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Effects of hepatitis B and hepatitis C virus replication on the actions of interferon

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Abstract

Many patients chronically infected with hepatitis B or C do not respond to interferon therapy. For hepatitis B infections it is now clear that a viral factor down regulates the cells ability to respond to interferon and hence prevents effective therapy in some patients. In chronic hepatitis C infections, interferon therapy leads to the selection of interferon-resistant viral strains, but the mechanism of this resistance is not yet known.

Key words: Hepatitis B; Hepatitis C; Interferon

1. Introduction

Chronic infection with hepatotrophic viruses (hepatitis B and hepatitis C (HBV and HCV)) is estimated to affect over 350 million people worldwide. Interferon alpha (IFN) is the treatment of choice for patients with chronic HBV infections (Jacyna and Thomas, 1990) and there is increasing evidence to show that it is also effective in the treatment of some patients with chronic HCV infection (Davis et al., 1989). Although many patients with HBV infection benefit from IFN therapy some 50% do not respond to treatment (Jacyna and Thomas, 1990). The proportion of patients infected with HCV who respond to IFN is still not clear – early reports

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Abbreviations: HCV, Hepatitis C virus; HBV, Hepatitis B virus; IFN, Interferon alpha; 2–5A, 2′–5′ oligo adenylate synthetase.

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suggested that over 50% of patients may be cured by IFN treatment (Jacyna et al., 1989) but further studies have shown that although many patients benefit from treatment (i.e., the degree of hepatic inflammation decreases) only a small proportion are cured (i.e., hepatic inflammation is permanently reduced and viraemia does not recur when treatment is stopped) (Davis et al., 1989). Hence a significant number of patients with chronic viral hepatitis are refractory to the antiviral effects of IFN. There is increasing evidence to show that IFN resistance is due to an effect of the infecting virus on the cellular response to IFN and in this review we shall discuss recent research that has examined the anti-IFN properties of HBV and HCV.

2. Antiviral properties of interferons in chronic viral hepatitis

Two different types of IFN are found in humans: Type I and Type II interferons (Pestka et al., 1987). In humans Type II IFNs consist of a single sub-type (IFN-γ) that functions as an immune system modulator. IFN-γ possesses little antiviral activity and we shall not discuss it further. Type I IFNs consist of a familly of some 23 different IFN-α subtypes and a single IFN-β sub-type. These IFNs are a group of closely related proteins that are all believed to act in a similar manner (Pestka et al., 1987). Type I IFNs are predominantly antiviral proteins and they exert their effects by activating the production of a wide variety of cellular proteins (Staeheli, 1990). The nature and function of many of these proteins is not yet clear but a small number of IFN inducible proteins have been characterised and they are of two distinct groups: one group has direct antiviral properties and the other acts to enhance the immunological recognition of infected cells. IFN inducible proteins that have direct antiviral effects act by inhibiting the growth of particular viruses – for example the Mx protein specifically inhibits the replication of influenza viruses without affecting other viruses (Staeheli, 1990). Other IFN induced proteins inhibit the replication of a small number of viruses, for example 2′–5′ oligo adenylate synthetase (2–5A) is an IFN-induced enzyme that is activated by double-stranded RNA. Once activated 2–5A is able to activate an RNase that can degrade double-stranded RNA and hence this protein inhibits the replication of viruses that contain double-stranded RNA. In a similar manner double-stranded RNA can activate another IFN-induced protein (p68 kinase) that, when activated, inhibits protein translation. Although the fuctions of some IFN-induced proteins have been elucidated the functions of many others remains obscure, no doubt many of the proteins identified to-date whose functions are unknown specifically inhibit the replication of certain viruses, although their viral targets have not yet been identified.

Type I IFNs also induce the production of proteins that activate the immune system. In order to be recognised by the immune system (cytotoxic T cells etc.) viral proteins must first be cleaved into small peptides. This cleavage is performed by a complex of proteases known as the proteosome (Kelly et al., 1991) and the products of proteosome cleavage are then transported into the endoplasmic reticulum by transporter proteins (Trowsdale et al., 1990). In the endoplasmic reticulum the peptide fragments are bound to MHC Class I molecules and then expressed on the cell

surface where they can be recognised by the immune system. All the proteins involved in this presentation are induced by IFNs (J. Trowsdale, Imperial Cancer Research Fund, London, unpublished results) and hence IFNs activate immunological recognition and lysis of virally-infected cells.

It is not yet clear precisely how IFNs act in chronic viral hepatitis. In patients with chronic HBV infection who ultimately respond to IFN the response occurs in two phases (Fig. 1). There is an initial decrease in viral replication (detected as a decrease in the serum concentration of HBV DNA) but this is insufficient to eliminate the virus. Approximately 8–12 weeks after commencing IFN therapy there is a second response that consists of an increase in the degree of hepatitis (i.e., the liver damage increases) (Jacyna and Thomas, 1990). This is followed by the development of antibodies directed against components of HBV (anti HBe) and presumably this second response is due to an immunological reaction directed against HBV ie infected cells are recognised by humoral or cellular components of the immune system that are able to selectively kill infected hepatocytes. This immunologically mediated lysis of infected cells causes a transient increase in liver damage that is followed by viral elimination. It thus seems likely that in chronic HBV infection IFN acts initially by inhibiting viral replication and subsequently by enhancing an antiviral immune response.

In chronic HCV infection the response to IFN is rather different. Successful therapy causes a decrease in viral replication that is sustained and may be sufficient to eliminate the virus completely. There is no detectable increase in hepatic injury during treatment [2,3] and it seems likely that IFN acts in HCV infection purely as a

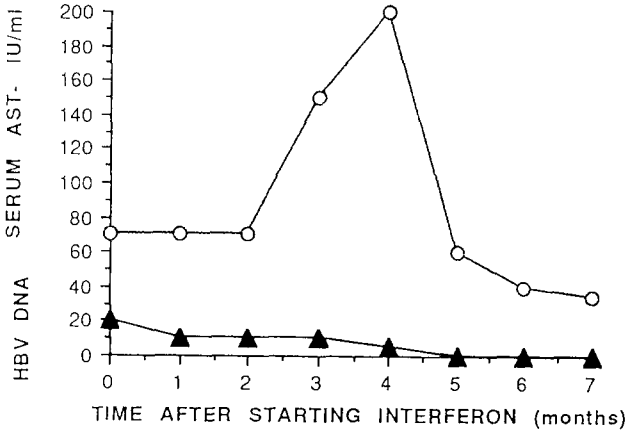

Fig. 1. Effects of IFN therapy in chronic HBV infection. Viral DNA in the serum (black triangles) decreases soon after starting therapy, suggesting that IFN has a direct antiviral effect. However the virus is not eliminated until a second response occurs some 2 to 3 months after starting therapy. This response involves an increase in liver damage (shown as an increase in the serum activity of an intrahepatic enzyme – AST (open circles)) and is due to the development of an immune response that eliminates infected cells.

direct antiviral agent – no evidence of immunological enhancement is currently apparent. The mode of action of IFN in HCV infection may thus be qualitatively different from its actions in chronic HBV infection.

3. Inhibition of IFNs effects in HBV infection

To avoid control by IFN, HBV would have to inhibit both the antiviral effects of IFN as well as its immune enhancing properties. There is an increasing body of evidence to show that HBV can inhibit both of these IFN-induced effects. In tissue culture systems cells infected with HBV show a reduced response to IFN (as measured by induction of the IFN inducible proteins that comprise the MHC Class I antigens) (Onji et al., 1989) and this inhibitory effect can be overcome by inhibitors of HBV replication (Takehara et al., 1992). In liver biopsy specimens taken from patients with chronic HBV infection two groups have shown that cells containing replicating HBV show a reduced expression of IFN inducible proteins [10,11] suggesting that in patients as well as in tissue culture systems HBV can inhibit the effects of IFN. This inhibitory effect acts to down regulate the induction of IFN inducible proteins and by preventing induction of IFN inducible proteins inhibits all the functions of IFN.

It is not yet clear how HBV inhibits the cellular response to IFN. There is some evidence to suggest that the polymerase protein of HBV can inhibit the cellular response to IFN (Foster et al., 1991) but this mechanism has not yet been elucidated. Studies from liver biopsies taken from patients with IFN-resistant HBV infections have shown that expression of the terminal protein domain of the polymerase protein is increased in patients who do not respond to IFN (Foster et al., 1993). This suggests that HBV may avoid the effects of IFN by overproducing the viral polymerase (or a related protein).

4. Inhibition of IFNs effects in chronic HCV infection

In chronic HBV infections both the antiviral and immunostimulatory effects of IFN must be inhibited to allow the virus to persist. This is not the case in chronic HCV infections where the virus need only inhibit the antiviral effects of IFN in order to survive during therapy. A number of studies have examined the expression of IFN inducible proteins in liver biopsies from patients with chronic HCV infection (Freni et al., 1991). In contrast to the situation in chronic HBV infections these studies have not detected any down regulation of MHC Class I expression in hepatocytes, suggesting that HCV does not inhibit the induction of IFN inducible proteins. However data from other studies indicates that HCV can avoid the antiviral effects of IFN. HCV is a highly variable virus and direct sequencing of the HCV genome during chronic infections has shown that a number of viral variants co-exist (Okada et al., 1992). These "quasi species" presumably represent variants containing mutations that have arisen during the infection. When patients chronically-in-

fected with HCV are treated with IFN the number of these quasi-species is significantly reduced but often a single HCV species persists (Okada et al., 1992), i.e., IFN therapy eliminates the majority of HCV strains but in many cases a particular quasi-species persists and gives rise to IFN resistant infection. This suggests that some HCV quasi-species are resistant to the antiviral effects of IFN. Since this resistance does not seem to be due to a global down regulation of IFNs effects, it seems likely that IFN resistant HCV strains selectively inhibit a particular action of IFN. A number of viruses are known to specifically inhibit certain IFN inducible proteins. For example the replication of adenoviruses can be inhibited by the IFN inducible protein p68 kinase. Certain adenoviral strains produce small RNA species (the VA RNAs) that bind to and inactivate this enzyme thus developing resistance to the antiviral effects of IFN (Kitajewski et al., 1986). It is possible that IFN resistance in chronic HCV infections is due to the development of HCV quasi species that are able to inhibit the anti-HCV effects of IFN. At present the mechanism of IFNs anti-HCV properties is unknown and the site of HCVs escape mechanism remains undetermined.

5. Conclusion

There is now strong evidence to show that both HBV and HCV develop resistance to the antiviral effects of IFN. For HBV the virus must avoid both the immunomodulatory and the antiviral effects of IFN and it now seems likely that HBV avoids these effects by inhibiting the cellular response to IFN, perhaps by overproducing the HBV polymerase protein. In the case of HCV infection current data suggests that the host defences fail to control the infection because of the presense of mutant viral strains that are able to inhibit the anti-HCV properties of IFN. The precise details of this inhibitory mechanism await elucidation.

References

Davis, G.L., Balart, L.A. and Schiff, E.R., Lindsay, K., Bodenheimer, H.C., Perillo, R.P., Carey, W., Jacobson, I.M., Payne, J. and Deenstag, J.L. (1991) Treatment of chronic hepatitis C with recombinant interferon alpha. N. Eng. J. Med. 321, 1501–1506.

Foster, G.R., Ackrill, A.M., Uoldin, R.D., Kerr, I.M., Thomas, H.C. and Stark, O.R. (1991) Expression of the terminal protein region of hepatitis B virus inhibits cellular responces to interferons alpha and gamma and double-stranded RNA. Proc. Natl. Acad. Sci. 88, 2888–2892.

Foster, U.R., Goldin, R.D., Hay, A., McUarvey, M.I., Stark, U.R. and Thomas, H.C. (1993) Expression of the terminal protein of hepatitis B virus is associated with a failure to respond to interferon therapy. Hepatology 17, 757–762.

Freni, M.A., Ajello, A., Resta, M.L., Gaeta, G.B., Spadaro, A., Fava, A., Calapristi, I., Alessi, N. and Ferrau, O. (1991) HCV infection, hepatic HLA display and composition of the mononuclear cell inflammatory infiltrate in chronic alcoholic liver disease. Eur. J. Clin. Invest. 21, 586–591.

Jacyna, M.R., Brooks, M.U., Loke, R.H.T., Main, J., Murray-Lyon. I.M. and Thomas, H.C. (1989) Randomised controlled trial of interferon alpha in chronic non-A non-B hepatitis. BMI 298, 80–82.

Jacyna, M.R. and Thomas, H.C. (1990) Antiviral therapy: hepatitis B. Brit Med. Bull. 46, 368–382 and Jacyna BMB.

Kelly, A., Powis, S.H., Glynne, R., Radley, E., Beck, S. and Trowsdale, J. (1991) Second proteosome related gene in the human class II region. Nature 353, 667–678.

Kitajewski, J., Schneider, R.I., Safer, B., Munemitsu, S.M., Samuel, C.E., Thimmappaya, B. and Shenk, T. (1986) VAI RNA antagonises the antiviral action of interferon by preventing activation of the interferon-induced eIF-2a kinase. Cell 45, 195–200.

Lau, J.Y.N., Bird, U.L.A., Naoumov, N.V. and Williams, R. (1993) Hepatic, H.L.A. antigen display in chronic hepatitis B virus infection, relation to hepatic expression of HBV genome/gene products and liver histology. Dig. Dis. Sci. 38, 888–895.

Okada, S., Akahane, Y., Suzuki, H., Okamoto, H. and Mishiro, S. (1992) The degree of variability in the amino terminal region of the E2/NS1 protein of hepatitis c virus correlates with responsiveness to interferon therapy in viremic patients. Hepatology 16, 619–624.

Onji, M., Lever, A.M.L., Saito, I. and Thomas, H.C. (1989) Defective response to interferon in cells transfected with the hepatitis B virus genome. Hepatology 9, 92–96.

Pestka, S., Langer, J.A., Zoon, K.C. and Samuel, C.E. (1987) Interferons and their actions. Ann. Rev. biochem. 56, 727–777.

Staeheli, P. (1990) Interferon-induced proteins and the antiviral state. Advances Virus Res. 38, 147–200.

Takehara, T., Hayashi, N., Katayama, K., Ueda, -K., Towata, T., Kasahara, A., Fusamoto, H. and Kamada, T. (1992) Enhanced expression of HLA Class I by inhibited replication of hepatitis B virus. J. Hepatol. 14, 232–236.

Trowsdale, J., Hansen, I., Mockridge, I., Beck, S., Townsend, A. and Kelly, A. (1990) Sequences encoded in the class II region of the MHC related to the ABC superfamilly of transporters. Nature 349, 7412–7414.