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A novel hybrid human interferon inhibits hepadnavirus replication in vitro and in vivo. BE Korba[1], B Fernie[1], BC Tennant[2], D Gangemi[3] and JL Gerin[1]. 1-Div. Molecular Virology & Immunology, Georgetown University Medical Center, Rockville, MD USA, 2-College of Veterinary Med., Cornell Univ., Ithaca, NY USA, 3-Clemson-Greenville Hospital Biomedical Alliance, Clemson, SC USA.

Alpha interferon has been shown to be an effective therapeutic agent against hepatitis B virus (HBV). While interferons are generally considered to be highly species specific, a recombinant hybrid of beta and delta human alpha interferon (B/DαIFN) has been shown to exhibit antiviral activity in several animal species. The HBV-producing 2.2.15 human hepatoblastoma cell was used to examine the mechanisms of the direct antiviral effects of B/DαIFN against HBV replication. B/DαIFN was effective at reducing the levels of intracellular HBV replication intermediates (RI) and extracellular virion DNA in 2.2.15 cells after 9 days of treatment (EC_{90}≈930 U/ml). By contrast, natural forms of alpha interferon (recombinant or lymphoblastoid) had no effect on HBV replication in 2.2.15 cells at 3000 U/ml. Treatment of 2.2.15 cells with 1000 U/ml B/DαIFN for 9 days reduced the levels of HBsAg and HBeAg in culture medium by 5-fold, but did not affect the levels of intracellular HBcAg, or the levels or apparent size of HBV RNA transcripts. Current studies are focused upon analyzing the relative levels of cellular markers of interferon induction of antiviral activity (e.g. $ß_2$ microglobulin, Mx, 2',5'-adenylate synthetase) following interferon treatment, as well as the levels, structure, and binding affinities of the alpha interferon receptors in 2.2.15 cells in order to determine the mechanisms of action of B/DαIFN against HBV. To determine the activity of B/DαIFN in an in vivo hepadnavirus model, Eastern woodchucks chronically infected with woodchuck hepatitis virus (WHV) were treated for 12 weeks ($5x10^6$ U/Kg B/DαIFN by subcutaneous injection, every 48 hr.). Treatment with B/DαIFN induced 100 to 3000-fold depressions in serum WHV DNA levels and 3 to 10-fold depressions in intracellular WHV DNA RI in the liver tissues of 5 of 6 treated animals, although WHV DNA levels returned to pretreatment levels within 8 weeks following the end of treatment in all animals. No changes in WHV DNA levels were observed in any of 6 control animals. Based upon these in vitro and in vivo activities, B/DαIFN appears to be a promising potential therapeutic agent against chronic HBV infection.

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Treatment of Chronic Woodchuck Hepatitis Virus Infection with Thymosin Alpha-1 (TA1). Tennant BC, Korba BE, Baldwin BH, Goddard LA, Hornbuckle WE, Cote PJ, and Gerin JL. College of Veterinary Medicine, Cornell University, Ithaca, NY and Division of Molecular Virology and Immunology, Georgetown University School of Medicine, Rockville, MD, USA.

TA1 is a member of a family of thymic polypeptide hormones that have immunoregulatory activity. TA1 is an acidic molecule containing 28 amino acids and is highly conserved among mammalian species. TA1 has been used in human patients to treat persistent HBV infection. Treatment was shown to decrease HBV replication and, in some patients, there was clearance of HBV and apparent recovery. In a study previously reported, 6 woodchucks with chronic WHV infection were treated subcutaneously with TA1 at a dose of 10 μg/kg twice weekly for 12 weeks, and serum WHV DNA decreased significantly during treatment compared to untreated controls. We have extended these studies to include groups of 6 WHV carriers treated with TA1 at doses of 10 μg/kg, 23 μg/kg, and 900 $\mu g/m^2$ twice weekly for 24 weeks. At the end of treatment, serum WHV DNA concentrations of all groups were 2 to 3 logs less than chronic WHV carrier controls. WHV DNA replicative intermediates in the liver of treated woodchucks also were significantly lower than controls at the end of treatment. WHV DNA of both serum and liver, however, gradually increased following treatment and after 12 weeks had reached values near those of controls.