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GENETIC ALTERNATION OF THE HEPATITIS C HYPERVARIABLE REGION IN CHILDREN WITH CHRONIC HEPATITIS C

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We previously reported that complete response (CR) rate of IFN therapy in children with chronic hepatitis C differs from their underlying disorders. Especially, in those children with hematologic malignancies, CR rate was relatively lower than those with non-malignancies. To determine the role of hypervariable region (HVR) variants in the mechanism of resistance to IFN, we evaluated genetic alternations of HVR by fluorescence SSCP & sequence analysis method (developed by Otsuka Assay Laboratory) before and after IFN treatment in 12 children with chronic hepatitis C (8 boys and 4 girls, mean age 11.3 yr. range 5-21 yr). In 8 children (3 with hematologic malignancies and 5 with non-malignancy), HCV RNA was eliminated by IFN treatment. In the remaining 4 children (all with hematologic malignancies), the change rate of HVR before IFN treatment was lower in children of a non-response to IFN than those of a CR. These observations suggest host immune surveillance is weaker in children with a history of immunosuppressive therapy than those without such a history. These differences in the immune conditions may be closely associated with response to IFN.

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A Novel Drug Delivery System for the Controlled Release of Antivirals in Combination Therapy. J.D. Gangemi[1], R. Schinazi[2], E.R. Kern[3], B. Korba[4], J. Corbett[5], J. Allen[5] and S. Shalaby[5]. GHS/CU Biomedical Cooperative[1] and Polymed, Inc.[5], Clemson, SC, USA; Emory University, Atlanta, GA[2]; University of Alabama, Birmingham, AL[3], Georgetown University, Rockville, MD[4].

We have previously reported that combinations of 3TC or acyclovir (ACV) and α-interferon (α-B/D) result in synergy when evaluated against hepatitis B (HBV) or herpes simplex (HSV) viruses, respectively. In this study, we have evaluated a new family of absorbable glycolate polyesters as carriers for the sustained release of either 3TC or ACV together with alpha interferon. These polyester carriers undergo phase change upon tissue contact and release both small and high molecular weight drugs following progressive hydrolytic dissociation of the polymer. Several strategies have been pursued to modulate the concurrent release of each drug at therapeutic levels. One of these includes incorporation of the low MW 3TC or ACV onto a solid microparticulate dispersed in a viscous matrix containing the relatively high MW alpha interferon. When placed in contact with mucosal surfaces, the viscous matrix formed an adherent depot for sustained release of both drugs. The therapeutic efficacy of this delivery system is under investigation.

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Differential sorting of hepatitis B virus (HBV) glycoproteins and DNA caused by unprocessed glycan

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We have shown that N-butyl-deoxynojirimycin (NBDNJ) prevents the secretion of HBV virions but not sub viral particles from infected liver cells. Preliminary work suggests some imino sugars can be derivatized to become 500 times more potent in their anti-HBV activity. Since NBDNJ is an effective inhibitor of endoplasmic reticular (ER) glucosidase (the enzyme mediator of the first step in N-glycan processing) the mechanism and site of it's antiviral action was studied. 2.2.15 cells chronically secrete HBV. In untreated 2.2.15 cells, viral envelope proteins and DNA are found in the same sub cellular compartments and are secreted within 3 hours of protein synthesis. However, glucosidase inhibited 2.2.15 cells accumulate vast amounts of replicative viral DNA in sub cellular, possibly lysosomal, compartments distinct from those to which envelope proteins are routed. Most significantly, the trafficking and sorting of envelope proteins is upset, with L, M and S returning to the ER long after they have reached the Golgi! M, but not S, ultimately is routed to compartments that may be lysosomes. HBV is thus unusually sensitive to the need for glucosidase function, since the secretion of many other host proteins (such as albumin or α-antitrypsin) are either not affected or moderately affected by NBDNJ. It is suggested that some glycoproteins, such as HBV L, M and S, with unprocessed glycan, are re-cycled in a retrograde transport from the Golgi to the ER and may eventually be degraded.

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THE EFFECT OF TREATMENT WITH INTERFERON COMBINED RIBAVIRIN ON CHRONIC HEPATITIS C VIRUS

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40 cases hepatitis patients have been tested by sera for AntiHAVM,HBsAg,AntiHBs,HBeAg, AntiHBC,Anti-HBcIgM are negative and for Anti-HCVwith PCR are positive. All of these patients are hepatitis C virus. 20 cases of them is treatment group treated with a-Interferon 10^6IU. im.combined Ribavirin 800mg i.v. every other day,three times a week for three months,17 cases of AntiHCV are negatative,the nagative rate is 85%.18 cases of sALT are recovery,the rate is 90%.20 cases of them is control group treated with a Interferon 10^6IU.im.every other day ,for three months.12 cases of AntiHCV are negative,the rate is 60%. 10 cases of sALT are recovery, the rate is 50%. The results show that is the better effect of treatment with a-Interferon combined Ribavirin for hepatitis C viruse.