ANTIOXIDANTS & REDOX SIGNALING
Volume 4, Number 3, 2002

Forum Review

Redox Imbalance and Its Control in HIV Infection

HAJIME NAKAMURA, HIROSHI MASUTANI, and JUNJI YODOI

ABSTRACT

Human immunodeficiency virus (HIV)-infected individuals are suffering from systemic oxidative stress. Reactive oxygen species act as second messengers for the activation of nuclear factor-κB (NF-κB), which augments the replication of HIV. Intracellular levels of glutathione (GSH), a major cytosolic antioxidant, in T cells decrease during the disease progression. Another redox-regulating molecule, thioredoxin (TRX), is also transiently down-regulated in the cells by acute HIV infection. In contrast, plasma levels of TRX are elevated in the late stage of HIV infection. Intracellular GSH and plasma TRX can be biomarkers to predict the prognosis of the disease. *N*-Acetylcysteine (NAC), a prodrug of cysteine that is necessary for GSH synthesis, has been used for HIV infection to prevent the activation of NF-κB and the replication of HIV. NAC shows some beneficial effects for HIV-infected individuals, although the intracellular GSH levels in lymphocytes are not significantly restored. The control of imbalanced redox status by antioxidants may be beneficial for the quality of life in HIV infection even in the era after the effective therapy with protease inhibitors has been applied. Redox control will be an important therapeutic strategy for oxidative stress-associated disorders including HIV infection. *Antioxid. Redox Signal.* 4, 455–464.

GLUTATHIONE DEFICIENCY IN HIV INFECTION

GLUTATHIONE (GSH), a cysteine-containing tripeptide (γ-glutamyl-cysteinyl-glycine), is a major cytosolic antioxidant that is present in the cells at millimolar concentrations. It was first reported by Dröge *et al.* that human immunodeficiency virus (HIV)-infected individuals have lower levels of cystine and methionine in plasma and lower levels of GSH in peripheral blood mononuclear cells (PBMCs) (21, 23). Buhl *et al.* also reported that total and reduced glutathione (GSH + GSSG and GSH) levels decrease in plasma and bronchoalveolar lavage fluids in HIV-infected individuals (10). Folks *et al.* have suggested that the inflammatory cytokines such as tumor necrosis factor-α play important roles in the progression of acquired immunodeficiency syndrome (AIDS) (27). Roederer *et al.* found that *N*-acetylcysteine (NAC), the acetylated cysteine that is converted into cysteine required for GSH synthesis, inhibits the cytokine-stimulated replication of HIV and activation of nuclear factor-κB (NF-κB) which controls the transcription of genes for HIV replication (68, 78). Furthermore, they revealed that GSH levels are different in subpopulations of PBMCs by fluorescence-activated cell sorter (FACS) analysis using monochlorobimane and that T cells are subdivided into high-GSH cells and low-GSH cells in healthy individuals. Thus, they found that high-GSH T cells are selectively lost in HIV-infected individuals (69). The intracellular GSH levels determined by FACS-measured glutathione-*S*-bimane fluorescence (GSB) in T cells decrease during the disease progression of AIDS (79). The suppressive effects of NAC on the activation of NF-κB and HIV replication were confirmed by other groups (35, 48, 65). Meanwhile, Schreck *et al.* reported that reactive oxygen species (ROS) serve as intracellular messengers for the activation of NF-κB and replication of HIV (75). These studies suggested that oxidative stress caused by elevated inflammatory cytokines and decreased GSH-dependent antioxidant functions in HIV infection promotes the activation of NF-κB and replication of HIV, resulting in the disease progression associated with the

Department of Biological Responses, Institute for Virus Research, Kyoto University, 53 Shogin-Kawaharacho, Sakyo, Kyoto 606-8507, Japan.

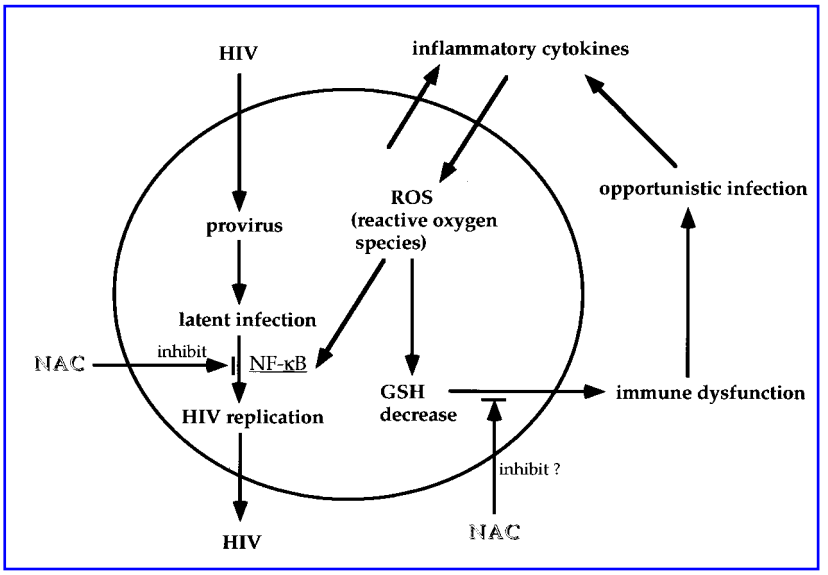

FIG. 1. Oxidative stress and GSH deficiency in HIV infection. Plasma inflammatory cytokine levels are elevated in HIV-infected individuals. ROS induced by inflammatory cytokines enhance the activation of NF-κB and HIV replication, which are inhibited by NAC. Intracellular GSH deficiency introduces the immune dysfunction and opportunistic infection, which lead to the elevation of inflammatory cytokines. Modified from Roederer *et al.,* 1993 (71).

$CD4^+$ T-cell loss, the immunodeficiency, and the opportunistic infection. Therefore, it was supposed that GSH replenishment might have a potential to shut down the malignant cycle in the disease progression of AIDS (Fig. 1). Thus, GSH replenishment with NAC provided a rationale for the treatment of AIDS (19, 22, 70, 71, 79). In addition to NAC, GSH precursors such as oxothiazolidine carboxylate, which is converted into cysteine by 5-oxoprolinase, were proposed to inhibit the replication of HIV (6, 66, 77). Recently, *S*-adenosylmethionine has been also reported to increase GSH and to be a potential for GSH deficiency in HIV infection (11). The reason why ROS levels are elevated and intracellular GSH levels decreased in HIV-infected cells is still not fully understood. Roederer *et al.* suggested that inflammatory cytokines such as tumor necrosis factor-α may enhance the intracellular production of ROS, which leads to the decrease of intracellular antioxidant GSH levels (70). Alternatively, the down-modulation of manganese superoxide dismutase by HIV tat may partly explain the mechanism (26). More recently, Breitkreutz *et al.* reported that HIV-infected patients experience a massive cysteine catabolism in the skeletal muscle tissues that drains largely the GSH pool (9). According to the data from the clinical trial by Herzenberg *et al.,* GSH deficiency is associated with impaired survival in HIV disease (32). Low intracellular GSH (FACS-measured GSB) levels may be a parameter to predict poor survival in HIV-infected subjects. Especially, GSH deficiency in $CD4^+$ T cells is associated with marked decreased survival.

THIOREDOXIN IN HIV INFECTION

Redox regulation by thioredoxin (TRX) and its related molecules

TRX is a 12-kDa multifunctional protein with a redox-active disulfide/dithiol within the conserved active site sequence: -Cys-Gly-Pro-Cys- (36). Human TRX was cloned as adult T cell leukemia (ATL)-derived factor, which was originally reported as an inducer of interleukin-2 receptor/α chain (81, 85, 89), or 3B6-interleukin-1, which was an autocrine growth factor for Epstein–Barr virus-transformed cells (86, 88). Intracellular concentration of TRX is at about the micromolar level, whereas GSH is existing at the millimolar level. Therefore, GSH plays a major role as an intracellular antioxidant in a physiological condition and TRX is induced by a variety of oxidative stress including GSH deficiency. However, recent studies have shown that TRX is more effective than GSH in reducing some specific substrates in the redox regulation of signal transductions. Several biological functions of TRX are schemed in Fig. 2. The promoter sequence of the human TRX gene contains oxidative stress-responsive element, cyclic AMP-responsive element, xenobiotics responsive element, and antioxidant responsive element (42, 56). Reduced TRX catalyzes the reduction of the protein disulfide, and oxidized TRX is reduced by NADPH and TRX reductase. TRX-dependent peroxidase, peroxiredoxin (Prx), acts as an endogenous antioxidant, as well as GSH peroxidase (13). Especially, TRX plays a crucial role as an extracellular antioxidant possibly together with the secreted isoform of Prx, Prx IV, because extracellular GSH concentration is limited (7, 60). The mechanism of the cytoprotective effect of extracellular TRX is still to be clarified. There is accumulating evidence that TRX is involved in many cellular responses, including redox regulation of signal transduction (53). TRX negatively regulates the activation of p38 mitogen-activated protein kinase (MAPK) (31) and apoptosis signal-regulating kinase-1 (ASK-1) (73). TRX regulates redox-sensitive transcription factors such as AP-1 and NF-κB in cooperation with Redox factor-1 in the nucleus more effectively than the GSH-dependent system (33, 46, 61). Overexpression of TRX in the cytoplasm suppresses the activation of NF-κB, whereas overexpressed TRX in the nucleus promotes the DNA binding of NF-κB (34). It is reported that the TRX system composed of TRX reductase, TRX, and Prx is deeply involved in the regulation of activation of NF-κB, which plays a key role in the replication of HIV (39). Therefore, it is supposed that the dysregulation of the TRX system may be associated with the replication of HIV and the disease progress in HIV infection.

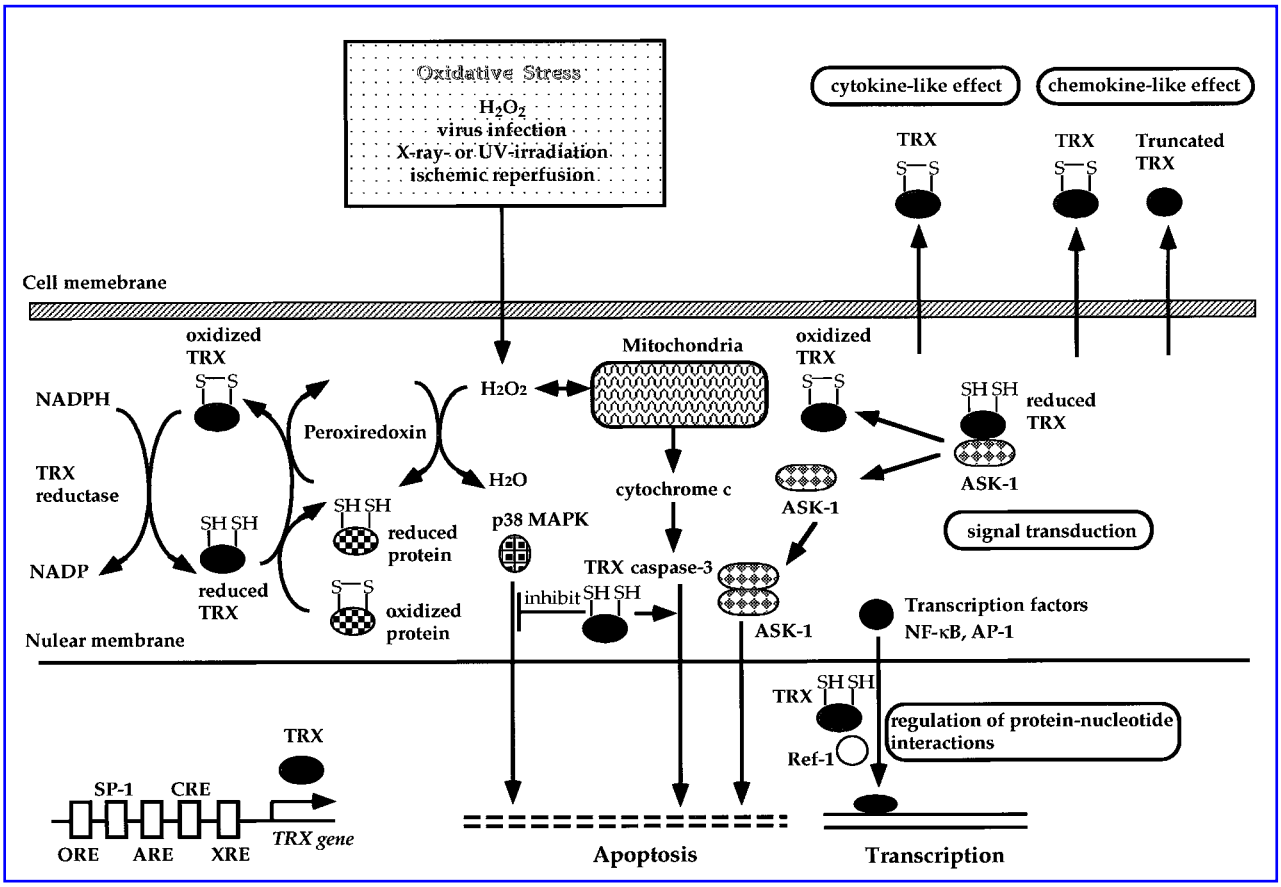

FIG. 2. Biological effects of TRX. TRX is induced by a variety of oxidative stresses via oxidative stress responsive element (ORE), antioxidant responsive element (ARE), cyclic AMP responsive element (CRE), xenobiotics responsive element (XRE), and SP-1 in the promoter sequence of TRX gene. Oxidized TRX is reduced by NADPH and TRX reductase. TRX and Prx act as radical scavengers. Transcription factors such as NF-κB and AP-1 are regulated by TRX and Ref-1. TRX also regulates the signal transduction in apoptosis by the suppression of p38 MAPK or regulation of caspase-3. Reduced TRX is a negative regulator of ASK-1, and ASK-1 is activated when TRX is oxidized and dissociated from ASK-1. TRX and truncated TRX are secreted from the cells and show cytokine-like and chemokine-like effects. The dithiol–disulfide exchange may be necessary for the signal transduction from extracellular TRX. The target molecules on the cell surface should be clarified.

TRX imbalance in HIV infection

Since the discovery of human TRX in the supernatant of human T-cell leukemia virus type-I (HTLV-I)-transformed ATL cells, we have found that TRX is overexpressed in HTLV-I-transformed cells. This prompted us to investigate the expression of TRX in another retroviral HIV infection. TRX high-expressing cells were significantly lost in the lymph nodes from AIDS patients (45). Acute infection of HIV on HTLV-I positive cells significantly decreased the expression of TRX inversely correlated with p24 antigen levels. Further study revealed that acute infection of HIV on monocytic cells induces a transient down-regulation of TRX and Bcl-2 and cellular apoptosis (2). NAC prevents the down-regulation of TRX and Bcl-2, suggesting that it is caused by oxidative stress induced by acute infection of HIV. The transient down-regulation of TRX and Bcl-2 was recovered from day 9 and day 11, respectively, after HIV infection toward a persistent infection. These results suggest that increased HIV replication is associated with oxidative stress and the transient down-regulations of TRX and Bcl-2 in monocytes. Moreover, hydrogen peroxide production is correlated with the viral load and the enhanced hydrogen peroxide production is associated with the decreased levels of TRX and Bcl-2 in monocytes from HIV-infected individuals whose CD4 cell counts are >200/mm^3. In contrast, in patients with AIDS, Bcl-2 levels return to normal and TRX levels are higher than in healthy controls (2). Restoration of these antioxidant and antiapoptotic molecules may explain the reason why monocyte numbers remain relatively stable throughout the disease (Fig. 3).

Plasma TRX levels as a marker for oxidative stress

Plasma levels of TRX were significantly elevated in HIV-infected individuals compared with uninfected healthy volunteers (26.1 ng/ml, n = 136 versus 12.3 ng/ml, n = 47) (52). Roughly 25% (34/136) of HIV-infected individuals had plasma TRX levels more than the highest level in uninfected individuals (37 ng/ml), which means more than threefold higher levels of uninfected controls. Plasma levels of TRX

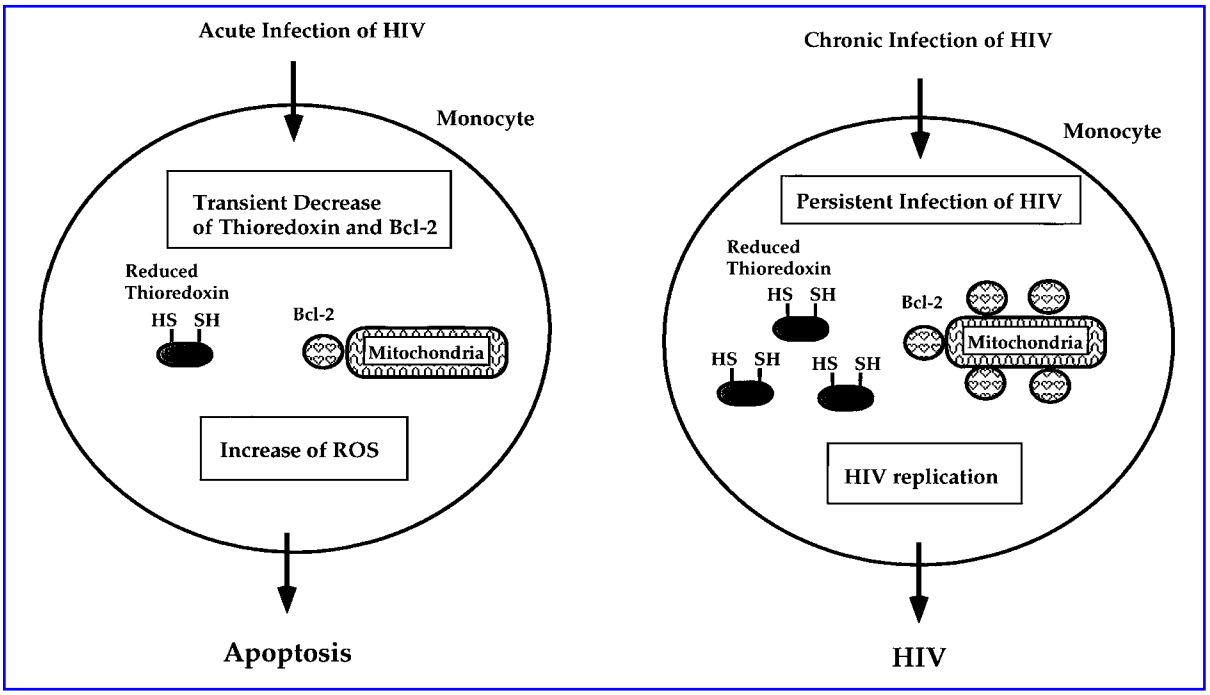

FIG. 3. TRX and Bcl-2 in monocytes in acute or persistent infection of HIV. Acute infection of HIV introduces the transient down-regulation of TRX and Bcl-2 associated with the increase of intracellular ROS, which results in the apoptosis of the cells. In persistent infection of HIV in monocytes, Bcl-2 levels return to normal, and TRX levels are higher than in healthy controls. Restoration of TRX and Bcl-2 may explain why monocytes remain stable during persistent infection of HIV.

were inversely correlated with intracellular GSH (FACS-measured GSB) levels in T cells, suggesting that oxidative stress in HIV infection leads to decreases of intracellular GSH levels and increases of plasma TRX levels. Roughly one third of HIV-infected individuals (57/173) had plasma TRX levels above 30 ng/ml, whereas <5% (2/46) of uninfected individuals had above this level. Among HIV-infected individuals whose CD4 counts were <200 /mm^3, Kaplan–Meier survival analysis showed that subjects with elevated TRX levels (>30 ng/ml) died more shortly than subjects with normal TRX levels (<30 ng/ml) (54). Taken together with the previous report showing that low intracellular GSH levels are also associated with impaired survival in HIV disease (32), these results suggest that elevation of plasma TRX and GSH deficiency in lymphocytes reflect massive oxidative stress and poor prognosis in HIV infection. Most of TRX in plasma is shown to be in the oxidized form (54). Our recent study shows that circulating TRX inhibits the neutrophil recruitment into the in-

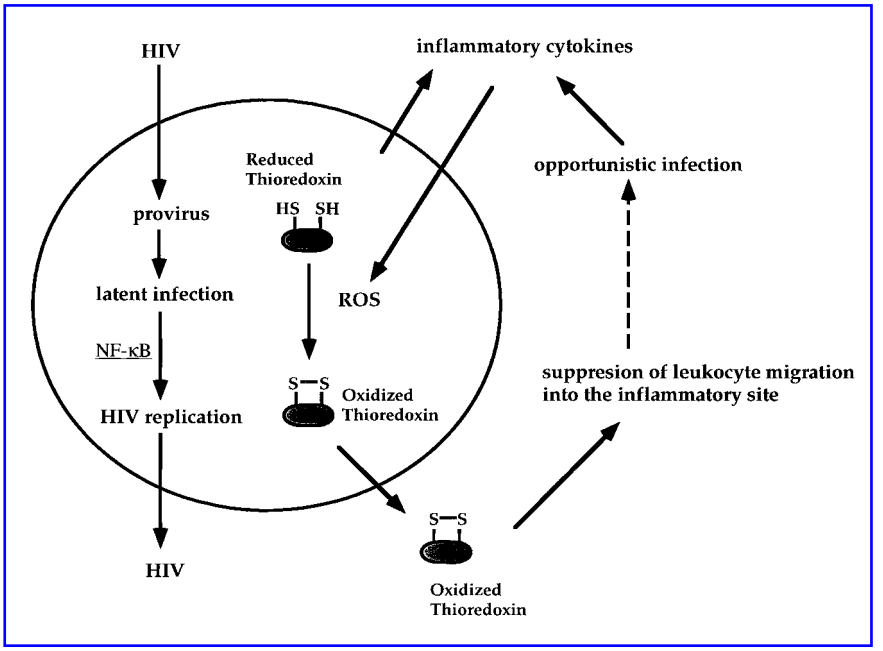

FIG. 4. Elevated plasma TRX levels associated with poor prognosis of HIV infection. TRX may be oxidized by the oxidative stress in HIV-infected cells and secreted into plasma. Circulating TRX suppresses the leukocyte migration into the inflammatory site, which may augment the incidence of opportunistic infection.

flammatory site in the mouse air pouch model (57). Therefore, it is possible that elevation of plasma TRX levels inhibits the neutrophil function as a primary response against infection and worsens the opportunistic infection in such immunocompromised hosts as AIDS, which may explain the reason why elevation of plasma TRX is associated with poor prognosis in AIDS (Fig. 4). However, plasma levels of TRX are also elevated in several oxidative stress-associated disorders other than AIDS. For examples, plasma/serum TRX levels are elevated in subjects with ischemia–reperfusion injury (54), rheumatoid arthritis (47, 90), hepatitis C virus infection (80), severe burns (1), and cancers (49, 55). It is supposed that TRX secretion into plasma may be a kind of host defense response against oxidative stress. Although the host immune function is not impaired, the inhibition of neutrophil migration into the inflammatory site by circulating TRX may suppress the inflammation. Actually, plasma TRX levels are not associated with the prognosis in these diseases other than AIDS. Even in HIV infection, plasma levels of TRX are not associated with the prognosis in the individuals whose CD4 cell counts are >200/mm^3. Therefore, elevated plasma levels of TRX may be associated with the impaired host defense only in the immunocompromised host such as those whose CD4 cell counts are <200/mm^3. In conclusion, measuring plasma TRX levels is one of the useful tools to see how much the host is suffering from oxidative stress. Plasma levels of the truncated form of TRX, which was originally reported to be an eosinophil cytotoxicity enhancing factor (76), remain to be analyzed in HIV infection, because the truncated form of TRX has been reported to be produced in HIV-infected macrophages (58), to be secreted by inflammatory cytokines (72), and to be present in human plasma (64).

REDOX CONTROL THERAPY FOR HIV INFECTION

NAC administration in HIV infection

NAC is a prodrug of cysteine capable of GSH synthesis, promoting detoxification, and acting directly as free radical scavengers. NAC has been clinically used to reverse GSH deficiency induced by acetaminophen or cyclophosphamide without any significant side effect. Therefore, NAC was proposed to be used for replenishment of GSH in HIV infection (19, 22, 70, 71, 79). However, the results of clinical trials to show that NAC could restore the intracellular GSH levels were controversial. De Quay *et al.* reported that oral administration of NAC restored the plasma cysteine levels and intracellular GSH levels 2 h after intake (17). Akerlund *et al.* reported that NAC restored the plasma cysteine levels in HIV-infected individuals with CD4 cell counts above 200/mm^3, but failed to restore them in those whose CD4 cell counts <200/mm^3 (3, 4). Witschi *et al.* reported that NAC failed to restore the GSH levels in lymphocytes and plasma of HIV-infected individuals (87). However, Kinscherf *et al.* reported that oral administration of NAC suppressed the decline of CD4$^+$ T cells in HIV-infected individuals (43). Breitkreutz *et al.* reported that NAC treatment restored immunological parameters including natural killer cell numbers in their randomized trials for HIV-infected individuals with and without antiretroviral therapy (8). Moreover, Herzenberg *et al.* reported that oral administration of NAC (6.9 g × 8 weeks) prolonged the survival of HIV-infected individuals in a randomized double-blinded, placebo-controlled study (18, 32). They also showed that oral administration of NAC restored the whole-blood GSH levels and GSB in T-cell subsets. There were no significant side effects in the rather high-dose (6.9 g/day) oral administration of NAC.

Although it was not clear that NAC could restore the intracellular GSH levels in lymphocytes in AIDS patients, NAC may be beneficial for AIDS therapy. There is accumulating evidence to support the beneficial effect of NAC. Recent studies have shown that NAC has several biological effects in addition to the replenishment of GSH. Nerve growth factor-dependent differentiation of PC12 cells is blocked by NAC but that is not inhibited by buthionine-[*S,R*]-sulfoximine treatment, suggesting that the effect of NAC is not mediated by the replenishment of intracellular GSH (40). The suppressive effects on NF-κB activation by NAC are dependent not only on its radical scavenging function, but also on other direct mechanisms. NAC inhibits the activation of NF-κB directly by suppression of I-κB kinases (59). Moreover, NAC can enhance the antibody-dependent cytotoxicity, interleukin-2 secretion, and production of anti-HIV chemokines (12, 25, 67). NAC restores lymphocyte mitogenicity and plasma albumin concentration in HIV-infected individuals (8). We also have data showing that NAC decreases the expression of CD21 on B- and T-cell surface independently on the intracellular GSH levels (Nishinaka *et al.,* submitted). As CD21 is also an enhancing factor for HIV infection (50), the down-regulation of CD21 by NAC may offer additional benefit for AIDS therapy. Interestingly, NAC suppresses TRX secretion from HTLV-I-transformed cells and shows the tendency to decrease plasma TRX levels in HIV-infected individuals (57). Therefore, NAC therapy will be beneficial for HIV infection, although the real mechanism is not fully understood. In addition to AIDS therapy, NAC will be valuable for the clinical application to several oxidative stress-associated disorders, including other infectious diseases, diabetes, rheumatoid arthritis, liver cirrhosis, parkinsonism, cachexia, and so on.

Other antioxidants for AIDS therapy

Besides NAC, several antioxidants have been tried for AIDS therapy. Selenium, vitamin C, vitamin E, lipoic acid, and β-carotene are representative of antioxidants used for HIV-infected individuals. The general concept is that replenishment of antioxidant functions are beneficial for HIV-infected subjects, because they are suffering from systemic oxidative stress caused by elevated inflammatory cytokines and decreased antioxidant functions, including GSH deficiency. Olmsted *et al.* reported that selenium levels in blood are decreased in HIV-infected subjects (62). Selenium supplement increases glutathione peroxidase (GPx) activity (74) and inhibits the activation of NF-κB (41) and replication of HIV (37). Recent studies have shown that not only GPx, but also TRX reductase, contains selenocysteine (83), suggesting that selenium levels are quite important for the maintenance of

systemic antioxidant functions. Ascorbic acid (vitamin C) was reported to suppress the replication of HIV by reduction of reverse transcriptase activity (30). Israel *et al.* reported that butylated hydroxyanisole or α-tocopherol (vitamin E) suppresses the activation of NF-κB independently of the increase of GSH (38). Then vitamin E and lipoic acid were proposed for AIDS therapy (63). Allard *et al.* reported that supplements of vitamin E and vitamin C reduced oxidative stress in HIV infection and produced a trend toward a reduction in viral load of HIV in a randomized placebo-controlled, double-blind study (5). In the case of β-carotene, several reports have shown that β-carotene supplement has no significant efficiency in HIV-infected individuals (14–16).

Redox control by TRX for AIDS therapy

Previous reports have shown that administration of TRX in at the micromolar level rather attenuates the cytotoxicity caused by oxidative stress in an *in vitro* study (51) and the ischemic–reperfusion injury in an *in vivo* model (28). TRX-transgenic mice where human TRX is overexpressed under the control of β-actin promoter are also more resistant to a variety of oxidative stresses, including focal cerebral ischemia (82), and survive longer than wild-type mice (Mitsui *et al.,* submitted). Therefore, TRX administration may be beneficial as replenishment of antioxidant function in oxidative stress-associated disorders. We have collected evidence that TRX administration prevents leukocyte extravasation into the inflammatory site (57) and bleomycin- and cytokine-induced interstitial pneumonia in mice (Hoshino *et al.,* submitted). A previous *in vitro* study also showed that full-length TRX suppresses the replication of HIV, whereas the truncated form of TRX, which has no reducing activity, promotes the replication of HIV (58). Further study will be necessary to clarify that TRX administration may be beneficial for prevention of disease progression in the early stage of HIV infection.

CONCLUSION

Oxidative stress plays a crucial role in the disease progression in HIV-infected individuals. In addition to the well known CD4 cell counts, intracellular GSH levels in lymphocytes and plasma levels of TRX are quite good prognostic markers for HIV infection. Recently, highly active antiretroviral therapy (HAART), which is a combination of three antiviral drugs including at least one protease inhibitor, has been recognized to be quite effective in suppressing the disease progression of HIV infection (44). In fact, serum levels of antioxidants in HIV-infected individuals treated with antiretroviral therapy including protease inhibitors are comparable to those in uninfected individuals (84). However, as HAART is quite expensive and now HIV infection is a more serious problem in developing countries, low-cost treatment would be important for HIV infection from the world-wide point of view. HIV-infected individuals have massive loss of sulfur, which is not ameliorated by HAART (9). Therefore, NAC is beneficial for the quality of life in patients with such low sulfur levels and even in patients under the condition of cancer cachexia (20, 29). Restoration of antioxidant functions by NAC or other relatively nonexpensive supplements may still be beneficial at least for the quality of life of HIV-infected individuals. In conclusion, redox control will be an important strategy for oxidative stress-associated disorders, including HIV infection.

ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by a Grant-in-Aid of Research for the Future Program from the Japan Society for Promotion of Science.

ABBREVIATIONS

AIDS, acquired immunodeficiency syndrome; ASK-1, apoptosis signal-regulating kinase-1; ATL, adult T-cell leukemia; FACS, fluorescence-activated cell sorter; GPx, glutathione peroxidase; GSB, glutathione-*S*-bimane fluorescence; GSH, glutathione; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HTLV-I, human T-cell leukemia virus type-I; MAPK, mitogen-activated protein kinase; NAC, *N*-acetylcysteine; NF-κB, nuclear factor-κB; PBMCs, peripheral blood mononuclear cells; Prx, peroxiredoxin; ROS, reactive oxygen species; TRX, thioredoxin.

REFERENCES

1. Abdiu A, Nakamura H, Sahaf B, Yodoi J, Holmgren A, and Rosén A. Thioredoxin blood level increases after severe burn injury. *Antioxid Redox Signal* 2: 707–716, 2000.
2. Aillet F, Masutani H, Elbim C, Raoul H, Chene L, Nugeyre MT, Paya C, Barre-Sinoussi F, Gougerot-Pocidalo MA, and Israel N. Human immunodeficiency virus induces a dual regulation of Bcl-2, resulting in persistent infection of CD4(+) T- or monocytic cell lines. *J Virol* 72: 9698–9705, 1998.
3. Akerlund B, Jarstrand C, Lindeke B, Sonnerborg A, Akerblad AC, and Rasool O. Effect of *N*-acetylcysteine (NAC) treatment on HIV-1 infection: a double-blind placebo-controlled trial. *Eur J Clin Pharmacol* 50: 457–461., 1996.
4. Akerlund B, Tynell E, Bratt G, Bielenstein M, and Lidman C. *N*-Acetylcysteine treatment and the risk of toxic reactions to trimethoprim-sulphamethoxazole in primary *Pneumocystis carinii* prophylaxis in HIV-infected patients. *J Infect* 35: 143–147, 1997.
5. Allard JP, Aghdassi E, Chau J, Tam C, Kovacs CM, Salit IE, and Walmsley SL. Effects of vitamin E and C supplementation on oxidative stress and viral load in HIV-infected subjects. *AIDS* 12: 1653–1659, 1998.
6. Barditch-Crovo P, Noe D, Skowron G, Lederman M, Kalayjian RC, Borum P, Buier R, Rowe WB, Goldberg D,

and Lietman P. A phase I/II evaluation of oral L-2-oxothiazolidine-4-carboxylic acid in asymptomatic patients infected with human immunodeficiency virus. *J Clin Pharmacol* 38: 357–363, 1998.
7. Björnstedt M, Xue J, Huang W, Akesson B, and Holmgren A. The thioredoxin and glutaredoxin systems are efficient electron donors to human plasma glutathione peroxidase. *J Biol Chem* 269: 29382–29384, 1994.
8. Breitkreutz R, Pittack N, Nebe CT, Schuster D, Brust J, Beichert M, Hack V, Daniel V, Edler L, and Dröge W. Improvement of immune functions in HIV infection by sulfur supplementation: two randomized trials. *J Mol Med* 78: 55–62, 2000.
9. Breitkreutz R, Holm S, Pittack N, Beichert M, Babylon A, Yodoi J, and Dröge W. Massive loss of sulfur in HIV infection. *AIDS Res Hum Retroviruses* 16: 203–209, 2000.
10. Buhl R, Jaffe HA, Holroyd KJ, Wells FB, Mastrangeli A, Saltini C, Cantin AM, and Crystal RG. Systemic glutathione deficiency in symptom-free HIV-seropositive individuals. *Lancet* 2: 1294–1298, 1989.
11. Castagna A, Le Grazie C, Accordini A, Giulidori P, Cavalli G, Bottiglieri T, and Lazzarin A. Cerebrospinal fluid *S*-adenosylmethionine (SAMe) and glutathione concentrations in HIV infection: effect of parenteral treatment with SAMe. *Neurology* 45: 1678–1683, 1995.
12. Cavallini L and Alexandre A. Oral *N*-acetyl-cysteome increases the production of anti HIV chemokines in peripheral blood mononuclear cells. *Life Sci* 67: 147–154, 2000.
13. Chae HZ, Chung SJ, and Rhee SG. Thioredoxin-dependent peroxide reductase from yeast. *J Biol Chem* 269: 27670–27678, 1994.
14. Coodley GO, Nelson HD, Loveless MO, and Folk C. β-Carotene in HIV infection. *Ann N Y Acad Sci* 691: 277–278, 1993.
15. Coodley GO, Coodley MK, Lusk R, Green TR, Bakke AC, Wilson D, Wachenheim D, Sexton G, and Salveson C. β-Carotene in HIV infection: an extended evaluation. *AIDS* 10: 967–973, 1996.
16. Coutsoudis A, Pillay K, Spooner E, Kuhn L, and Coovadia HM. Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. South African Vitamin A Study Group. *AIDS* 13: 1517–1524, 1999.
17. De Quay B, Malinverni R, and Lauterburg BH. Glutathione depletion in HIV-infected patients: role of cysteine deficiency and effect of oral *N*-acetylcysteine. *AIDS* 6: 815–819, 1992.
18. De Rosa SC, Zaretsky MD, Dubs JG, Roederer M, Anderson MT, Green A, Mitra D, Watanabe N, Nakamura H, Tjioe I, Deresinski SC, Moore WA, Ela SW, Parks D and Herzenberg LA. *N*-Acetylcysteine replenishes glutathione in HIV infection. *Eur J Clin Invest* 30: 915–929, 2000.
19. Dröge W. Cysteine and glutathione deficiency in AIDS patients: a rationale for the treatment with *N*-acetyl-cysteine. *Pharmacology* 46: 61–65, 1993.
20. Dröge W and Breitkreutz R. *N*-Acetyl-cysteine in the therapy of HIV-positive patients. *Curr Opin Clin Nutr Metab Care* 2: 493–498, 1999.
21. Dröge W, Eck HP, Naher H, Pekar U, and Daniel V. Abnormal amino-acid concentrations in the blood of patients with acquired immunodeficiency syndrome (AIDS) may contribute to the immunological defect. *Biol Chem Hoppe Seyler* 369: 143–148, 1988.
22. Dröge W, Eck HP, and Mihm S. HIV-induced cysteine deficiency and T-cell dysfunction—a rationale for treatment with *N*-acetylcysteine. *Immunol Today* 13: 211–214, 1992.
23. Eck HP, Gmunder H, Hartmann M, Petzoldt D, Daniel V, and Dröge W. Low concentrations of acid-soluble thiol (cysteine) in the blood plasma of HIV-1-infected patients. *Biol Chem Hoppe Seyler* 370: 101–108, 1989.
24. Elbim C, Pillet S, Prevost MH, Preira A, Girard PM, Rogine N, Masutani H, Hakim J, Israel N, and Gougerot-Pocidalo MA. Redox and activation status of monocytes from human immunodeficiency virus-infected patients: relationship with viral load. *J Virol* 73: 4561–4566, 1999.
25. Eylar EH, Baez I, Vazquez A, and Yamamura Y. *N*-Acetylcysteine (NAC) enhances interleukin-2 but suppresses interleukin-4 secretion from normal and HIV+ CD4+ T-cells. *Cell Mol Biol (Noisy-le-grand)* 41 (Suppl 1): S35–40, 1995.
26. Flores SC, Marecki JC, Harper KP, Bose SK, Nelson SK, and McCord JM. Tat protein of human immunodeficiency virus type 1 represses expression of manganese superoxide dismutase in HeLa cells. *Proc Natl Acad Sci U S A* 90: 7632–7636, 1993.
27. Folks TM, Clouse KA, Justement J, Rabson A, Duh E, Kehrl JH, and Fauci AS. Tumor necrosis factor alpha induces expression of human immunodeficiency virus in a chronically infected T-cell clone. *Proc Natl Acad Sci U S A* 86: 2365–2368, 1989.
28. Fukuse T, Hirata T, Yokomise H, Hasegawa S, Inui K, Mitsui A, Hirakawa T, Hitomi S, Yodoi J, and Wada H. Attenuation of ischaemia reperfusion injury by human thioredoxin. *Thorax* 50: 387–391, 1995.
29. Hack V, Breitkreutz R, Kinscherf R, Rohrer H, Bartsch P, Taut F, Benner A, and Dröge W. The redox state as a correlate of senescence and wasting and as a target for therapeutic intervention. *Blood* 92: 59–67, 1998.
30. Harakeh S, Jariwalla RJ, and Pauling L. Suppression of human immunodeficiency virus replication by ascorbate in chronically and acutely infected cells. *Proc Natl Acad Sci U S A* 87: 7245–7249, 1990.
31. Hashimoto S, Matsumoto K, Gon Y, Furuichi S, Maruoka S, Takeshita I, Hirota K, Yodoi J, and Horie T. Thioredoxin negatively regulates p38 MAP kinase activation and IL-6 production by tumor necrosis factor-alpha. *Biochem Biophys Res Commun* 258: 443–447, 1999.
32. Herzenberg LA, De Rosa SC, Dubs JG, Roederer M, Anderson MT, Ela SW, and Deresinski SC. Glutathione deficiency is associated with impaired survival in HIV disease. *Proc Natl Acad Sci U S A* 94: 1967–1972, 1997.
33. Hirota K, Matsui M, Iwata S, Nishiyama A, Mori K, and Yodoi J. AP-1 transcriptional activity is regulated by a direct association between thioredoxin and Ref-1. *Proc Natl Acad Sci U S A* 94: 3633–3638, 1997.
34. Hirota K, Murata M, Sachi Y, Nakamura H, Takeuchi J, Mori K, and Yodoi J. Distinct roles of thioredoxin in the

cytoplasm and in the nucleus. A two-step mechanism of redox regulation of transcription factor NF-kappaB. *J Biol Chem* 274: 27891–27897, 1999.

35. Ho WZ and Douglas SD. Glutathione and *N*-acetylcysteine suppression of human immunodeficiency virus replication in human monocyte/macrophages in vitro. *AIDS Res Hum Retroviruses* 8: 1249–1253, 1992.
36. Holmgren A. Thioredoxin. *Annu Rev Biochem* 54: 237–271, 1985.
37. Hori K, Hatfield D, Maldarelli F, Lee BJ, and Clouse KA. Selenium supplementation suppresses tumor necrosis factor alpha-induced human immunodeficiency virus type 1 replication in vitro. *AIDS Res Hum Retroviruses* 13: 1325–1332, 1997.
38. Israel N, Gougerot-Pocidalo MA, Aillet F, and Virelizier JL. Redox status of cells influences constitutive or induced NF-kappa B translocation and HIV long terminal repeat activity in human T and monocytic cell lines. *J Immunol* 149: 3386–3393, 1992.
39. Jin DY, Chae HZ, Rhee SG, and Jeang KT. Regulatory role for a novel human thioredoxin peroxidase in NF-kappaB activation. *J Biol Chem* 272: 30952–30961, 1997.
40. Kamata H, Tanaka C, Yagisawa H, Matsuda S, Gotoh Y, Nishida E, and Hirata H. Suppression of nerve growth factor-induced neuronal differentiation of PC12 cells. *N*-Acetylcysteine uncouples the signal transduction from ras to the mitogen-activated protein kinase cascade. *J Biol Chem* 271: 33018–33025, 1996.
41. Kim IY and Stadtman TC. Inhibition of NF-kappaB DNA binding and nitric oxide induction in human T cells and lung adenocarcinoma cells by selenite treatment. *Proc Natl Acad Sci U S A* 94: 12904–12907, 1997.
42. Kim YC, Masutani H, Yamaguchi Y, Itoh K, Yamamoto M, and Yodoi J. Hemin-induced activation of the thioredoxin gene by Nrf2: a differential regulation of the antioxidant responsive element (ARE) by switch of its binding factors. *J Biol Chem* 276: 18399–18406, 2001.
43. Kinscherf R, Fischbach T, Mihm S, Roth S, Hohenhaus-Sievert E, Weiss C, Edler L, Bartsch P, and Droge W. Effect of glutathione depletion and oral *N*-acetyl-cysteine treatment on CD4+ and CD8+ cells. *FASEB J* 8: 448–451, 1994.
44. Ledergerber B, Egger M, Opravil M, Telenti A, Hirschel B, Battegay M, Vernazza P, Sudre P, Flepp M, Furrer H, Francioli P, and Weber R. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. *Lancet* 353: 863–868, 1999.
45. Masutani H, Naito M, Takahashi K, Hattori T, Koito A, Takatsuki K, Go T, Nakamura H, Fujii S, Yoshida Y, Okuma M, and Yodoi J. Dysregulation of adult T-cell leukemia-derived factor (ADF)/thioredoxin in HIV infection: loss of ADF high-producer cells in lymphoid tissues of AIDS patients. *AIDS Res Hum Retroviruses* 8: 1707–1715, 1992.
46. Matthews JR, Wakasugi N, Virelizier JL, Yodoi J, and Hay RT. Thioredoxin regulates the DNA binding activity of NF-kappa B by reduction of a disulphide bond involving cysteine 62. *Nucleic Acids Res* 20: 3821–3830, 1992.
47. Maurice MM, Nakamura H, van der Voort EA, van Vliet AI, Staal FJ, Tak PP, Breedveld FC, and Verweij CL. Evidence for the role of an altered redox state in hyporesponsiveness of synovial T cells in rheumatoid arthritis. *J Immunol* 158: 1458–1465, 1997.
48. Mihm S, Ennen J, Pessara U, Kurth R, and Dröge W. Inhibition of HIV-1 replication and NF-kappa B activity by cysteine and cysteine derivatives. *AIDS* 5: 497–503, 1991.
49. Miyazaki K, Noda N, Okada S, Hagiwara Y, Miyata M, Sakurabayashi I, Yamaguchi N, Sugimura T, Terada M, and Wakasugi H. Elevated serum level of thioredoxin in patients with hepatocellular carcinoma. *Biotherapy* 11: 277–288, 1998.
50. Montefiori DC, Stewart K, Ahearn JM, Zhou J, Aillet F, Masutani H, Elbim C, Raoul H, Chene L, Nugeyre MT, Paya C, Barre-Sinoussi F, Gougerot-Pocidalo MA, and Israel N. Complement-mediated binding of naturally glycosylated and glycosylation-modified human immunodeficiency virus type 1 to human CR2 (CD21). *J Virol* 67: 2699–2706, 1993.
51. Nakamura H, Matsuda M, Furuke K, Kitaoka Y, Iwata S, Toda K, Inamoto T, Yamaoka Y, Ozawa K, and Yodoi J. Adult T cell leukemia-derived factor/human thioredoxin protects endothelial F-2 cell injury caused by activated neutrophils or hydrogen peroxide. *Immunol Lett* 42: 75–80, 1994.
52. Nakamura H, De Rosa S, Roederer M, Anderson MT, Dubs JG, Yodoi J, Holmgren A, and Herzenberg LA. Elevation of plasma thioredoxin levels in HIV-infected individuals. *Int Immunol* 8: 603–611, 1996.
53. Nakamura H, Nakamura K, and Yodoi J. Redox regulation of cellular activation. *Annu Rev Immunol* 15: 351–369, 1997.
54. Nakamura H, Vaage J, Valen G, Padilla CA, Bjornstedt M, and Holmgren A. Measurements of plasma glutaredoxin and thioredoxin in healthy volunteers and during open-heart surgery. *Free Radic Biol Med* 24: 1176–1186, 1998.
55. Nakamura H, Bai J, Nishinaka Y, Ueda S, Sasada T, Ohshio G, Imamura M, Takabayashi A, Yamaoka Y, and Yodoi J. Expression of thioredoxin and glutaredoxin, redox-regulating proteins, in pancreatic cancer. *Cancer Detect Prev* 24: 53–60, 2000.
56. Nakamura H, Masutani H, and Yodoi J. Thioredoxin-dependent redox regulation in biological responses. In: *Free Radicals in Chemistry, Biology and Medicine*, edited by Yoshikawa T, Toyokuni S, Yamamoto Y, and Naito Y. London: OICA International, 2000, pp. 172–181.
57. Nakamura H, De Rosa SC, Yodoi J, Holmgren A, Ghezzi P, and Herzenberg LA. Chronic elevation of plasma thioredoxin: inhibition of chemotaxis and curtailment of life expectancy in AIDS. *Proc Natl Acad Sci U S A* 98: 2688–2693, 2001.
58. Newman GW, Balcewicz-Sablinska MK, Guarnaccia JR, Remold HG, and Silberstein DS. Opposing regulatory effects of thioredoxin and eosinophil cytotoxicity-enhancing factor on the development of human immunodeficiency virus 1. *J Exp Med* 180: 359–363, 1994.
59. Oka S, Kamata H, Kamata K, Yagisawa H, and Hirata H. *N*-Acetylcysteine suppresses TNF-induced NF-kappaB ac-

tivation through inhibition of IkappaB kinases. *FEBS Lett* 472: 196–202, 2000.
60. Okado-Matsumoto A, Matsumoto A, Fujii J, and Taniguchi N. Peroxiredoxin IV is a secretable protein with heparin-binding properties under reduced conditions. *J Biochem (Tokyo)* 127: 493–501, 2000.
61. Okamoto T, Ogiwara H, Hayashi T, Mitsui A, Kawabe T, and Yodoi J. Human thioredoxin/adult T cell leukemia-derived factor activates the enhancer binding protein of human immunodeficiency virus type 1 by thiol redox control mechanism. *Int Immunol* 4: 811–819, 1992.
62. Olmsted L, Schrauzer GN, Flores-Arce M, and Dowd J. Selenium supplementation of symptomatic human immunodeficiency virus infected patients. *Biol Trace Elem Res* 20: 59–65, 1989.
63. Packer L and Suzuki YJ. Vitamin E and alpha-lipoate: role in antioxidant recycling and activation of the NF-kappa B transcription factor. *Mol Aspects Med* 14: 229–239, 1993.
64. Pekkari K, Gurunath R, Arner ES, and Holmgren A. Truncated thioredoxin is a mitogenic cytokine for resting human peripheral blood mononuclear cells and is present in human plasma. *J Biol Chem* 275: 37474–37480, 2000.
65. Poli G and Fauci AS. The effect of cytokines and pharmacologic agents on chronic HIV infection. *AIDS Res Hum Retroviruses* 8: 191–197, 1992.
66. Raju PA, Herzenberg LA, and Roederer M. Glutathione precursor and antioxidant activities of *N*-acetylcysteine and oxothiazolidine carboxylate compared in in vitro studies of HIV replication. *AIDS Res Hum Retroviruses* 10: 961–967, 1994.
67. Roberts RL, Aroda VR, and Ank BJ. *N*-Acetylcysteine enhances antibody-dependent cellular cytotoxicity in neutrophils and mononuclear cells from healthy adults and human immunodeficiency virus-infected patients. *J Infect Dis* 172: 1492–1502, 1995.
68. Roederer M, Staal FJ, Raju PA, Ela SW, and Herzenberg LA. Cytokine-stimulated human immunodeficiency virus replication is inhibited by *N*-acetyl-L-cysteine. *Proc Natl Acad Sci U S A* 87: 4884–4888, 1990.
69. Roederer M, Staal FJ, Osada H, and Herzenberg LA. CD4 and CD8 T cells with high intracellular glutathione levels are selectively lost as the HIV infection progresses. *Int Immunol* 3: 933–937, 1991.
70. Roederer M, Ela SW, Staal FJ, and Herzenberg LA. *N*-Acetylcysteine: a new approach to anti-HIV therapy. *AIDS Res Hum Retroviruses* 8: 209–217, 1992.
71. Roederer M, Staal FJ, Ela SW, and Herzenberg LA. *N*-Acetylcysteine: potential for AIDS therapy. *Pharmacology* 46: 121–129, 1993.
72. Sahaf B and Rosén A. Secretion of 10-kDa and 12-kDa thioredoxin species from blood monocytes and transformed leukocytes. *Antioxid Redox Signal* 2: 717–726, 2000.
73. Saitoh M, Nishitoh H, Fujii M, Takeda K, Tobiume K, Sawada Y, Kawabata M, Miyazono K, and Ichijo H. Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. *EMBO J* 17: 2596–2606, 1998.
74. Sappey C, Legrand-Poels S, Best-Belpomme M, Favier A, Rentier B, and Piette J. Stimulation of glutathione peroxidase activity decreases HIV type 1 activation after oxidative stress. *AIDS Res Hum Retroviruses* 10: 1451–1461, 1994.
75. Schreck R, Rieber P, and Baeuerle PA. Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF-kappa B transcription factor and HIV-1. *EMBO J* 10: 2247–2258, 1991.
76. Silberstein DS, McDonough S, Minkoff MS, and Balcewicz-Sablinska MK. Human eosinophil cytotoxicity-enhancing factor. Eosinophil-stimulating and dithiol reductase activities of biosynthetic (recombinant) species with COOH-terminal deletions. *J Biol Chem* 268: 9138–9142, 1993.
77. Simon G, Moog C, and Obert G. Effects of glutathione precursors on human immunodeficiency virus replication. *Chem Biol Interact* 91: 217–224, 1994.
78. Staal FJ, Roederer M, Herzenberg LA, and Herzenberg LA. Intracellular thiols regulate activation of nuclear factor kappa B and transcription of human immunodeficiency virus. *Proc Natl Acad Sci U S A* 87: 9943–9947, 1990.
79. Staal FJ, Ela SW, Roederer M, Anderson MT, and Herzenberg LA. Glutathione deficiency and human immunodeficiency virus infection. *Lancet* 339: 909–912, 1992.
80. Sumida Y, Nakashima T, Yoh T, Nakajima Y, Ishikawa H, Mitsuyoshi H, Sakamoto Y, Okanoue T, Kashima K, Nakamura H, and Yodoi J. Serum thioredoxin levels as an indicator of oxidative stress in patients with hepatitis C virus infection. *J Hepatol* 33: 616–622, 2000.
81. Tagaya Y, Maeda Y, Mitsui A, Kondo N, Matsui H, Hamuro J, Brown N, Arai K, Yokota T, Wakasugi H, and Yodoi J. ATL-derived factor (ADF), an IL-2 receptor/Tac inducer homologous to thioredoxin; possible involvement of dithiol-reduction in the IL-2 receptor induction. *EMBO J* 8: 757–764, 1989.
82. Takagi Y, Mitsui A, Nishiyama A, Nozaki K, Sono H, Gon Y, Hashimoto N, and Yodoi J. Overexpression of thioredoxin in transgenic mice attenuates focal ischemic brain damage. *Proc Natl Acad Sci U S A* 96: 4131–4136, 1999.
83. Tamura T and Stadtman TC. A new selenoprotein from human lung adenocarcinoma cells: purification, properties, and thioredoxin reductase activity. *Proc Natl Acad Sci U S A* 93: 1006–1011, 1996.
84. Tang AM, Smit E, Semba RD, Shah N, Lyles CM, Li D, and Vlahov D. Improved antioxidant status among HIV-infected injecting drug users on potent antiretroviral therapy. *J Acquir Immune Defic Syndr* 23: 321–326, 2000.
85. Teshigawara K, Maeda M, Nishino K, Nikaido T, Uchiyama T, Tsudo M, Wano Y, and Yodoi J. Adult T leukemia cells produce a lymphokine that augments interleukin 2 receptor expression. *J Mol Cell Immunol* 2: 17–26, 1985.
86. Wakasugi H, Rimsky L, Mahe Y, Kamel AM, Fradelizi D, Tursz T, and Bertoglio J. Epstein–Barr virus-containing B-cell line produces an interleukin 1 that it uses as a growth factor. *Proc Natl Acad Sci U S A* 84: 804–808, 1987.
87. Witschi A, Junker E, Schranz C, Speck RF, and Lauterburg BH. Supplementation of *N*-acetylcysteine fails to increase glutathione in lymphocytes and plasma of patients with AIDS. *AIDS Res Hum Retroviruses* 11: 141–143, 1995.

88. Wollman EE, d'Auriol L, Rimsky L, Shaw A, Jacquot JP, Wingfield P, Graber P, Dessarps F, Robin P, Galibert F, *et al.* Cloning and expression of a cDNA for human thioredoxin. *J Biol Chem* 263: 15506–15512, 1988.
89. Yodoi J and Uchiyama T. Diseases associated with HTLV-I: virus, IL-2 receptor dysregulation and redox regulation. *Immunol Today* 13: 405–411, 1992.
90. Yoshida S, Katoh T, Tetsuka T, Uno K, Matsui N, and Okamoto T. Involvement of thioredoxin in rheumatoid arthritis: its costimulatory roles in the TNF-alpha-induced production of IL-6 and IL-8 from cultured synovial fibroblasts. *J Immunol* 163: 351–358, 1999.

Address reprint request to:
Dr. Hajime Nakamura
Department of Biological Responses
Institute for Virus Research
Kyoto University
53 Shogin-Kawaharacho, Sakyo
Kyoto 606-8507, Japan

E-mail: hnakamur@virus.kyoto-u.ac.jp

Received for publication May 30, 2001; accepted August 20, 2001.

This article has been cited by:

1. Xingxiang Chen, Fei Ren, John Hesketh, Xiuli Shi, Junxian Li, Fang Gan, Kehe Huang. 2012. Reactive oxygen species regulate the replication of porcine circovirus type 2 via NF-#B pathway. *Virology* . [CrossRef]
2. Risa Maeda , Chiharu Tabata , Rie Tabata , Ryoji Eguchi , Yoshihiro Fujimori , Takashi Nakano . 2011. Is Serum Thioredoxin-1 a Useful Clinical Marker for Malignant Pleural Mesothelioma?. *Antioxidants & Redox Signaling* **15**:3, 685-689. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
3. Kenneth D Tew, Danyelle M Townsend. 2011. Redox platforms in cancer drug discovery and development. *Current Opinion in Chemical Biology* **15**:1, 156-161. [CrossRef]
4. Alison Morris, David M Guidot. 2010. Obstructive lung disease and HIV/AIDS in the HAART era. *HIV Therapy* **4**:1, 41-54. [CrossRef]
5. Alessandra Fraternale, Maria Filomena Paoletti, Anna Casabianca, Lucia Nencioni, Enrico Garaci, Anna Teresa Palamara, Mauro Magnani. 2009. GSH and analogs in antiviral therapy. *Molecular Aspects of Medicine* **30**:1-2, 99-110. [CrossRef]
6. Vittorio Calabrese, Carolin Cornelius, Cesare Mancuso, Giovanni Pennisi, Stella Calafato, Francesco Bellia, Timothy E. Bates, Anna Maria Giuffrida Stella, Tony Schapira, Albena T. Dinkova Kostova, Enrico Rizzarelli. 2008. Cellular Stress Response: A Novel Target for Chemoprevention and Nutritional Neuroprotection in Aging, Neurodegenerative Disorders and Longevity. *Neurochemical Research* **33**:12, 2444-2471. [CrossRef]
7. E. V. Kalinina, N. N. Chernov, A. N. Saprin. 2008. Involvement of thio-, peroxi-, and glutaredoxins in cellular redox-dependent processes. *Biochemistry (Moscow)* **73**:13, 1493-1510. [CrossRef]
8. Chul-Woong Pyo, Young Lae Yang, Na-Kyung Yoo, Sang-Yun Choi. 2008. Reactive oxygen species activate HIV long terminal repeat via post-translational control of NF-#B. *Biochemical and Biophysical Research Communications* **376**:1, 180-185. [CrossRef]
9. N MAULIK, D DAS. 2008. Emerging potential of thioredoxin and thioredoxin interacting proteins in various disease conditions. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1780**:11, 1368-1382. [CrossRef]
10. Hiroaki Okuyama, Aoi Son, Md. Kaimul Ahsan, Hiroshi Masutani, Hajime Nakamura, Junji Yodoi. 2008. Thioredoxin and thioredoxin binding protein 2 in the liver. *IUBMB Life* **60**:10, 656-660. [CrossRef]
11. R MICHALEK. 2008. The requirement of reactive oxygen intermediates for lymphocytic choriomeningitis virus binding and growth. *Virology* **379**:2, 205-212. [CrossRef]
12. Stefano Aquaro, Fernanda Scopelliti, Michela Pollicita, Carlo Federico Perno. 2008. Oxidative stress and HIV infection: target pathways for novel therapies?. *Future HIV Therapy* **2**:4, 327-338. [CrossRef]
13. Craig Webb, Tracy Lehman, Kelly McCord, Paul Avery, Steven Dow. 2008. Oxidative stress during acute FIV infection in cats. *Veterinary Immunology and Immunopathology* **122**:1-2, 16-24. [CrossRef]
14. A. Fraternale, M.F. Paoletti, A. Casabianca, C. Orlandi, G.F. Schiavano, L. Chiarantini, P. Clayette, J. Oiry, J.-U. Vogel, J. Cinatl, M. Magnani. 2008. Inhibition of murine AIDS by pro-glutathione (GSH) molecules. *Antiviral Research* **77**:2, 120-127. [CrossRef]
15. Y LIU, H ZHANG, L ZHANG, Q ZHOU, X WANG, J LONG, T DONG, W ZHAO. 2007. Antioxidant N-acetylcysteine attenuates the acute liver injury caused by X-ray in mice. *European Journal of Pharmacology* **575**:1-3, 142-148. [CrossRef]
16. Sandra Parra, Carlos Alonso-Villaverde, Blai Coll, Natàlia Ferré, Judit Marsillach, Gerard Aragonès, Michael Mackness, Bharti Mackness, Lluis Masana, Jorge Joven, Jordi Camps. 2007. Serum paraoxonase-1 activity and concentration are influenced by human immunodeficiency virus infection. *Atherosclerosis* **194**:1, 175-181. [CrossRef]

17. Ulla Schwertassek, Yves Balmer, Marcus Gutscher, Lars Weingarten, Marc Preuss, Johanna Engelhard, Monique Winkler, Tobias P Dick. 2007. Selective redox regulation of cytokine receptor signaling by extracellular thioredoxin-1. *The EMBO Journal* **26**:13, 3086-3097. [CrossRef]
18. F Sabot, A H Schulman. 2006. Parasitism and the retrotransposon life cycle in plants: a hitchhiker's guide to the genome. *Heredity* **97**:6, 381-388. [CrossRef]
19. Chava B. Pocernich, Rukhsana Sultana, Hafiz Mohmmad-Abdul, Avindra Nath, D. Allan Butterfield. 2005. HIV-dementia, Tat-induced oxidative stress, and antioxidant therapeutic considerations. *Brain Research Reviews* **50**:1, 14-26. [CrossRef]
20. Kumuda C. Das . 2005. Thioredoxin and Its Role in Premature Newborn Biology. *Antioxidants & Redox Signaling* **7**:11-12, 1740-1743. [Abstract] [Full Text PDF] [Full Text PDF with Links]
21. Anne Burke-Gaffney, Matthew E.J. Callister, Hajime Nakamura. 2005. Thioredoxin: friend or foe in human disease?. *Trends in Pharmacological Sciences* **26**:8, 398-404. [CrossRef]
22. Ylva Hamnell-Pamment, Christina Lind, Carina Palmberg, Tomas Bergman, Ian A. Cotgreave. 2005. Determination of site-specificity of S-glutathionylated cellular proteins#. *Biochemical and Biophysical Research Communications* **332**:2, 362-369. [CrossRef]
23. Hajime Nakamura . 2005. Thioredoxin and Its Related Molecules: Update 2005. *Antioxidants & Redox Signaling* **7**:5-6, 823-828. [Abstract] [Full Text PDF] [Full Text PDF with Links]
24. W. Li, D. Galey, Mark P. Mattson, Avindra Nath. 2005. Molecular and cellular mechanisms of neuronal cell death in HIV dementia. *Neurotoxicity Research* **8**:1-2, 119-134. [CrossRef]
25. Charles B Stephensen, Grace S Marquis, Steven D Douglas, Craig M Wilson. 2005. Immune Activation and Oxidative Damage in HIV-Positive and HIV-Negative Adolescents. *JAIDS Journal of Acquired Immune Deficiency Syndromes* **38**:2, 180-190. [CrossRef]
26. Isabella Dalle-Donne, Andrea Scaloni, Daniela Giustarini, Eleonora Cavarra, Gianluca Tell, Giuseppe Lungarella, Roberto Colombo, Ranieri Rossi, Aldo Milzani. 2005. Proteins as biomarkers of oxidative/ nitrosative stress in diseases: The contribution of redox proteomics. *Mass Spectrometry Reviews* **24**:1, 55-99. [CrossRef]
27. Giuseppe Lazzarino, Angela Maria Amorini, Giovanna Fazzina, Roberto Vagnozzi, Stefano Signoretti, Sonia Donzelli, Enrico Di Stasio, Bruno Giardina, Barbara Tavazzi. 2003. Single-sample preparation for simultaneous cellular redox and energy state determination. *Analytical Biochemistry* **322**:1, 51-59. [CrossRef]
28. Danyelle M. Townsend, Kenneth D. Tew, Haim Tapiero. 2003. The importance of glutathione in human disease. *Biomedicine & Pharmacotherapy* **57**:3-4, 145-155. [CrossRef]