Intracellular glutathione as a possible direct blocker of HIV type 1 reverse transcription

In AIDS patients, chronic inflammation and elevated levels of cytokines seem to be associated with reduced levels of glutathione (GSH). GSH has been proposed to inhibit the activation of NF-kB, which results in the inhibition of HIV-1 replication. Here, we show the evidence that GSH and N-acetylcysteine, but not L-cysteine or dithiothreitol, could inhibit the reverse transcriptase (RT) process of HIV-1. Such inhibition was not observed with the RT of murine leukemia virus. Kameoka M, Okada Y, Tobiume M, Kimura T, Ikuta K. *AIDS Res Hum Retroviruses* 1996 Nov 20;12(17):1635-8.

Inhibition of murine AIDS by reduced glutathione

The imbalance of the redox state in cells and body fluids in HIV-1-infected patients may result in progression of the disease as well as in immunologic disfunctions. In this report, we have evaluated whether the direct administration of high doses of reduced glutathione (GSH) exerts any antiviral activity and/or improves immune functions in a murine immunodeficiency animal model. Intramuscular administration of 50 or 100 mg GSH/mouse for five consecutive days weekly to LP-BM5-infected mice did not show local or systemic signs of acute toxicity. During the first 3 weeks from infection, a period in which clinical signs of disease were not yet detectable, GSH significantly reduced the viral load in lymph nodes and spleen as evaluated by a PCR semiquantitative assay of the proviral DNA content. At 10 weeks a GSH concentration-dependent reduction of splenomegaly, lymphadenopathy and hypergammaglobulinemia was evident in all treated mice. Evaluation of proviral DNA content showed that GSH was effective in inhibiting LP-BM5 infectivity in lymph nodes, spleen, and bone marrow at 100 mg/day, while it was less effective when administered at 50 mg/day. At 10 weeks some animals receiving the highest GSH dose died, thus only the mice receiving 50 mg GSH were followed up to 15 weeks without signs of toxicity. In this case, almost not significant differences among infected untreated or treated animals were observed. Thus, GSH is effective in reducing the proviral DNA load in the first period of infection. These data and the failure of sulfhydryl supplementation to further counteract the progression of disease after 10 weeks of infection suggest that combinations of GSH and other antiviral agents may be useful for improving current antiviral therapies. Palamara AT, Garaci E, Rotilio G, Ciriolo MR, Casabianca A, Fraternale A, Rossi L, Schiavano GF, Chiarantini L, Magnani M. *AIDS Res Hum Retroviruses* 1996 Sep 20;12(14):1373-81.

Antiretroviral effect of combined zidovudine and reduced glutathione therapy in murine AIDS

A combination of antiretroviral drugs acting at different points in the virus replication cycle was evaluated in a murine retrovirus-induced immunodeficiency model of AIDS (MAIDS). Intramuscular administration of high doses of reduced glutathione (GSH, 100 mg/mouse/day) and AZT (0.25 mg/ml in drinking water) was found to reduce lymphoadenopathy (92%), splenomegaly (80%), and hypergammaglobulinemia (90%) significantly more than AZT alone. Combined treatment resulted in a reduction in proviral DNA content of 69, 66, and 60%, respectively, in lymph nodes, spleen, and bone marrow. Furthermore, the stimulation index of B cells was also significantly higher in animals receiving GSH and AZT whereas additional responses were not observed in the T cell stimulation index and blood lymphocyte phenotype analyses. In conclusion, the administration of high doses of GSH and AZT, a new combination of antiviral drugs, seems to provide additional advantages compared to single-agent therapy. Magnani M, Fraternale A, Casabianca A, Schiavano GF, Chiarantini L, Palamara AT, Ciriolo MR, Rotilio G, Garaci E. *AIDS Res Hum Retroviruses* 1997 Sep 1;13(13):1093-9.

Evidence for antiviral activity of glutathione: in vitro inhibition of herpes simplex virus type 1 replication

The role of glutathione (GSH) in the in vitro infection and replication of human herpes simplex virus type 1 (HSV-1) was investigated. Intracellular endogenous GSH levels dramatically decreased in the first 24 h after virus adsorption, starting immediately after virus challenge. The addition of exogenous GSH was not only able to restore its intracellular levels almost up to those found in uninfected cells, but also to inhibit > 99% the replication of HSV-1. This inhibition was concentration-dependent, not related to toxic effects on host cells and also maintained if the exogenous GSH was added as late as 24 h after virus challenge, i.e. when virus infection was fully established. Electron microscopic examination of HSV-1-infected
cells showed that GSH dramatically reduced the number of extracellular and intracytoplasmic virus particles, whereas some complete nucleocapsids were still detected within the nuclei of GSH-treated cells. Consistent with this observation, immunoblot analysis showed that the expression of HSV-1-glycoprotein B, crucial for the release and the infectivity of virus particles, was significantly decreased. Data suggest that exogenous GSH inhibits the replication of HSV-1 by interfering with very late stages of the virus life cycle, without affecting cellular metabolism. Palamara AT, Perno CF, Cirilo MR, Dini L, Balestra E, D'Agostini C, Di Francesco P, Favalli C, Rotilio G, Garaci E. *Antiviral Res* 1995 Jun;27(3):237-53.

**Growth inhibition and prostaglandin metabolism in the R3230AC mammary adenocarcinoma by reduced glutathione**

The effect of reduced glutathione (GSH) administered to tumor-bearing rats was studied on growth of the R3230AC mammary adenocarcinoma. A significant inhibition in both tumor weight and volume was observed in rats given 2 g/kg body weight/day of GSH. Prostaglandin content of processed tumors was measured (ng/g wet weight tissue) and in vitro prostaglandin synthesis by microsomal prostaglandin synthetase was studied (ng/mg protein/15 min). Tumor PGE2 content and in vitro synthesis were decreased in tumors from GSH-treated rats. However, PGE1, PGF2 alpha, 6-keto-PG-F1 alpha and TXB2 content of these tumors was increased, and with the exception of PGE1, the trends in tumor content and in vitro enzyme activity were similar. The effect of GSH treatment on PGE2 content of normal mammary tissue was similar to that observed in the mammary tumors. These studies suggest that a selective inhibition in tumor PGE2 by in vivo treatment of rats with GSH may be associated with GSH-induced tumor growth inhibition. Karmali RA. *Cancer Biochem Biophys* 1984 Jun;7(2):147-54.

**Protective effect of reduced glutathione against cis-dichlorodiammine platinum (II)-induced nephrotoxicity and lethal toxicity**

Pretreatment of Swiss mice and Sprague-Dawley rats with glutathione (GSH) reduced the acute lethal toxicity of cis-dichlorodiammine platinum (II) (cis-DDP) in a dose-dependent manner. The protection was accompanied by reduction of both body weight loss and by reduction of nephrotoxicity, as measured by a rise in serum blood urea nitrogen (BUN), creatinine levels and by histopathologic changes, which occurred 4 days following cis-DDP treatment. The antitumor effects of cis-DDP on experimental tumor models (P388 and Gross leukemia) were not significantly altered by GSH treatment. It is suggested that the partial protection by GSH from acute toxicity of the antitumor drug is directly related to protection of renal function. Zunino F, Tofanetti O, Besati A, Cavalletti E, Savi G. *Tumori* 1983 Apr 30;69(2):105-11.

**Relation between reduced glutathione content and Heinz body formation in sheep erythrocytes**

To clarify the oxidant defense functions of reduced glutathione (GSH) in erythrocytes, the effect of GSH deficiency on in vitro oxidant defense was studied, using GSH-deficient sheep erythrocytes (low-GSH cells). The formation of Heinz bodies in low-GSH cells was higher than that in high-GSH cells when the cells were incubated with an oxidant drug, acetylphenylhydrazine (APH). Artificial depletion of GSH by 1-chloro-2,4-dinitrobenzene in high-GSH cells resulted in increased Heinz body formation in these cells incubated with APH. Furthermore, high negative correlation was observed between Heinz body formation and GSH content in sheep erythrocytes exposed to APH. These results clearly indicate that erythrocyte GSH is indispensable for erythrocyte defense against oxidative damage induced by APH, and support the previous observations that sheep with low-GSH erythrocytes were more susceptible to oxidative agents than were sheep with high-GSH erythrocytes. Goto I, Agar NS, Maede Y. *Am J Vet Res* 1993 Apr;54(4):622-6.