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In vitro modulation of the activity of anti-HIV drugs in monocytes by GM-CSF and other cytokines.

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We evaluated the in vitro activity of granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), granulocyte-colony stimulating factor (G-CSF), and erythropoietin (Epo) on either HIV replication or the antiviral activity of several anti-HIV drugs in monocyte/macrophage system (M/M). Normal M/M exposed for 5 days to 100 U/ml GM-CSF, 1,000 U/ml M-CSF, 500 U/ml G-CSF, or 2 U/ml Epo were challenged with HIV-Ba-L in the presence of different concentrations of AZT, dideoxycytidine (ddC), dideoxyinosine (ddI) or 9-(2- phosphonyl methoxy-ethyl)-adenine (PMEA). 100 U/ml GM-CSF and 1,000 U/ml M-CSF potently enhanced HIV replication in M/M (about 10-100 fold) compared to untreated M/M, while G-CSF and Epo showed no significant effect. M-CSF substantially down-modulates the antiviral activity of all four drugs tested (up to 10 times for ddI and PMEA), GM-CSF enhanced the antiviral activity of AZT and reduced the efficacy of ddC, ddI and PMEA. G-CSF and Epo did not significantly modulate the antiviral activity of each drug tested in this M/M system. Thus some cytokines acting in vitro and in vivo may modulate the activity of anti-HIV drugs and should be considered in preclinical screening. Studies are currently undergoing investigation to evaluate the metabolism of these drugs in M/M activated with these cytokines.

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In Vivo Administration of Tumor Necrosis Factor-α:Association with Antiviral Activity in Human Peripheral Mononuclear Cells. R. Pollard, D. Matzke, M. Jennings, and M. Nokta. The University of Texas Medical Branch at Galveston, TX USA.

Tumor Necrosis Factor (TNF) has a spectrum of biological effects and has been shown to exert an antiviral effect in fibroblasts, in vitro. The in vivo administration of TNF (40-160 ug/m^2 I.V. over 2 hours) and its effect on vesicular stomatitis virus (VSV) replication in peripheral blood mononuclear cells (PBMCs) from patients with malignancy was investigated. Blood was obtained before, during, and after infusion. The PBMCs were separated and infected with VSV at a multiplicity of infection (MOI) of 0.005 PFU/cell and virus yields were determined 72 hours later. The TNF inhibited VSV yields by as much as 99% in a dose dependent manner with the inhibition initially observed during the first hour of infusion. Despite a rapid reduction in TNF serum levels, the higher doses still produced antiviral effects 4 hours after the infusion. Sera obtained at identical times had no interferon activity. Human interferon gamma (IFN-γ) (25 u/ml) added in vitro augmented the TNF-induced inhibitory activity both in magnitude and duration. Percentages of lymphocytes and monocytes in peripheral blood were reduced at 4 hours after TNF administration and the monocyte/lymphocyte ratio was diminished and temporally coincided with the loss of TNF-induced antiviral state. These data suggest that the in vivo administration of TNF has a direct inhibitory activity on VSV replication in human PBMs that was enhanceable by IFN-γ and possibly monocyte-mediated.