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Stressed to death: Implication of lymphocyte apoptosis for psychoneuroimmunology

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Abstract

Psychological and physical stressors best exemplify the intercommunication of the immune and the nervous systems. It has been shown that stress significantly impacts leukocyte cellularity and immune responses and alters susceptibility to various diseases. While acute stress has been shown to enhance immune responses, chronic stress often leads to immunosuppression. Among many criteria examined upon exposure to chronic stress, the reduction in lymphocyte mitogenic response and lymphocyte cellularity are commonly assessed. We have reported that chronic restraint stress could induce lymphocyte reduction, an effect dependent on endogenous opioids. Interestingly, the effect of endogenous opioids was found to be exerted through increasing the expression of a cell death receptor, Fas, and an increased sensitivity of lymphocytes to apoptosis. Stress-induced lymphocyte reduction was not affected by adrenalectomy. In this review, based on available literature and our recent data, we will discuss the role of the hypothalamic–pituitary–adrenal axis and endogenous opioids and examine the mechanisms by which chronic stress modulates lymphocyte apoptosis.

Keywords: Chronic stress; Endogenous opioids; Fas (CD95); Apoptosis; Corticosteroid; Immunosuppression; Lymphocytes

1. Introduction

The effect of physical and psychological stress on the immune system has been noticed since the 1940s (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Various studies with different model systems have demonstrated that depending on the mood and duration, stress could either enhance or reduce immune function (Ader & Cohen, 1993). It is generally accepted that acute stress could improve the function of the immune system, while chronic stress often results in reduction of immune responses (Dhabhar & McEwen, 1997). It has been shown that acute stress-promoted immune responses are dependent on the hypothalamic–pituitary–adrenal (HPA) axis (Dhabhar & McEwen, 1999), while the mechanisms by which chronic stress exerts its effect remain controversial. Our studies have shown that chronic restraint stress-induced lymphocyte reduction occurs through endogenous opioid-mediated Fas expression, which in turn induces apoptosis (Yin, Mufson, Wang, & Shi, 1999, 2000). In this paper we will briefly review lymphocyte apoptosis and its role in the regulation of lymphocyte homeostasis and immune responses. Our particular attention will be focused on chronic stress-induced lymphocyte apoptosis and the mechanisms controlling this process.

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2. Apoptosis and lymphocyte homeostasis

Apoptosis is an evolutionary conserved 'cell suicide' program present in all nucleated metazoan cells (Chinnaiyan & Dixit, 1996; Meier, Finch, & Evan, 2000). Despite its highly conserved nature, it is only recently that any of the molecular mechanisms underlying apoptosis have been identified (Rich, Watson, & Wyllie, 1999). Apoptosis is now known as an active cell death process characterized by the activation of proteases, auto-destruction of chromatin, nuclear condensation, cellular membrane blebbing, and vesicularization of internal components (Chang & Yang, 2000; Merino & Cordero-Campana, 1998). This gene-directed cell death process is responsible for the widespread and deliberate elimination of excessive cells during development and pathophysiological processes. In the immune system, apoptosis occurs physiologically during lymphocyte repertoire selection and immune responses to various diseases.

One of the best-characterized systems in which apoptosis can be demonstrated is activation-induced cell death (AICD) in T cells. We have demonstrated that apoptosis can be induced specifically in immature thymocytes in vivo by administration of antibodies to the T-cell antigen receptor (TCR) complex (Shi et al., 1991; Shi, Sahai, & Green, 1989). This was also observed in fetal thymic organ culture, using either antibodies to CD3 (Smith, Williams, Kingston, Jenkinson, & Owen, 1989) or superantigen, staphylococcal enterotoxin B (Lin et al., 1992). AICD in immature thymocytes is believed to account for negative selection of autoreactive T cells during their development in the thymus. It is generally believed that mature T cells are resistant to AICD. However, when primary activated mature T cells are further activated, the majority of them undergo apoptosis. This type of AICD has been shown to be operative in both mouse (Lenardo et al., 1999) and human cells (Wesselborg, Janssen, & Kabelitz, 1993). It is hypothesized to be a fundamental mechanism for the removal of excess peripheral lymphocytes, which is believed to be part of the mechanism for maintaining immune homeostasis after an immune response (Lenardo et al., 1999). Defects in this programmed removal mechanism could thus lead to the accumulation of potentially autoreactive lymphocytes. On the other hand, too much apoptosis could lead to immunodeficiency. One such example is HIV-induced T helper cell apoptosis in acquired immunodeficiency syndrome (AIDS) (Roshal, Zhu, & Planelles, 2001). In addition, some therapeutic reagents, such as steroid hormones, could also lead to excessive apoptosis in T cells. Our recent experiments have shown that exogenous opioids and stress-induced endogenous opioids could promote apoptosis in lymphocytes via induction of Fas both in vitro and in vivo. This finding may be related to the immunosuppressive status of drug addicts and chronically stressed individuals.

3. Fas (CD95/APO-1) and Fas ligand (FasL/CD95L)

Fas antigen is a type I membrane protein of 45 kDa that belongs to the tumor necrosis factor (TNF)/nerve growth factor receptor family (Itoh et al., 1991). It is expressed on a variety of cell types including activated T- and B cells, hepatocytes, and ovarian epithelial cells (Watanabe-Fukunaga et al., 1992). It is also detected in solid tumors of the breast, ovary, colon, prostate, and liver. Ligation of this molecule with specific antibodies or its natural ligand (FasL) usually induces rapid apoptotic cell death (Itoh et al., 1991; Watanabe-Fukunaga et al., 1992). On the other hand, Fas ligand is a type II membrane protein of 40 kDa that belongs to the TNF family (Takahashi et al., 1994a, 1994b). FasL expression has been detected on activated T cells, NK cells, Sertoli cells of the testis, corneal epithelium, and the retina of the eye (Green & Ware, 1997). Tumors also express FasL, which could be a mechanism of avoiding immune surveillance (Hug, 1997; O'Connell, Bennett, O'Sullivan, Collins, & Shanahan, 1999). AICD in peripheral T cells is dependent on Fas and FasL interaction, though TNF may also play a role in this process (Sytwu, Liblau, & McDevitt, 1996). Mutation of either Fas (lpr) or FasL (gld) causes lymphadenopathy and splenomegaly, and accelerates autoimmune disease in both mice and humans (Lenardo et al., 1999; Lenardo, 1996). Our studies have revealed that TCR activation-induced expression of Fas is mediated by PKC translocation in a TDAG51 dependent manner, while the expression of FasL requires both PKC activation and calcium influx (Wang, Zhang, Yin, Mufson, & Shi, 1998). In addition, the expression of Fas could be induced by both exogenously administered or endogenously produced opioids (Yin et al., 1999, 2000).

4. Opioids and immunosuppression

Opiates are an old class of drugs derived from the milky latex of poppy of the opium poppy *Papaver somniferum* and have been used for centuries as analgesics. Morphine is the primary alkaloid in opium. Opioids have effects on perception of pain, consciousness, motor control, mood, and autonomic function, and often induce physical dependence or addiction (Kieffer & Evans, 2002). In the mid 1970s, scientists discovered the existence of an endogenous morphine-like substance, enkephalin, in the brain (Kieffer & Evans, 2002). Several endogenous opioid peptides have been identified from mammals and humans (Gajdos, 1977; Kosterlitz & Hughes, 1977). Both exogenous and endogenous opioids exert their effects through specific cell surface receptors, all of which are 60 kDa proteins and are currently classified into three groups, μ, δ, and κ (Grudt & Williams, 1995; Stefano, 1998).

The existence of different opioid receptors was predicted mainly by pharmacological approaches and they differ in their affinity for various opioid ligands and in their pharmacological profiles (Connor & Christie, 1999; Narita, Funada, & Suzuki, 2001; Olley, 1989). Opioid antagonists such as naloxone or naltrexone could specifically block these receptors (Crabtree, 1984; Hameroff, 1983; O'Malley, 1996). These antagonists, bearing opioid-related chemical structures, bind to the receptors and displace opioids. These drugs are used as an antidote to opioids. Molecular cloning of MOR-1 (μ), DOR-1 (δ), KOR-1 (κ), and OLR1 (OLR) was achieved only recently (Wei & Loh, 2002; Zaki et al., 1996). The various opioid receptors are encoded by distinct genes located on different chromosomes. It is now known that all of these receptors are G-protein coupled, possessing seven membrane-spanning regions (Connor & Christie, 1999).

It is interesting to note that lymphocytes possess opioid receptors and also produce endogenous opioid peptides upon activation (Madden, Falek, Donahoe, Ketelson, & Chappel, 1991). It has been shown that administration of morphine in mice induces apoptosis and hypoplasia in both thymus and the spleen (Fuchs & Pruett, 1993; Sei, Yoshimoto, McIntyre, Skolnick, & Arora, 1991; Yin et al., 1999). Opioids have also been shown to reduce bone marrow cell proliferation (Roy, Loh, & Lee, 1991a, 1991b). In fact the immature $CD4^+CD8^+$ cells are the most sensitive cells to morphine treatment (Lopez et al., 1993; Roy et al., 2001). Recent studies have revealed that the reduction in thymocytes is due to the induction of apoptosis (Fuchs & Pruett, 1993). In fact, overwhelming evidence repeatedly suggests that opioid use affects both innate and adaptive immunity (Roy & Loh, 1996).

5. Lymphocyte apoptosis induced by chronic stress

Various studies have clearly demonstrated that the immune system is very sensitive to either physiological or psychological stress. Stress has been demonstrated in both humans and animals to be immunomodulatory and alter the pathogenesis of tumor development, autoimmunity, and infectious diseases by influencing the onset, course, and outcome of the pathological processes (Rabin, Cohen, Ganguli, Lysle, & Cunnick, 1989). Although acute stress is generally believed to exert positive effects on the immune system, chronic stress frequently leads to immunosuppression, which is at least in part due to the reduction of lymphocytes (Berthiaume, Aparicio, Eungdamrong, & Yarmush, 1999; Pariante et al., 1997; Zorrilla et al., 2001). Stress-induced lymphopenia has been observed in surgical patients (Galinowski, 1993; Iwagaki, Morimoto, Kodera, & Tanaka, 2000; Kunes & Krejsek, 2000), over exercised athletes (Pedersen, Bruunsgaard, Jensen, Krzywkowski, & Ostrowski, 1999, 1997), persons under various psychological stress (Capitanio & Lerche, 1991; Zakowski, McAllister, Deal, & Baum, 1992), and animals subjected to physical restraint (Padgett, Marucha, & Sheridan, 1998; Sheridan et al., 1998; Yin et al., 1999). Due to the rapid advancement of apoptosis research, a variety of methods have been devised to detect apoptotic cells. By using these technologies, research in several laboratories has concluded that lymphopenia observed after exposure to stress is in fact due to the induction of apoptosis (Yin et al., 1999).

We have employed the physical restraint mouse model and examined the effect of chronic stress on lymphocyte apoptosis (Yin et al., 1999). We subjected BALB/c mice aged 7–9 weeks to a 12-h physical restraint regimen daily for 2 days (Bonneau, Sheridan, Feng, & Glaser, 1993) and found that this treatment dramatically affected splenic cellularity. These mice showed approximately a 35–40% reduction in the number of lymphocytes in the spleen as compared to unstressed controls. To investigate whether the cell death is due to apoptosis, we performed terminal deoxyribonucleotidyl transferase-mediated dUTP-digoxigenin nick-end labeling (TUNEL) assay on spleen histological section from control and mice that underwent stress treatment. We found that there is a significant increase in TUNEL positive cells, indicating that the reduction of splenic cellularity is due, at least in part, to the induction of apoptosis (Yin et al., 2000).

It is generally believed that stress-induced apoptosis in peripheral lymphoid organs becomes apparent after 12 h or longer upon exposure. Stress also causes a marked increase in apoptosis in the thymus, and a reduction in the total number of thymocytes. Interestingly, the thymus appears to be more sensitive to stress. Apoptosis in the thymus occurs within 6 h. Among all thymic cell populations, the proportion of CD4 and CD8 double positive thymocytes are more sensitive, suggesting that the increased apoptosis mainly affected cells of the immature phenotype (Ayala, Herdon, Lehman, Ayala, & Chaudry, 1996; Dominguez-Gerpe & Rey-Mendez, 2001).

In a recent study, Dominguez-Gerpe and Rey-Mendez (2001) studied chronic stress on various populations of T cells. Although the overall trend is that the majority of lymphocytes are reduced, there is some variation among different populations. Mature T cells are more sensitive than B cells. Interestingly, circulating immature T cells (CD3+PNA+) increase. The most significant increase in T cell numbers occurs in the bone marrow, suggesting a possible effect of chronic stress on cell migration.

Increases in T cell apoptosis have also been observed in patients undergoing surgical procedures (Delogu et al., 2000; Delogu et al., 2001; Oka et al., 1996; Schroeder et al., 2001). It seems that monocytes play an important

role in the induction of T cell apoptosis. Co-culture of T cells with monocytes from stressed patients induced apoptosis of T cells, whereas co-culture with monocytes from unstressed patients did not (Kono et al., 2001). This observation may lead to the identification of cells responsible for providing a death signal to lymphocytes.

6. The mechanisms

Bi-directional communication between the nervous and immune systems occurs through neuroendocrine mechanisms and interaction with lymphoid tissue. It is clear that psychological or physical stressors that activate these pathways can alter immunity and disease resistance. Many mechanisms have been proposed to account for stress-induced alterations in immunity, including changes in the lymphocytes signaling process, migration pattern, and viability. We will review the literature regarding cell viability with particular emphasis on endogenous opioids, Fas, glucocorticoids, and free radical species (Yin et al., 2000).

6.1. Endogenous opioids

Though it is known that several tissues and organs possess specific receptors for both endogenous and exogenous opioids, most information concerning the biological functions of opioid receptors is derived from studies of neuronal cells (Hyman, 1996; O'Brien, 1997). However, the immune system is also profoundly affected by opioids as demonstrated by various in vitro and in vivo experimental systems (McCarthy, Wetzel, Sliker, Eisenstein, & Rogers, 2001). It is now known that endogenous opioids play an important role in the interaction between the nervous and immune systems (Cabot, 2001; Salzet, Vieau, & Day, 2000; Vaccarino & Kastin, 2000). The role of opioid receptors in the regulation of lymphocyte apoptosis was investigated mainly with exogenous opioids. The effect of exogenous opioids on apoptosis was first observed in the thymus in 1993 (Freier & Fuchs, 1993). They found that the in vivo administration of morphine could induce apoptosis in immature thymocytes. It is interesting to note that the effect of exogenous opioids on the immune system seems to be exerted through the μ-opioid receptor (Wang et al., 2001).

In our studies, we employed naloxone and naltrexone as specific antagonists of opioid receptors and determined the role of endogenous opioids in stress-induced lymphocyte reduction in the spleen (Yin et al., 2000). Although treatment of mice with opioid antagonists did not alter the number of splenocytes in unstressed mice, administration of naltrexone or naloxone prior to physical restraint completely blocked stress-induced reduction in splenocyte numbers. When apoptosis in spleen was analyzed by the TUNEL assay, we found that both antagonists inhibited the appearance of TUNEL positive cells. Therefore, physical restraint-induced lymphocyte reduction appears to require endogenous opioids.

6.2. Fas

Fas–FasL interaction plays a critical role in the regulation of the immune system (Maher, Toomey, Condron, & Bouchier-Hayes, 2002; Sharma et al., 2000). We have reported that in vivo administration of exogenous opioids could induce Fas expression in various tissue types including the spleen. Blocking of Fas and FasL interaction with Fas fusion protein, antibody to FasL could block morphine-induced lymphocyte reduction, indicating the importance of Fas in opioid-induced immunosuppression (Yin et al., 1999). Surprisingly, we also found that chronic restraint stress-induced lymphocyte reduction is also related to Fas expression (Yin et al., 2000). We have found that restraint stress could increase Fas expression in lymphocytes. Blocking of opioid receptors with nalaxone or naltrexone would inhibit stress-induced Fas expression. To verify the role of FAS in stress-induced lymphocyte reduction, we injected mice with serum from SCID mice bearing tumor either of 3T3 fibrosarcoma engineered to secrete with Fas–Ig fusion protein (Ju et al., 1995) or of nonengineered 3T3 fibrosarcoma. Fas–Ig containing serum blocked the reduction in splenocytes, while normal mouse serum did not exhibit such an effect. When the Fas–Ig containing serum was adsorbed with protein A–Sepharose beads, its protective effect was eliminated. In addition, the Fas–Ig serum did not change the number of splenocytes in unstressed mice. We also found that a blocking antibody to CD95L, MFL3 (Kayagaki et al., 1997), but not the isotype control, also blocked stress-induced reduction in lymphocyte numbers. Therefore, the interaction between Fas and FasL are critical for stress-induced reduction of lymphocytes. To further investigate the role of FAS in physical restraint stress-induced reduction in lymphocyte numbers, we subjected mice which bear autosomal recessive mutation in FAS, and their appropriate background control, C3H/HeJ, to physical restraint. Stress-induced reduction in the numbers of splenocytes was only observed in C3H/HeJ, but not in C3H.MRL.Fas^{lpr} mice (Yin et al., 2000). Therefore mice with a loss of function mutation of FAS lose their sensitivity to stress-induced reduction in lymphocyte numbers, further supporting the conspicuous role of FAS in the stress response.

A recent study reported that immobilization restraint of rats results in apoptosis in the testicular tubule (Barnes, Covington, Cameron, & Lee, 1998). Since it has been shown that the Sertoli cells in the testis express high levels of FasL (Bellgrau et al., 1995), the apoptosis in this model system may be mediated via stress-induced Fas expression, a result reminiscent of our experiment with lymphocytes. Although we have demonstrated the role of Fas

in stress-induced lymphocyte reduction, we do not know where the FasL originates. In our experiments, we could not find the induction of FasL in lymphocytes. Further investigation of the origin of FasL is critical for the understanding of how stress affects the immune system.

6.3. Glucocorticoids

High doses of steroid hormones have been shown to be immunosuppressive. In fact, the apoptosis associated characteristic 200-base pair genomic DNA fragmentation ladder was first identified from dexamethasone treated rat thymocytes (Wyllie, 1980). This finding led many investigators to characterize apoptosis phenotypes with steroid hormones. Interestingly, steroid hormones have been suggested to play an important role in stress-induced modulation of the immune system, however, some studies in the literature have challenged the general role of steroids in stress situations (Jefferies, 1991; Minton, 1994). To examine the role of steroids in restraint induced lymphocyte reduction, we performed adrenectomy on mice. Both adrenectomized and sham treated mice were subjected to restraint stress. We found that there is no significant difference in the restraint stress-induced lymphocyte reduction in the two groups of mice (Yin et al., 2000). Therefore, the HPA axis is unlikely to be involved in mediating the reduction of splenocytes in this chronic restraint stress model. Our finding of the absence of an effect of adrenalectomy on chronic stress induced splenocyte reduction is in contrast with the role of the adrenal gland in acute stress induced enhancement of delayed-type hypersensitivity response reported (Dhabhar & McEwen, 1996). This discrepancy is likely to be due to the stress duration and the evaluation parameters. Indeed, McEwen et al. (1997) have suggested that the spleen is a relatively privileged site and is relatively inaccessible to endogenously produced corticosteroids. Therefore, our observation of the dispensability of adrenal glands in chronic stress-induced splenocyte reduction strongly suggests that the effects of endogenous opioids are likely exerted directly on splenocytes.

Recent studies indicate that stress-induced apoptosis in thymocytes is largely mediated by corticosteroids. The experiments performed by Freier and Fuchs (1993) showed that in vitro exposure of thymocytes to morphine could not induce apoptosis, indicating the effect of morphine in vivo could be indirect. Nevertheless, the effect could be completely blocked by the antagonist naltrexone. Furthermore, the effect of in vivo administered morphine could also be blocked by the glucocorticoid receptor antagonist RU-486 (Fuchs & Pruett, 1993), indicating a critical role of the HPA axis in this process. Therefore, a synthesis of the overall literature suggests that stress-induced apoptosis in immature T cells is through the HPA axis, while in mature T cells is mediated directly by endogenous opioids.

6.4. Free radicals

A redox imbalance caused by an over-production of prooxidants or a decrease in antioxidants plays an important role in the regulation of apoptosis, especially in the cells of the immune system. Various studies have shown that antioxidant could block stress induced lymphocyte reduction (Brohee & Neve, 1994; Meerson, Sukhikh, & Pletsityi, 1985; Singh, Failla, & Deuster, 1994; Venkatraman & Pendergast, 2002). It has been suggested that lymphocytes under oxidative stress are more prone to undergo apoptosis. However, the mechanisms underlining redox sensitized cell death are not known. In light of our investigation of the role of Fas and FasL interaction in stress induced lymphocyte apoptosis, we hypothesize that redox produced under stress conditions promotes Fas-induced apoptosis. To test this hypothesis, we subjected splenocytes from unstressed mice to either H_2O_2, JO2 (agonist antibody to Fas), or the combination and analyzed for apoptosis by DNA content analysis. We found that when either H_2O_2 or JO2 was applied alone, there was minimal induction of apoptosis. However, when both reagents added to the culture at the same time, there is a significant increase in the number of cells underwent apoptosis (Fig. 1). Therefore, we believe that the expression of Fas and the production of redox could act synergistically in the induction of apoptosis. This study provides an important link between redox and Fas in the stress-induced lymphocyte apoptosis. Further investigation of the molecular mechanisms by which redox promote Fas-mediated apoptosis will lead to a better understanding of how stress affect the immune system. It is suggested that oxidative stress is a physiological mediator of programmed cell death in lymphoid cells, and that HIV disease represents an extreme case of what can happen when regulatory safeguards are compromised.

6.5. Lymphocyte apoptosis and cancer

The theory of immune surveillance of Lewis Thomas and Macfarlane Burnet was formed 40 years ago, which stated that the immune system provided surveillance against cancer (Lanier, 2001). In this theory, it is hypothesized that at any one time within an average individual, it is estimated that 2–5 cells have the potential to become a tumor. Although the original theory of immunosurveillance proposed the critical role of T cells in this process, it is only recently that an increase in carcinogen-induced cutaneous tumor was observed in T cell deficient mice (Girardi et al., 2001). It is clear that a healthy immune system is important for maintaining a tumor free status. Numerous studies have shown that immunodeficiency, induced either by immunosuppressive agents or by infections, is often accompanied by a highly increased tumor risk (Deeg & Socie, 1998; Levine,

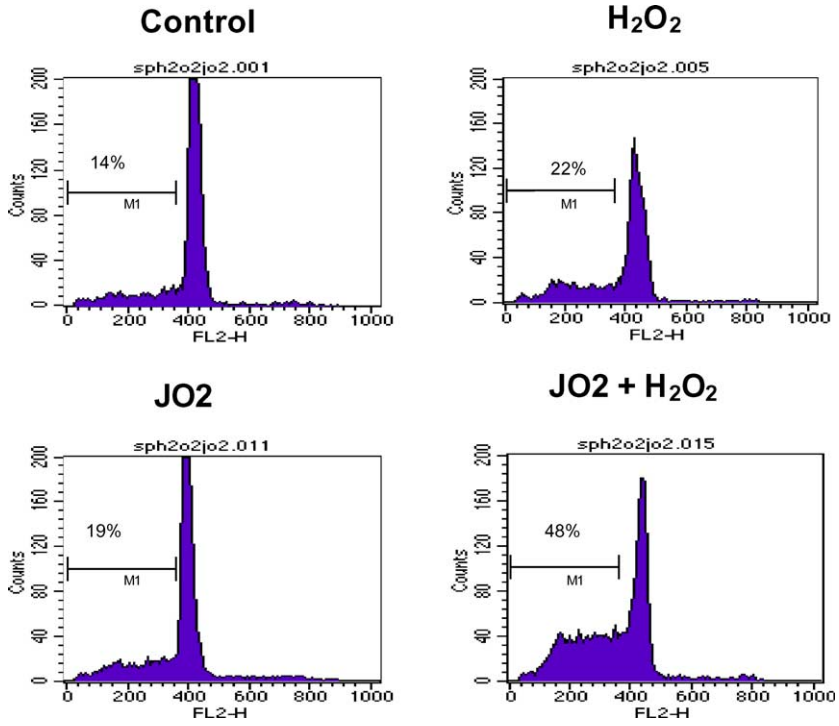

Fig. 1. The synergistic effect of Fas and redox in the induction of apoptosis in lymphocytes. Freshly isolated splenocytes was treated with H_2O_2 at 25 nM, JO2 at 100 ng/ml or both for 24 h. Apoptosis was determined by DNA content analysis. The subdiploid peaks represent apoptotic cells.

Seneviratne, & Tulpule, 2001; Swinnen, 2000). It has been reported that HIV infection leads to a significantly increased risk of Hodgkin's disease, multiple myeloma, brain cancer, and seminoma (Rabkin, 1998). In addition, upon HIV infection, failure of the immune system to control herpes or other viral infections may contribute to these malignant diseases. It is important to note that stress could dramatically reduce the resistance to herpes infection (DeLano & Mallery, 1998; Sheridan et al., 1998). Thus, immunodeficiency resulted from prolonged stress could also leads to increases in infection with oncogenic viruses. These infections in stressed individuals, who have an already weakened immune system, could dramatically increase the risk of cancer.

Besides enhancing the susceptibility to infections with oncogenic viruses, stressors themselves have been shown to increase the likelihood of cell transformation. Kiecolt-Glaser et al. have reported that human lymphocytes isolated from patients newly admitted to the psychiatric clinic possessed reduced levels of DNA repair capability. Since accumulation of damaged DNA is a major cause of cell transformation, this study provided an important link between stress and cancer. Further investigation has revealed that methyltransferase, an enzyme important for DNA repair, in stressed rats is dramatically reduced. In addition, it has been shown that stress could induce chromatid exchange in rats subjected to swim stress. Therefore, like oncogenic viral infection, the genomic changes induced directly by stress could also increase cancer opportunity in stressed individuals with reduced immunity.

Since lymphocytopenia is associated with both physical and psychological stress, reduction in lymphocyte number has been found to be associated with increased cancer incidence and tumor growth. We have discussed that stress could lead to lymphocyte reduction and increase in oncogenic virus infections and DNA damage. Recent studies have shown that some tumor cells could express FasL at high levels, a mechanism that is believed to operate by tumors to evade the immune system. Considering our finding of the increase in Fas expression in lymphocytes under stressed conditions (Yin et al., 2000), it is conceivable that this increase in Fas could promote lymphocyte apoptosis induced by FasL expressed on tumor cells. Therefore, the immune system could be further weakened.

7. Summary

Chronic stress often leads to the suppression of the immune system. In this paper, we have summarized

current literature related to stress-induced lymphocyte apoptosis under stress conditions. Based on available knowledge, stress induced-lymphocyte apoptosis does may play a prominent role in the pathogenesis of various diseases. Increasing evidence suggests that a compromised immune system may be a major contributor to cancer development and can impact the outcome of cancer therapies. We believe that further studies on how lymphocytes undergo stress-induced apoptosis will provide novel strategies for the prevention and management of infectious diseases and cancer.

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