low resolution mapping around the flavivirus resistance locus (Flv) on mouse chromosome 5. Mamm. Genome 6, 454–458.

Wu, D.A., Bu, X., Warden, C.H., Shen, D.D., Jeng, C.Y., Sheu, W.H., Fuh, M.M., Katsuya, T., Dzau, V.J., Reaven, G.M., Lusis, A.J., Rotter, J.I., Chen, Y.D.I., 1996. Quantitative trait locus mapping of human blood pressure to a genetic region at or near the lipoprotein lipase gene locus on chromosome 8p22. J. Clin. Invest. 97, 2111–2118.