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Psychoneuroimmunology and Cancer: Fact or Fiction?

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There is substantial evidence from both healthy populations as well as individuals with cancer linking psychological stress with immune downregulation. This discussion highlights natural killer (NK) cells, because of the role that they may play in malignant disease. In addition, distress or depression is also associated with two important processes for carcinogenesis: poorer repair of damaged DNA, and alterations in apoptosis. Conversely, the possibility that psychological interventions may enhance immune function and survival among cancer patients clearly merits further exploration, as does the evidence suggesting that social support may be a key psychological mediator. These studies and others suggest that psychological or behavioural factors may influence the incidence or progression of cancer through psychosocial influences on immune function and other physiological pathways. © 1999 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

SEVERAL LINES of research suggest that psychological or behavioural factors can influence the incidence or progression of cancer [1–6]. In this paper, we first briefly review psychoneuroimmunology (PNI) research involving healthy individuals and then discuss how these data may have relevance to cancer. Next, we describe evidence suggesting that distress or depression is associated with three important processes for carcinogenesis: poorer repair of damaged DNA, an increase in the frequency of sister chromatid exchange (SCE) and alterations in apoptosis. Finally, we focus on data from cancer patients, and the implications for cancer progression and treatment.

Our discussion of stress-related immune changes will highlight natural killer (NK) cells, because of their importance for cancer. NK cells play an important role in a variety of immune functions, including defence against viral infections [7] and surveillance of tumour cells [8]. Cytokines such as recombinant interferon-gamma (rIFN-γ) and recombinant interleukin-2 (rIL-2) can enhance NK cell and lymphocyte-activated killer (LAK) cell cytotoxicity, respectively, *in vitro* [8]. However, NK cell cytotoxicity can be downregulated by stress, presumably through neuroendocrine mechanisms [5, 9–11]. In addition, there is evidence that stress can modulate IFN-γ and IL-2 synthesis by mitogen treated peripheral blood lymphocytes (PBLs), and stress can also inhibit the response of NK cells to rIFN-γ and rIL-2 [12, 13].

Before reviewing the evidence regarding stress-related immunological changes, it should be noted that one recurrent condition in the literature is the question of the significance of the immune system for cancer. The best evidence suggests that there may be considerable variability related to different types of cancer: immunological defences appear more important for some types than for others. Moreover, supporting the 'immune surveillance' theory [8], there is evidence that subjects who are immunosuppressed (either through pharmacological means, or via immunodeficiency diseases) have an increased risk of cancer [14]. Additionally, some researchers have questioned whether stress-related immune changes are of either the type or magnitude to influence tumour growth and metastases [3, 14]. While such issues are beyond the scope of this paper, studies involving both animals and humans suggest that NK cells are particularly important in the elimination of metastatic tumour cells [15, 16].

STRESS AND IMMUNOLOGICAL CHANGE

Data from prospective studies suggest that even common-place stressful events are associated with transient decrements in a number of immunological functions. For example, significant declines in NK cell activity were found in blood samples obtained from 75 medical students on the day of final examinations, in contrast to baseline samples collected during a lower-stress period 1 month previously [17]. The drop in NK cell activity was replicated in two additional medical student samples [9, 18].

The magnitude of change in the immune response to stressors is sometimes dramatic. For example, the production of interferon by lymphocytes stimulated with concanavalin A (Con A) plummeted from a mean of 2000 μ/ml at baseline to 80 μ/ml during final exams in blood samples from 40 second-year medical students, a finding subsequently replicated across several exam. series [19]. Interferon is a major regulator of NK cells, stimulating their growth and differentiation, as well as enhancing their ability to destroy target cells [20].

A further study tested the hypothesis that a stress-reducing intervention might enhance immunity. Among 45 older adults who were randomly assigned to one of three protocols (relaxation training, social contract or no intervention), relaxation subjects showed a significant enhancement in NK cell activity at the end of the 1-month intervention with concomitant decreases in distress-related symptomatology, in comparison with non-significant changes in the other two groups [21]. These data provided the first well-controlled demonstration of immune enhancement via a behavioural intervention.

Several subsequent studies have also suggested a link between personal relationships and NK cell cytotoxicity, consistent with the broad literature on social support and health [22]. For example, bereaved spouses had elevated cortisol and decreased NK cell lysis [23]. Lonelier medical students had lower levels of NK cell activity than their contemporaries who were less lonely [17]. Among spouses of cancer patients, those who reported lower levels of social support had lower levels of NK cell cytotoxicity [24]. In a study of newlywed couples, those who were more negative or hostile during a discussion of marital problems with the spouse showed greater downward change in NK cell activity 24 h later [25]. Irwin and colleagues [26] investigated the consequences of a chronic stressor—caregiving for a spouse with Alzheimer's disease—on sympathetic nervous system activity and NK cell cytotoxicity. Plasma levels of neuropeptide Y (NPY) were significantly elevated in older caregivers compared with older controls, and NPY was negatively correlated with NK cell activity among caregivers; however, caregivers and controls did not differ in terms of NK cell activity.

In a further study, we examined differences among current caregivers of spouses with dementia, former (bereaved) caregivers whose spouse had died and non-caregiving controls [12]. Although an average of over 2 years had elapsed since bereavement, former caregivers did not differ from continuing caregivers on depressive symptomatology or perceived distress; however, both groups were significantly more depressed and reported more stress than control subjects. Consistent with Irwin and colleagues [26], we found no differences in NK cell cytotoxicity between either the continuing or former caregiver groups and control subjects in the ability of their NK cells to respond to rIFN-γ or rIL-2 *in vitro*: both caregiver groups had a significantly poorer response than controls.

The NK cell cytotoxicity of the continuing and former caregivers was highly skewed towards low responding (i.e. responding below the median for the population) following stimulation with either rIFN-γ or rIL-2 [12]. Caregivers whose NK cells were less responsive to both cytokines reported significantly less positive social support, less emotional closeness in their social contacts and more physician visits for infectious illness symptoms, compared with caregivers whose NK cells were good responders to at least one cytokine. Although our former caregivers could still be defined as compromised in the response of their NK cells to cytokine stimulation even 2 years post-bereavement, there may be eventual recovery; caregivers who had been bereaved for longer periods of time had NK cells that responded better to both cytokines.

A follow-up study using cell preparations enriched for NK cells (approximately 90%) replicated the previously observed group differences between caregivers (current and former) and controls [13]. In addition, higher levels of social support were associated with heightened NK cell responses to cytokines, independent of the level of depression.

Even though we have reviewed only a fraction of the relevant studies, it is clear that stress can alter NK cell activity in normal populations. Stress can also depress the ability of NK cells to respond to the cytokines necessary for effective cell killing of appropriate tumour or virally infected cells. We focused on NK cells because of their cancer relevance, but it should be noted that a large number of other potentially relevant immunological activities are also adversely affected by psychosocial stress [27]. Thus, these data suggest that stress can alter a potentially important defence against malignant disease.

STRESS AND CARCINOGENESIS

While most of the human research linking stress to carcinogenesis has focused on immune function, there are also alterations in other cancer-relevant processes. Most carcinogens appear to induce cancer by damaging the DNA in cells, thereby producing mutant cells [28]. The body's defences include enzymes that destroy chemical carcinogens, processes for identifying and repairing damaged DNA and the destruction of mutant or unrepaired DNA by the immune system [29]. The processes for repair or destruction of damaged DNA are critical, since faulty DNA repair is associated with an increased incidence of cancer [28].

The possibility of a linkage between emotional distress and DNA repair was explored in work using blood samples obtained from 28 non-psychotic, non-medicated new psychiatric admissions and 28 age- and gender-matched blood bank controls [30]. Following exposure to X-radiation, the lymphocytes from psychiatric patients demonstrated a reduced ability to repair damaged cellular DNA relative to controls. In addition, within the inpatient group, those patients who were more depressed showed significantly poorer repair of damaged DNA than their less depressed counterparts.

In a further study exploring the possibility that stress would impair one component of the DNA repair process, 45 rats ingested the carcinogen dimethylnitrosamine, and half were assigned to a rotational stress condition [31]. The levels of methyltransferase, an important DNA repair enzyme

induced in response to carcinogen damage, were significantly lower in stressed animals' splenic lymphocytes, as compared with splenic lymphocytes obtained from the control rats. Thus, consistent with the depression-related deficits in DNA repair found in psychiatric patients, these data also suggest that stress may alter the DNA repair process.

It is important to consider the stress-related DNA repair deficits in light of the previously discussed stress-related decrements in NK activity. Taken together, these data suggest that stress might have direct effects on carcinogenesis through alterations in DNA repair, as well as indirect effects through the poorer destruction or elimination of abnormal cells.

Data from a study with rats show that several different types of stress can induce sister chromatid exchange (SCE) in bone marrow cells [32]. Rats were stressed using cold and warm water swim stress and inescapable foot shock. All stressors induced a significant increase in the frequency of SCE. These data are consistent with our data on stress and DNA repair [30, 31]. There is evidence that SCE frequencies are linked to an increased incidence of cancer [33, 34].

A subsequent study showed that examination stress altered another process relative to carcinogenesis. Apoptosis is a process of genetically programmed alterations in cell structure that leads to failure of proliferation and differentiation and eventual cell death. Induced by a variety of toxic insults including growth factor deprivation and ionising radiation, apoptosis is thought to function to protect against the appearance of heritable phenotypic changes in cells, and may be a critical factor in normal cellular immune function.

Using the same academic stress paradigm described earlier, Tomei and coworkers [35, 36] showed that the tumour-promoting phorbol esters were able to block ionising radiation-induced apoptosis *in vitro*. In a follow-up study, we showed that low concentrations of the tumour-promoting phorbol ester, 12-0-tetradeconoyl-phorbol-13-acetate (TPA), specifically blocked apoptosis in peripheral blood lymphocytes (PBLs) induced by ionising radiation and that stress enhanced this process [37]. The PBLs obtained from medical students at the time of examination (as compared with PBLs obtained at two baseline low stress periods, that is before and after the examination) survived treatment with TPA and radiation. Apoptosis was blocked, cellular DNA fragmentation was inhibited, and PBLs survived with a significant increase in total cellular DNA. If stress can induce similar changes in apoptosis in the body, the survival of cells with abnormal levels of DNA could increase the risk of the development of malignant cells.

These alterations in apoptosis provide additional evidence of pathways through which psychological stress could contribute to increased cancer risk by modifying cell responses to environmental factors such as tumour promoters and oncogenic viruses [38]. These physiological changes could operate independently and/or in conjunction with the stress-induced immune downregulation described earlier, particularly the decrements in NK cell lysis [9, 17, 39]. This is especially pertinent since it has been demonstrated that target cell death requires gene expression and initiation of apoptosis.

Control of the expression of apoptosis is critical to the function of several cell types, including the target cells of cytotoxic effector cells [40]. Therefore, the inhibition of the expression of apoptosis could result in suppression of immune function. If these interpretations are correct, then psychological distress could ultimately lead to progressive

accumulation of errors within the cell genome, reduced immune competence and increased risk of environmentally associated malignant and infectious diseases. The mechanism linking the physiological changes induced by stress and the observed changes in DNA repair, apoptosis and sister chromatid exchange is not known. Since the hypothalamic–adrenal–pituitary axis and the autonomic nervous system are activated by stress, it is possible that one or more 'stress' hormones may mediate these responses.

PSYCHONEUROIMMUNOLOGY: IMPLICATIONS FOR CANCER PROGRESSION AND TREATMENT

Research that has attempted to link psychosocial stressors with tumour development or progression has faced many obvious difficulties [1]. For example, stage of disease can have a profound effect on how patients feel, and cancer treatments such as chemotherapy and radiation are associated with a number of side-effects, including immunological alterations.

One obvious area of interest is the possibility of influencing the course of cancer through behavioural interventions. Properly designed intervention studies provide a powerful tool for examining psychosocial factors. By random assignment of patients who have the same kind of stage of cancer to control and intervention conditions, researchers can assess psychological, immunological and disease changes.

Following the initial demonstration of behaviourally mediated immune enhancement among older adults [21], a number of researchers have confirmed our finding that stress-reducing interventions can improve immune function [41]. One of the best studies in this area evaluated both the immediate and longer-term effects of a 6-week structured group intervention that consisted of health education, enhancement of problem-solving skills regarding diagnosis, stress management techniques such as relaxation, and psychological support [42, 43]. The patients had stage I or II malignant melanoma, and they had not received any treatment after surgical excision of the cancer. Noteworthy effects included reduced psychological distress and significant increases in the per cent of NK cells, as well as an increase in NK cell cytotoxicity, compared with controls.

A 6-year follow-up of these patients showed a trend towards greater recurrence, as well as a significantly higher mortality rate in the control group than in intervention patients. The group differences remained significant after adjusting for the size of the initial malignant melanoma lesion, a key risk factor.

Consistent with results of the intervention study with melanoma patients, Spiegel and colleagues [44] showed that a year of weekly supportive group therapy sessions with self-hypnosis for pain was associated with extended survival time in women with metastatic breast cancer. It is not known if these data reflect immunological alterations that influenced the course of the cancer, and a number of other interpretations are plausible. As the authors note, patients in the intervention condition could have been more compliant with medical treatment, and/or they might have had better health behaviours such as exercise and diet. Such behavioural differences could contribute to the observed outcome.

One particularly intriguing study suggests that immunosuppression may be conditioned in association with chemotherapy. Work by Bovbjerg and colleagues [45] assessed proliferative responses of PBLs to T cell mitogens in women

receiving chemotherapy for ovarian cancer. Comparisons of data obtained at home several days before a scheduled treatment showed greater lymphocyte proliferation when compared with samples drawn in the hospital just prior to the treatment, even after controlling for increased activity. Consistent with the interpretation of the process as conditioned immune suppression, patients also demonstrated an increase in conditioned nausea prior to treatment.

Other researchers have linked stress to poorer immune function in cancer patients whose immune systems are already affected by disease. Among 116 women recently treated surgically for invasive breast cancer, greater stress (assessed via a self-reported measure of intrusive and avoidant thoughts and behaviours related to cancer) was associated with lower proliferative responses of PBLs to mitogens and to a monoclonal antibody against the T cell receptor [2]. Importantly, stress was also related to lower NK cell lysis, as well as diminished responsiveness of NK cells to rIFN-γ.

Earlier studies from Levy and Herberman and colleagues [4, 5] had shown that three variables accounted for 51% of variance in baseline NK cell activity among women with breast cancer: patient 'adjustment', lack of social support and fatigue/depressive symptoms. On reassessment of NK cell activity after 3 months, the investigators found that they could account for 30% of the variance on the basis of baseline NK cell activity, fatigue/depression and lack of social support. Most importantly, NK cell activity remained markedly lower in patients with positive nodes than in patients with negative nodes, that is average levels of NK cell activity were lower for patients with greater tumour burden. Even though neither radiation nor chemotherapy appeared to be related to subsequent NK cell activity, tumour burden was again associated with NK cell activity.

Additional data collected from breast cancer patients were consistent with evidence described earlier linking NK cell activity with social support in healthy individuals [46]. Among women with stage I or II cancer, higher NK cell activity was associated with the perception of high-quality emotional support from a spouse or significant other, perceived social support from the patient's physician, oestrogen-receptor negative tumour status, having an excisional biopsy as surgical treatment, and actively seeking social support as a major coping strategy.

In summary, there is substantial evidence from both healthy populations under stress as well as individuals with cancer-associated psychological stress for immune downregulation. Stress may also enhance carcinogenesis through alternations in DNA repair and/or apoptosis [30, 31, 37]. Work by Bovbjerg and colleagues [45] suggests classical conditioning of immune suppression during chemotherapy, an important arena for further research. In addition, the possibility that psychological interventions may enhance immune function and survival among cancer patients clearly merits further exploration [42, 43], as does the evidence suggesting that social support may be a key psychological mediator. These studies and others suggest that psychological or behavioural factors may influence the incidence or progression of cancer through psychosocial influences on immune function.

1. Andersen BL, Kielcolt-Glaser JK, Glaser R. A biobehavioural model of cancer stress and disease course. *Am Psychol* 1994, **49**, 389–404.

2. Andersen BL, Farrar WB, Golden-Kretuz D, *et al*. Stress and immune responses after surgical treatment for regional breast cancer. *J Natl Cancer Inst* 1998, **90**, 30–36.
3. Bovbjerg DH. Psychoneuroimmunology: implications for oncology? *Cancer* 1991, **67**, 828–832.
4. Levy SM, Herberman RB, Maluish AM, Schlien G, Lippman M. Prognostic risk assessment in primary breast cancer by behavioural and immunological parameters. *Health Psychol* 1985, **4**, 99–113.
5. Levy SM, Herberman R, Lippman M, d'Angelo T. Correlation of stress factors with sustained depression of natural killer cell activity and predicted prognosis in patients with breast cancer. *J Clin Oncol* 1987, **5**, 348–353.
6. Spiegel D, Kato PM. Psychosocial influences on cancer incidence and progression. *Harv Rev Psychiat* 1996, **4**, 10–26.
7. Welsh RM. Regulation of virus infections by natural killer cells. *Natural Immunity Cell Growth Regul* 1996, **5**, 169–199.
8. Herberman RB, Ortaldo JR. Natural killer cells: their role in defenses against disease. *Science* 1981, **214**, 24–30.
9. Glaster R, Rice J, Speicher CE, Stout JC, Kiecolt-Glaser JK. Stress depresses interferon production by leukocytes concomitant with a decrease in natural killer cell activity. *Behav Neurosci* 1986, **100**, 675–678.
10. Irwin M, Daniels M, Bloom ET, Smith TL, Weiner H. Life events, depressive symptoms, and immune function. *Am J Psychiat* 1987, **144**, 437–441.
11. Dobbin JP, Harth M, McCain GA, Martin RA, Cousin K. Cytokine production and lymphocyte transformation during stress. *Brain, Behav Immun* 1991, **5**, 339–348.
12. Esterling B, Kiecolt-Glaser J, Bodnar J, Glaser R. Chronic stress, social support and persistent alterations in the natural killer cell response to cytokines in older adults. *Health Psychol* 1994, **13**, 291–299.
13. Esterling BA, Kiecolt-Glaser JK, Glaser R. Psychosocial modulation of cytokine-induced natural killer cell activity in older adults. *Psychosomat Med* 1996, **58**, 264–272.
14. Cohen S, Rabin B. Psychologic stress, immunity, and cancer. *J Natl Cancer Inst* 1998, **90**, 3–4.
15. Whiteside TT, Herberman RB. The role of natural killer cells in human disease. *Clin Immun Immunopathol* 1989, **53**, 1–23.
16. Page GG, Ben-Eliyahu S, Liebeskind JC. The role of LGL, NK cells in surgery-induced promotion of metastasis and its attenuation by morphine. *Brain Behav Immun* 1994, **8**, 241–250.
17. Kiecolt-Glaser JK, Garner W, Speicher CE, Penn G, Glaser R. Psychosocial modifiers of immunocompetence in medical students. *Psychosomat Med* 1984, **46**, 7–14.
18. Kiecolt-Glaser JK, Glaser R, Strain EC, *et al*. Modulation of cellular immunity in medical students. *J Behav Med* 1986, **9**, 311–320.
19. Glaser R, Rice J, Sheridan J, *et al*. Stress-related immune suppression: health implications. *Brain Behav Immun* 1987, **1**, 7–20.
20. Herberman R, Ortaldo J, Riccardi C, *et al*. Interferon and NK cells. In Merigan TC, Friedman RM, eds. *Interferons*. London, Academic Press, 1982, 287–294.
21. Kiecolt-Glaser JK, Glaser R, Williger D, *et al*. Psychosocial enhancement of immunocompetence in a geriatric population. *Health Psychol* 1985, **4**, 25–41.
22. Uchino BN, Cacioppo JT, Kiecolt-Glaser JK, *et al*. The relationship between social support and physiological processes: a review with emphasis on underlying mechanisms. *Psychol Bull* 1996, **119**, 488–531.
23. Irwin M, Daniel M, Risch SC, Bloom E, Weiner H. Plasma cortisol and natural killer cell activity during bereavement. *Biol Psychiat* 1988, **24**, 173–178.
24. Baron RS, Cutrona CE, Hicklin D, Russell DW, Lubaroff DM. Social support and immune function among spouses of cancer patients. *J Person Soc Psychol* 1990, **59**, 344–352.
25. Kiecolt-Glaser JK, Malarkey WB, Chee M, *et al*. Negative behaviour during marital conflict is associated with immunological down-regulation. *Psychosomat Med* 1993, **55**, 395–409.
26. Irwin M, Brown M, Patterson T, Hauger R, Mascovich A, Grant I. Neuropeptide Y and natural killer cell activity: findings in depression and Alzheimer caregiver stress. *FASEB J* 1991, **5**, 3100–3107.
27. Glaser R, Kiecolt-Glaser JK. *Handbook of Human Stress and Immunity*. San Diego, Academic Press, 1994.

28. Setlow RB. Repair deficient human disorders and human cancer. *Nature* 1978, **271**, 713–717.
29. Fox BH. Premorbid psychological factors as related to cancer incidence 1. *J Behav Med* 1978, **1**, 45–133.
30. Kiecolt-Glaser JK, Stephens R, Lipitz P, Speicher CE, Glaser R. Distress and DNA repair in human lymphocytes. *J Behav Med* 1985, **8**, 311–320.
31. Glaser R, Thorn BE, Tarr KL, Kiecolt-Glaser JK, d'Ambrosio SM. Effects of stress on methyltransferase synthesis: an important DNA repair enzyme. *Health Psychol* 1985, **4**, 403–412.
32. Fischman HK, Kelly DD. Sister chromatid exchanges induced by behavioural stress. *Ann New York Acad Sci* 1987, **496**, 426–435.
33. Dhillon VS, Dhillon IK. Chromosome aberrations and sister chromatid exchange studies in patients with prostate cancer possible evidence of chromosome instability. *Cancer Genetics* 1998, **100**, 143–147.
34. Li GY, Yao KT, Glaser R. Sister chromatid exchange and nasopharyngeal carcinoma. *Int J Cancer* 1989, **43**, 613–618.
35. Kanter P, Leister KJ, Tomei LK, Wenner PA, Wenner CE. Epidermal growth factor and tumor promoters prevent DNA fragmentation by different mechanisms. *Biochem Biophys Res Commun* 1984, **118**, 393–399.
36. Tomei LD, Kanter P, Wenner CE. Inhibition of radiation-induced apoptosis *in vitro*. *Biochem Biophys Res Commun* 1988, **155**, 324–331.
37. Tomei LD, Kiecolt-Glaser JK, Kennedy S, Glaser R. Psychological stress and phorbol ester inhibition of radiation-induced apoptosis in human PBLs. *Psychiat Res* 1990, **33**, 59–71.
38. Tomei LD, Noyes I, Blocker D, Holliday J, Glaser R. Epstein Barr virus dependent transformation of normal primary human skin epithelial cells. *Nature* 1987, **329**, 73–75.
39. Kiecolt-Glaser JK, Glaser R. Psychosocial moderators of immune function. *Ann Behav Med* 1987, **9**, 16–20.
40. Ucker DS. Cytotoxic T-lymphocytes and glucocorticoids activate an endogenous suicide process in target cells. *Nature* 1987, **327**, 62–64.
41. Kiecolt-Glaser JK, Glaser R. Psychoneuroimmunology: can psychological interventions modulate immunity? *J Consult Clin Psychol* 1992, **60**, 569–575.
42. Fawzy IF, Kemeny ME, Fawzy NW, *et al*. A structured psychiatric intervention for cancer patients. *Arch Gen Psychiat* 1990, **47**, 729–735.
43. Fawzy FI, Fawzy NW, Hyun CS, *et al*. Malignant melanoma: effects of an early structured psychiatric intervention, coping and affective state on recurrence and survival 6 years later. *Arch Gen Psychiat* 1993, **50**, 681–689.
44. Spiegel D, Bloom JR, Kraemer HC, Gottheil E, *et al*. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989, **2**, 888–901.
45. Bovbjerg DH, Redd WH, Maier LA, *et al*. Anticipatory immune suppression and nausea in women receiving cyclic chemotherapy for ovarian cancer. *J Consult Clin Psychol* 1990, **58**, 153–157.
46. Levy SM, Herberman RB, Whiteside T, Sanzo K, Lee J, Kirkwood J. Perceived social support and tumor estrogen/progesterone receptor status as predictors of natural killer call activity in breast cancer patients. *Psychosomat Med* 1990, **52**, 73–85.