DOI: 10.1093/annonc/mdf655

Psycho-oncology and cancer: psychoneuroimmunology and cancer

J. K. Kiecolt-Glaser[1,2,5], T. F. Robles[3], K. L. Heffner[1], T. J. Loving[1] & R. Glaser[2,4,5]

[1]Department of Psychiatry, [2]The Ohio State University Comprehensive Cancer Center, [3]Department of Psychology, [4]Department of Molecular Virology, Immunology and Medical Genetics, [5]The Institute for Behavioral Medicine Research, The Ohio State University Medical Center, Columbus, Ohio, USA

Introduction

A growing body of research linking psychological and behavioral factors to the incidence and progression of cancer suggests that psychosocial factors may have an impact on some types of cancer [1–6]. In this paper, we suggest that it is through the impact these behavioral and psychological factors have on the cellular immune response, including natural killer (NK) cell function, that they may ultimately affect the occurrence and progression of certain tumors. Our discussion of this link begins with a brief overview of the evidence that psychoneuroimmunology (PNI) research with healthy individuals may be relevant to cancer. Next, to link extant PNI research findings with tumorigenesis, we draw upon two important PNI findings relating psychological distress to two important aspects of carcinogenesis: (i) poorer repair of damaged cellular DNA and (ii) modulation of apoptosis. Finally, we focus on the implications of intervention research in cancer patients for cancer progression and treatment.

Before reviewing the evidence regarding stress-related immunological changes, it should be noted that one recurrent concern in the literature is the question of the significance of the immune system for cancer. Cancer is comprised of a heterogeneous group of diseases with multiple etiologies [1], and immunological involvement varies across different cancers. Those cancers that are induced by chemical carcinogens (e.g. lung cancer) may be less influenced by psychological, behavioral and immunological factors than cancers that are associated with a virus, such as Epstein–Barr Virus (EBV), which are immunogenic. Suppression of cellular immunity is associated with a higher incidence of certain types of tumors, particularly EBV-associated lymphoproliferative diseases in organ transplant patients, and Kaposi's sarcoma and EBV-associated B-cell lymphoma in AIDS patients [7]. Additionally, some researchers have questioned whether stress-related immune changes are of either the type or the magnitude to influence tumor growth and metastases [3, 8]. While such issues are beyond the scope of this paper, compelling evidence exists for the role of cells, such as NK cells, in resisting the progression and metastatic spread of tumors once they have developed [7].

Stress and immune dysregulation

Across a broad number of studies, stressors are associated with dysregulation of the immune system. In particular, decreased lymphocyte proliferation and reduced NK cell cytotoxicity are consistently observed in the literature [9]. As noted above, our discussion of stress-related immune changes highlights NK cells because of their importance for cancer [10]. NK cells play an important role in a variety of immune functions, including defense against viral infections [11] and surveillance of tumor cells [12]. NK cell cytotoxicity can be downregulated by stress, presumably through neuroendocrine mechanisms [5, 13, 14].

Cytokines such as interferon-γ (IFN-γ) and interleukin-2 (IL-2) can enhance NK cell and lymphocyte-activated killer (LAK) cell cytotoxicity [12]. There is evidence that stress can modulate IFN-γ and IL-2 synthesis by mitogen treated peripheral blood leukocytes (PBLs) [15, 16]. Interferon is a major regulator of NK cells, stimulating their growth and differentiation, as well as enhancing their ability to destroy target cells [7]. Among 40 second-year medical students, the production of IFN-γ 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 [13], a finding subsequently replicated across several exam series [15].

Studies using individuals who were caregiving for a spouse with Alzheimer's disease provided data on the immunological consequences of chronic stress in older individuals. One series of studies focused on NK cells. We examined differences in NK cell activity among current dementia spousal caregivers, former (bereaved) caregivers whose spouse had died, and noncaregiving controls. Consistent with other work [17], we found no differences in NK cell cytotoxicity in PBLs obtained from continuing or former caregiver groups or control subjects. However, PBLs from both continuing and former caregivers had a significantly poorer NK cell response to recombinant interferon-γ (rIFN-γ) or recombinant interleukin 2 (rIL-2) *in vitro* [18]. Moreover, caregivers who were low NK cell responders 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 who were high

responders to at least one of the two cytokines. A follow-up study using effector cell preparations enriched for NK cells (approximately 90%) replicated the previously observed group differences between caregivers (current and former) and controls [19].

Several subsequent studies have also suggested a link between personal relationships and NK cell cytotoxicity, consistent with the wide range of literature on social support and health [20]. For example, bereaved spouses had elevated cortisol and decreased NK cell activity [21]. Among spouses of cancer patients, those who reported lower levels of social support had lower levels of NK cell cytotoxicity [22]. 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 [23]. Evidence using rodent models shows that social stressors not only decrease NK cell cytotoxicity, they also enhance metastasis of transplantable tumors [24, 25].

Collectively, these studies demonstrate that stress can dysregulate NK cell function, including depressing the stimulatory response of NK cells to cytokines. Psychosocial factors may also act in concert with other risk factors for cancer to promote immune dysregulation. For instance, depression and smoking had synergistic effects on reduced NK cell lysis [26]. It should be noted that there is good evidence that several aspects of the cellular immune response are also adversely affected by psychosocial stress [9, 27]. It is, therefore, possible that stress could alter potentially important defenses against malignant disease.

The past two decades of PNI research on stress and cancer have primarily focused on nonspecific immune responses, including NK cell function, mitogen stimulation of PBLs and subsequent cytokine production. An important future direction for PNI and cancer research is exploring tumor-specific T-cell and antibody responses to immunogenic tumors [28].

Effects of psychological distress on cellular DNA repair and apoptosis

In the previous section, we presented evidence that psychological stress can affect the ability of NK cells to function properly, and thereby have an impact on one aspect of how the immune system defends the body against the spread of tumor cells. Stress may also have a direct effect on the initiation and/or production of abnormal cells independent of the immune system. Most carcinogens appear to induce tumors by damaging cellular DNA producing abnormal cells [29]. The body's defenses against this process include enzymes that destroy chemical carcinogens, processes for repairing damaged cellular DNA and the destruction of abnormal cells by the immune system [30]. Given that faulty DNA repair is associated with an increased incidence of abnormal cells [29], the processes for repair or destruction of damaged cellular DNA are critical when it comes to defending the body against carcinogens.

The possibility of a linkage between emotional distress and DNA repair was explored in a study using PBLs obtained from 28 nonpsychotic, nonmedicated new psychiatric admissions and 28 age- and gender-matched blood bank controls [31]. Following exposure to X-radiation, lymphocytes from psychiatric patients demonstrated greater impairments, relative to controls, in their ability to repair damaged cellular DNA. In addition, within the inpatient group, those patients who were more depressed showed significantly poorer repair of damaged DNA than their less depressed counterparts.

An additional study also suggests that stress may alter the DNA repair process [32]. Forty-five rats, half of which were assigned to a rotational stress condition, ingested the carcinogen dimethylnitrosamine. The levels of methyltransferase, an important DNA repair enzyme induced in response to carcinogen damage, were significantly lower in stressed animals' spleenic lymphocytes. 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 [32].

In a more recent study utilizing an academic stress model, DNA repair capacity (DRC) of 16 first- and second-year medical students was assessed using a host-cell reactivation assay [33]. An index of DNA damage, DRC refers to the ability of cells with damaged DNA to self-repair, a necessary process for maintaining a normal cell cycle. In this study, DRC was positively associated with medical students' levels of perceived stress. Although these findings are in apparent contrast with the psychiatric inpatient study [31], the authors caution that a number of important methodological differences between the two studies warrant consideration and do not necessarily imply that the studies contradict each other (e.g. characteristics of subject populations, assays employed to measure DNA repair, the impact of acute versus chronic stress). Clearly additional research is warranted in order to gain a fuller understanding of the role of psychosocial stressors on DNA repair. Importantly, regardless of the interpretation of the results, both of these studies suggest that psychosocial factors may impact on DNA repair. Thus, it is possible that stress might have direct effects on carcinogenesis through alteration in DNA repair, as well as affecting the ability of the specific and innate immune responses to eliminate growth-transformed as well as fully malignant cells.

In addition to the effects of stress on DNA repair, additional research has documented the impact of stress on apoptosis, a process of genetically programmed alterations in cell structure that leads to failure of proliferation and differentiation, and eventual cell suicide [34]. Control of the expression of apoptosis is critical to the function of several cell types, including target cells of cytotoxic effector cells. Therefore, the inhibition of apoptosis could result in suppression of immune function.

Utilizing an academic stress paradigm Tomei et al. [34] studied phorbol ester inhibition of radiation-induced apoptosis in PBLs obtained from medical students during an examination and at a time point before and after the examination.

Low concentrations of a tumor-promoting phorbol ester specifically blocked apoptosis induced by either growth factor deprivation or ionizing radiation [35, 36]; examination stress enhanced this process.

Toxic stress induced by treatment may also curb the efficacy of some anti-tumor cancer therapies. Specifically, cytotoxic insults that result from virus infection, chemical exposure or ionizing radiation can elicit the expression of gene-directed cell death marked by the appearance of extensive and characteristic fragmentation of cellular DNA. Szende et al. [37] presented evidence that the anti-tumor effects of analogs of somatostatin and luteinizing hormone releasing hormone are a consequence of their effect on control of apoptosis. These actions may involve the restoration of the ability of the tumor cells to initiate apoptosis. Thus stress-related modulation of apoptosis could have maladaptive consequences. The data obtained in this study provide additional evidence of pathways through which psychological stress could contribute to increased cancer risk by modifying cell responses to environmental factors such as tumor promoters and oncogenic viruses [38]. These physiological changes could operate independently and/or in conjunction with the stress-induced immune dysregulation described earlier [39]. This is especially pertinent since it has been demonstrated that target cell death requires gene expression and initiation of apoptosis [40]. If these interpretations are correct, then psychosocial stressors could ultimately lead to progressive accumulation of errors within cell genomes as well as reducing tumor specific and innate immune responses.

PNI and cancer progression: behavioral interventions and treatment issues

The research discussed to this point suggests mechanisms whereby psychosocial stressors could play a role in the immunological and cellular processes that underpin tumor development; however, difficulties arise when attempts are made to directly link psychosocial stressors and tumor development/progression in humans [1]. Importantly, the stage of disease can have a profound effect on how patients feel, and cancer treatments such as chemotherapy and radiation therapy are associated with a number of side effects, including immunological alterations.

In a study of 45 healthy, older adults who were randomly assigned to one of three protocols (relaxation training, social contact 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 to nonsignificant changes in the other two groups [41]. These data provided the first well-controlled demonstration of immune enhancement via a behavioral intervention. Following this initial demonstration of a behaviorally mediated enhancement of NK cell activity among older adults [41], a number of researchers have confirmed these findings that stress-reducing interventions can improve immune function [42].

Well-designed behavioral intervention studies hold great promise for the understanding of psychoneuroimmunological processes associated with cancer progression providing investigators take into account such issues as disease stage and treatment. By randomly assigning patients who have the same tumor histopathology and stage of disease to control and intervention conditions, it may be possible to assess psychological, immunological and clinical outcomes in a meaningful way.

One of the most comprehensive intervention studies in cancer research 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 and stress management techniques, such as relaxation, and psychological support [43, 44]. The patients had stage I or II malignant melanoma and had not received any treatment after surgical excision of the tumor. Noteworthy effects included reduced psychological distress and significant immunological changes in intervention patients compared with controls; the former showed significant increases in the percentage of NK cells, as well as an increase in NK cell cytotoxic activity, compared with controls.

A 6-year follow-up of these patients showed a trend toward greater recurrence, as well as higher mortality rates among patients in the control group when compared with patients in the intervention group [44]. The group differences remained significant after adjusting for the size of the initial tumor lesion, a key risk factor.

Results of studies examining the longer-term effects of interventions on survival outcomes of cancer patients have been inconsistent. Spiegel et al. [45] 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. More recently, in an attempt to replicate the results of Spiegel et al. [45], Goodwin et al. [46] found no difference in survival for metastatic breast cancer patients who received supportive-expressive group therapy when compared with controls, but the support group did exhibit improved mood and perception of pain compared with controls. Other studies have also yielded inconsistent results [47], but aside from the work of Fawzy et al. [43, 44], much of the survival research has not attended to shorter-term alterations in immune function concurrent with behavioral interventions. Without such information, it is difficult to discern whether the psychosocial effects of interventions were also accompanied by immunological changes, which may be necessary to enhance longevity of cancer patients. Further, as noted by Spiegel et al. [45], patients in the intervention condition could have been more compliant with medical treatment, and/or they might have had better health behaviors such as exercise and diet. Such behavioral differences could have contributed to the observed outcome. These uncertainties illustrate the need for further comprehensive study of both

shorter-term immunological effects of interventions and their associated, longer-term morbidity and mortality outcomes. The differences in the outcome of studies by Fawzy et al. [43, 44] and the breast cancer intervention studies [45, 46] may be related to the fact that malignant melanoma is an immunogenic tumor. If behavioral intervention is employed as a procedure to up-regulate the immune response to a tumor, studying patients with immunogenic tumors should enhance the possibility of showing some clinical outcome.

Finally, 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 behaviors 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. These findings suggest that therapeutic interventions could be beneficial in the reduction of both the stress associated with cancer and the concomitant stress-related immune down-regulation.

In summary, there is substantial evidence from both healthy populations as well as individuals with cancer linking psychological stress with immune dysregulation. Stress may also enhance carcinogenesis through alterations in DNA repair and/or apoptosis [31–33]. In addition, the possibility that psychological interventions may enhance immune function and survival among cancer patients is still an open question [43, 44], as is the evidence suggesting that social support may be a key psychological mediator. However, these studies and others suggest that psychological or behavioral factors could influence the initiation/progression of cancer. Further studies to explain these relationships need to be performed.

Acknowledgements

Work on this article was supported by grants R37 MH42096, K02 MH01467, T32 MH18831, P01 AG16321, MO1-RR-0034, and P50 DE13749, and an NSF Graduate Research Fellowship to the second author.

References

1. Andersen BL, Kiecolt-Glaser JK, Glaser R. A biobehavioral model of cancer stress and disease course. Am Psychol 1994; 49: 389–404.
2. Andersen BL, Farrar WB, Golden-Kreutz 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 et al. Prognostic risk assessment in primary breast cancer by behavioral and immunological parameters. Health Psychol 1985; 4: 99–113.
5. Levy S, Herberman RB, Lipmann 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. Harvard Rev Psychiatry 1996; 4: 10–26.
7. Herberman RB. Immunotherapy. In Lenhard RE Jr, Osteen RT, Gansler T (eds): Clinical Oncology. Atlanta, GA: American Cancer Society 2001; 215–223.
8. Cohen S, Rabin B. Psychologic stress, immunity, and cancer. J Natl Cancer Inst 1998; 90: 3–4.
9. Zorrilla EP, Luborsky L, Mackay JR et al. The relationship of depression and stressors to immunological assays: A meta-analytic review. Brain Behav Immun 2001; 15: 199–226.
10. Whiteside TT, Herberman RB. Role of natural killer cells in human disease. Clin Immunol Immunopathol 1989; 53: 1–23.
11. Welsh RM. Regulation of virus infections by natural killer cells. Nat Immun Cell Growth Regul 1996; 5: 169–199.
12. Herberman RB, Ortaldo JR. Natural killer cells: Their role in defenses against disease. Science 1981; 214: 24–30.
13. Glaser R, Rice J, Speicher CE et al. Stress depresses interferon production by leukocytes concomitant with a decrease in natural killer cell activity. Behav Neurosci 1986; 100: 675–678.
14. Irwin M, Daniels M, Bloom ET et al. Life events, depressive symptoms, and immune function. Am J Psychiatry 1987; 144: 437–441.
15. Dobbin JP, Harth M, McCain GA et al. Cytokine production and lymphocyte transformation during stress. Brain Behav Immun 1991; 5: 339–348.
16. Glaser R, Rice J, Sheridan J et al. Stress-related immune suppression: Health implications. Brain Behav Immun 1987; 1: 7–20.
17. Irwin M, Daniels M, Smith TL et al. Impaired natural killer cell activity during bereavement. Brain Behav Immun 1987; 1: 98–104.
18. Esterling BA, Kiecolt-Glaser JK, Bodnar JC, 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.
19. Esterling BA, Kiecolt-Glaser JK, Glaser R. Psychosocial modulation of cytokine-induced natural killer cell activity in older adults. Psychosom Med 1996; 58: 264–272.
20. Uchino BN, Cacioppo JT, Kiecolt-Glaser JK. The relationship between social support and physiological processes: A review with emphasis on underlying mechanisms and implications for health. Psychol Bull 1996; 119: 488–531.
21. Irwin M, Daniels M, Risch C et al. Plasma cortisol and natural killer cell activity during bereavement. Biol Psychiatry 1988; 24: 173–178.
22. Baron RS, Cultrona CE, Hicklin D et al. Social support and immune function among spouses of cancer patients. J Pers Soc Psychol 1990; 59: 344–352.
23. Kiecolt-Glaser JK, Malarkey WB, Chee M et al. Negative behavior during marital conflict is associated with immunological down-regulation. Psychosom Med 1993; 55: 395–409.
24. Stefanski V. Social stress in laboratory rats: Behavior, immune function, and tumor metastasis. Physiol Behav 2001; 73: 385–391.
25. Wu W, Yamamura T, Murakami K et al. Social isolation stress enhanced liver metastasis of murine colon 26-L5 carcinoma cells by suppressing immune responses in mice. Life Sci 2000; 66: 1827–1838.
26. Jung W, Irwin M. Reduction of natural killer cytotoxic activity in major depression: Interaction between depression and cigarette smoking. Psychosom Med 1999; 61: 263–270.

27. Glaser R, Kiecolt-Glaser JK (eds). Handbook of Human Stress and Immunity. San Diego, CA: Academic Press 1994.
28. Finn OJ. Assessing the important effector mechanisms in the immune response against cancer. In Baum A and Andersen BL (eds): Psychosocial Interventions for Cancer. Washington, DC: American Psychological Association 2001; 175–191.
29. Setlow RB. Repair deficient human disorders and human cancer. Nature 1978; 271: 713–717.
30. Fox BH. Premorbid psychological factors as related to cancer incidence. J Behav Med 1978; 1: 45–133.
31. Kiecolt-Glaser JK, Stephen RE, Lipetz PD et al. Distress and DNA repair in human lymphocytes. J Behav Med 1985; 8: 311–320.
32. Glaser R, Thorn BE, Tarr KL et al. Effects of stress on methyltransferase synthesis: An important DNA repair enzyme. Health Psychol 1985; 4: 403–412.
33. Cohen L, Marshall GD, Cheng L et al. DNA repair capacity in healthy medical students during and after exam stress. J Behav Med 2000; 23: 531–544.
34. Tomei LD, Kiecolt-Glaser JK, Kennedy S, Glaser R. Psychological stress and phorbol ester inhibition of radiation-induced apoptosis in human PBLs. Psychiatry Res 1990; 33: 59–71.
35. Tomei LD, Kanter P, Wenner CE. Inhibition of radiation-induced apoptosis *in vitro*. Biochem Biophys Res Commun 1988; 155: 324–331.
36. Kanter P, Leister KJ, Tomei LD et al. Epidermal growth factor and tumor promoters prevent DNA fragmentation by different mechanisms. Biochem Biophys Res Commun 1984; 118: 392–399.
37. Szende B, Srkalovic G, Schally AV et al. Inhibitory effects of analogs of luteinizing hormone-releasing hormone (LH-RH) and somatostatin on pancreatic cancers in hamsters: Events which accompany tumor regression. Cancer 1990; 65: 2279–2290.
38. Tomei LD, Noyes I, Blocker D et al. Epstein–Barr virus dependent transformation of normal primary human skin epithelial cells. Nature 1987; 329: 73–75.
39. Kiecolt-Glaser JK. Norman Cousins Memorial Lecture 1998. Stress, personal relationships, and immune function: Health implications. Brain Behav Immun 1999; 13: 61–72.
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, Wiliger D et al. Psychosocial enhancement of immunocompetence in a geriatric population. Health Psychol 1985; 4: 25–41.
42. Kiecolt-Glaser JK, Glaser R. Psychoneuroimmunology: can psychological interventions modulate immunity? J Consult Clin Psychol 1992; 60: 569–575.
43. Fawzy IF, Kemeny ME, Fawzy NW et al. A structured psychiatric intervention for cancer patients. Arch Gen Psychiatry 1990; 47: 729–735.
44. 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 Psychiatry 1993; 50: 681–689.
45. Spiegel D, Bloom JR, Kraemer H, Gottheil E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. Lancet 1989; 2: 888–901.
46. Goodwin PJ, Leszcz M, Ennis M et al. The effect of group psychosocial support on survival in metastatic breast cancer. N Engl J Med 2001; 345: 1719–1726.
47. Edelman S, Craig A, Kidman AD. Can psychotherapy increase the survival time of cancer patients? J Psychosom Res 2000; 49: 149–156.