101

IN-VITRO ANTI HIV EFFECT OF RECOMBINANT IFN-α (BDBB HYBRID) IN MACROPHAGES AND MT-2 CELLS, by J.K.Lazdins,M.R.Walker,K.A.Woods-Cook and E.Alteri, CIBA-GEIGY LTD, Pharma Research Laboratories, CH-4002 Basle, Switzerland.

Suppression of HIV replication in macrophages (Mø) is of outmost relevance,since virus can be easily detected in tissue Mø from AIDS patients,where these cells may serve as viral reservoir. Interferons are known to modulate Mø functions,thus we investigated the effect of IFN-α on virus replication in these cells as well as in the T-cell line MT-2. In-vitro differentiated blood monocytes were infected with the monocytotropic HIV isolate ADA. Infection was characterized by virus production(RT in supernatants and cell associated p24 viral antigen) and formation of giant cells without cytopathic effect. Pretreatment of Mø with IFN-α (100U/ml) suppressed virus replication by 85%. Moreover, this pretreatment potentiated the antiviral effect of AZT. When IFN-α was added to Mø after infection,virus replication was suppressed in a dose-related manner and was function of viral inoculum. This effect was also manifested by the lack of giant cell formation. When chronically infected Mø were exposed to IFN-α ,a suppression of virus replication was observed. Maximal effect was obtained when the drug was given repeatedly. Next, the effect of IFN-α on virus production (RT in supernatant) and syncytia formation in MT-2 cells infected with HIV-LAV was examined. A dose-dependent reduction of RT levels in cell supernatants was observed. However, no effect on syncytia formation was found. The antiviral effect of IFN-α in MT-2 cells was achieved at a dose 10 to 20 fold higher than that required in the Mø. In conclusion, IFN-α seems to act by two different mechanisms depending on the cell type: in Mø probably acts at a translational level, while in T-cells it interferes with assembly and release of the virus. The above described observations may explain the beneficial activity of IFN-α in AIDS patients.

102

Interferon Inducers and Other Biological Response Modifiers in Murine Retrovirus Models. M.A. Ussery[1], P.L. Black[2], J.T. Rankin, Jr.[2], and M.A. Chirigos[3]. [1]Food & Drug Administration, Rockville, MD, [2]Southern Research Institute-Frederick Research Center and [3]USAMRIID, Ft. Detrick, MD, U.S.A.

Our drug discovery group has employed two murine retrovirus models, the Rauscher leukemia virus (RLV) and the LP-BM-5 murine AIDS (MAIDS) virus, to screen biological response modifiers (BRMs) and antiviral agents for potential therapeutic activity against AIDS. RLV rapidly produced splenomegaly and viremia, both of which served as measures of disease progression. In the MAIDS model several parameters can be measured, including splenomegaly, hypergammaglobulinemia, lymphadenopathy, susceptibility to opportunistic infections, survival, and growth of virus in splenocytes and macrophages. Poly [I,C]-LC, Ampligen, CL-246,738 (acridine HCl), MVE-2, soluble glucan, and 7-thia-8-oxoguanosine are among many BRMs that we have tested in these models. Poly [I,C]-LC, MVE-2 and CL-246,738 consistently demonstrated antiviral activity. Glucan and 7-thia-8-oxoguanosine did not evidence any antiviral activity, while Ampligen did occasionally. CL-246,738 was more effective when given prophylactically, while Poly [I,C]-LC was more effective when given therapeutically rather than prophylactically (i.e. when treatment began after virus infection, rather than before). In contrast, MVE-2 had antiviral activity only when given prophylactically and consistently exacerbated disease when given therapeutically. With all these BRMs, a consistent pattern emerged, namely that antiviral activity has thus far always correlated with augmentation of natural killer (NK) cell activity in infected animals. For example, poly [I,C]-LC boosted NK activity much more in infected mice treated on a therapeutic as opposed to a prophylactic schedule. NK activity was boosted in infected mice pretreated with MVE-2, but slightly depressed in mice when treatment was initiated after infection. Those BRMs (e.g. soluble glucan) that did not augment NK activity in infected mice did not have demonstrable antiviral activity, regardless of whether they boosted NK activity in uninfected animals (as soluble glucan did). These results lead us to speculate about the importance of the augmentation of NK cell activity in the antiviral efficacy of BRMs in these murine models. It seems likely that NK cells are involved in resistance to retroviral infections.

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