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Role of NK Cells and Interferon in Immunomodulator/Biological Response Modifier (BRM)-Mediated Resistance Against HSV-2 and MCMV Infection in Immunosuppressed Mice. S.C. Kunder, K.M. Kelly, L. Wu and P.S. Morahan. Medical College of Pennsylvania, Philadelphia, PA 19129.

Effective BRMs against HSV-2 and MCMV infections include microbial materials (C. parvum, OK-432), polyanions (poly ICLC, MVE-2), recombinant interferons, and small molecular weight compounds (CL246,738). The best protection is observed with prophylactic or early therapeutic treatment. Because BRMs have pleiotropic immunomodulatory effects, it has been difficult to establish whether one cell type or mediator provides a unified antiviral mechanism. Treatment of CD-1 mice with monoclonal antibody NK1.1 abrogated BRM-induced NK cell cytotoxicity but did not significantly affect protection induced by prophylactic treatment with several BRMs against lethal HSV-2 or MCMV infections. Only rHu-IFN-α B/D partially lost its protective effect against MCMV infection when NK cells were depleted. Treatment with antisera to interferon α/β abrogated polyICLC-induced IFN and also negated the antiviral protection of poly ICLC and CL246,738 against lethal HSV-2 infection. In preliminary experiments, SCID mice were protected by MVE-2 against lethal MCMV infection, which strongly suggest the role of non-specific effector cells in antiviral resistance mediated by BRMs. These antiviral effects in immunosuppressed states emphasize the potential for BRM treatment in immunocompromised hosts, as well as elucidating the relative role of NK cells and interferons in BRM treatment.

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Efficacy of HPMPC and DHPG in the treatment of murine cytomegalovirus infection in Severe Combined Immune Deficiency (SCID) mice
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The *in vivo* efficacy of potential anti-CMV drugs is generally evaluated in young mice experimentally infected with murine cytomegalovirus (MCMV). Although virus can be isolated from different organs in these mice, they usually do not relapse from the MCMV disease after termination of therapy. A major problem encountered with the current DHPG [ganciclovir, 9-(1,3-dihydroxy-2-propoxymethyl)guanine] treatment of human cytomegalovirus (HCMV) infection in immunocompromised patients is the relapse of disease after cessation of therapy. We have now used mice with severe combined immune Deficiency (SCID) to establish an animal model that mimics CMV disease progression in the immunocompromised host more closely than the commonly used animal models. SCID mice inoculated intraperitoneally with MCMV develop a wasting syndrome at 3 to 4 days, and die at 6 to 9 days, after the infection. DHPG and (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) were compared for their efficacy against MCMV-induced disease and mortality in SCID mice. Under all treatment conditions (i.e. administration of the test compounds for 5 consecutive days starting on the day of infection (day 0); or for 5 consecutive days starting on day 4 after the infection; or 2 periods of 3 consecutive days starting on day 0 and 9 after infection; or as a single dose on day 3 before infection), HPMPC proved far superior to DHPG in delaying onset of the disease and increasing the life-span of the MCMV-infected mice.