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Two New (newborn) Mouse Models - Harvey Murine Sarcoma Virus (MSV-Har) and Rauscher Murine Leukaemia Virus (RLV), for Anti Retroviral Drug Testing

J.J. Harvey, M. Botcherby. Antigen Presentation Research Group, MRC Clinical Research Centre, Northwick Park, Harrow, U.K.

Murine oncornaviruses have proved of use in testing certain antiviral drugs directed against HIV. RLV has had considerable use as a murine model, using young adult mice. Newborn mice require considerably less drug (mg/kg dosage) - an advantage if quantities of test drug are limited. Balzarini (1) using MSV-Moloney in newborn mice, described the antiviral effect of zidovudine against rapid (8-9 days) tumour induction. We have established two models using newborn mice. MSV-Har, in addition to tumours (and unlike MSV-Mol) also causes a significant splenomegaly, useful as a measure of virus. We have also adapted RLV infection as a model system in newborn mice. Newborn (1-2g) mice were infected with MSV-Har (i.m.) or RLV (i.p.). Zidovudine was injected immediately (s.c.), then one injection per day for 2-4 days only; concentrations from 20-250mg/kg were tested. At 10-12 days post-infection parameters used to measure virus (and antiviral effectiveness) were splenomegaly, infectious virus in splenocytes and viral reverse transcriptase (RT) in sera. MSV-Har also caused tumours at the injection site. Zidovudine at doses as low as 40mg/kg for 3 days (i.e. 20 mice+drug = 3mg per experiment) prevented tumour formation, also reduced or eliminated splenomegaly, infectious virus and RT in sera. We have used these models to compare zidovudine with other antiviral drugs such as d4T and novel nucleotide derivatives: experiments were based on equimolar concentrations indicated by antiviral tests *in vitro* (S+L-assay).

1. Balzarini J. (1989). J. Biol. Chem. 264, 6127-33.

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Zidovudine (AZT)-Induced Down Regulation of Erythropoietin-Receptors (Epo-R) and Inhibition of Protein Kinase C (PKC) in the Primate Bone Marrow Cells (BMC). K.C. Agrawal, S.R. Gogu, C.A. Leissinger, C. Nosbisch and J.D. Unadkat. Depts. of Pharmacology and Medicine, Tulane Univ. School of Medicine, New Orleans, LA 70112 and Dept. of Pharmaceutics, School of Pharmacy, Univ. of Washington, Seattle, WA 98195, USA

Treatment of AZT-induced anemia with Epo has been ineffective in patients whose endogenous levels of Epo were >500 IU/L, suggesting a relative resistance to the action of Epo on the BMC. We have previously reported that AZT down regulated Epo-R in murine BMC. We have now investigated the effect of AZT on Epo-R expression and function in human and monkey BMC. The quantitation of Epo-R was achieved with ^{125}I-Epo binding assays in enriched erythroid progenitor cells. The levels of Epo-R mRNA were measured by slot blot analysis using a 39-mer oligonucleotide probe end-labelled with α-^{32}P-dCTP. Treatment of the BMC with AZT (1 to 10 μM) in vitro for 24 hr caused a concentration-dependent decrease in Epo-R expression. At 10 μM, AZT decreased the specific binding of ^{125}I-Epo by approximately 60% in both the human and monkey BMC. This decrease in Epo-R correlated with a decline (43%) in mRNA levels of the receptor in monkey BMC. Furthermore, treatment of human BMC with AZT also caused a concentration and time dependent decrease in PKC activity. AZT (1.0 μM) inhibited PKC activity by 40% within 3 hr. These results suggest that AZT down regulates Epo receptor expression and inhibits Epo-R mediated signal transduction at the level of PKC in erythroid progenitor cells.