

## Psychologic Stress, Immunity, and Cancer

Sheldon Cohen, Bruce S. Rabin\*

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Why publish an article in a major cancer journal that demonstrates an association between psychologic stress and cellular immune function in cancer patients? The potential interest in articles such as Andersen et al. (1), published in this issue of the Journal, is based on the premise that stress may alter the function of the immune system in a manner that influences the development or growth of malignant tissue. This premise is quite controversial and we use this editorial to discuss its underlying assumptions.

1) *Psychologic stress can alter immune function.*

There is evidence for a number of mechanisms through which psychologic stress might alter immune function (2). These include direct innervation of lymphatic tissue by the central nervous system and stress-elicited release of hormones from the brain that bind to and alter the functions of immunologically active cells. The mechanisms also include behavioral changes that often occur in response to stress: an increase in smoking, an increase in drinking alcohol, a loss of sleep, a reduction in exercise, a degradation of the diet, and a decrease in adherence to medical regimens.

In fact, healthy humans exposed to stressful tasks that last only a few minutes, including difficult cognitive tasks and tasks that induce social anxiety, show suppression of T-cell mitogenesis, and increased numbers of circulating CD8 and natural killer cells (3). Studies of real-life stressors show similar alterations. Living near the Three Mile Island nuclear power plant at the time of the accident, caretaking for a relative with Alzheimer's disease, taking medical school examinations, and clinical depression have all been associated with alterations in both the numbers and functions of various subpopulations of lymphocytes (4). These alterations include a reduced proliferative response to mitogen stimulation, reduced natural killer cell cytotoxicity, as well as changes in the production of cytokines. Although the range of stress' effects on immune function is

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\*Affiliations of authors: S. Cohen, Department of Psychology, Carnegie Mellon University, Pittsburgh, PA; B. S. Rabin, Department of Pathology, University of Pittsburgh School of Medicine.

Correspondence to: Sheldon Cohen, Ph.D., Department of Psychology, Carnegie Mellon University, Pittsburgh, PA 15213.

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wide, the magnitude of the effects is small, with stress-suppressed patients usually functioning within the normal range.

2) *The immune system plays a role in regulating tumor growth.*

Burnet (5) promoted the "immune surveillance" theory which postulated that the immune system was capable of eliminating neoplastic cells that developed in the normal individuals. It is likely that the mechanisms of cellular immunity are important to the functioning of immune surveillance. Indeed, subjects who undergo suppression of immune function by pharmacologic means, or who have immunodeficiency diseases, have an increased risk of cancer. This has led to the experimental use of treatment strategies designed to increase the function of the immune system and to focus immune reactants at the site of malignant tissue. The use of immune-enhancing therapies, primarily in patients with malignant melanoma and renal cell carcinoma, has produced limited antitumor responses (6).

3) *Immune changes under stress are of the type that would influence tumor growth and metastasis.*

There are a variety of stress-induced changes in lymphocyte surface molecules, the potential for cell division, and cytokine production that may play a role in immune regulation of cancer growth. Although there is no direct evidence associating these changes in immunity with disease progression in patients with cancer, animal models suggest that the antitumor cytotoxicity of CD8 and NK lymphocytes and the localized inflammatory response mediated by CD4 lymphocytes may influence tumor growth and metastasis (7). These data are suggestive, but specific immune mechanisms that may suppress cancer in humans are not yet known. Therefore, it is speculative at best to assume that psychologic stress modifies immune components involved in the regulation of tumor growth in cancer patients.

4) *Immune changes under stress are of the magnitude that would influence tumor growth and metastasis.*

The evidence for an association between suppressed immune function and the onset of cancer derives from cases of profound immunosuppression. These cases include tissue transplant recipients receiving immunosuppressive drugs and individuals with immunodeficiency diseases. However, the associations between stress and immune system function is quite mild in other individuals, with immune function still remaining within normal parameters (4). Such changes seem unlikely to have a clinically significant effect on tumor growth. Even so, stress has been found to be an important predictor of other diseases that occur when there is a failure in immune regulation, including greater susceptibility to and severity of respiratory infections and the onset and severity of autoimmune diseases (4). That stress is a risk factor for these diseases raises the possibility that even small stress-induced changes in immune function might be important clinically. It also suggests that, even if stress does not influence the course of cancer, it might alter the risk of infection and for other immune-related diseases, especially among patients receiving chemotherapy.

5) *Stress-reduction interventions will influence the progression of disease.*

There is evidence that the reduction of stress by the provision of social support may be associated with an amelioration in the course of some malignant diseases. For example, a study of women with metastatic breast cancer showed an 18-month increase in survival (8), and a study of men and women with melanoma showed increased survival and reduced recurrence after 5–6 years (9). Although the latter study found that the intervention was also effective in increasing natural killer cell cytotoxicity, no associations were observed between this change in immune function and disease recurrence or mortality.

It can be argued that attempts to increase immune function by stress reduction strategies may have only limited effects on immunity and consequently on disease progression. Moreover, the effectiveness of these interventions may be further reduced by the influence of chemotherapeutic agents on immune function. Nevertheless, the provocative findings that social support interventions reduce mortality are hard to ignore. However, it is not clear that the effects of these interventions on mortality are mediated through immune mechanisms. It is possible that the interventions might work through other pathways, such as by increasing adherence to medication or nutritional regimens or by ameliorating the direct effects of stress-induced endocrine response on tumor growth.

In sum, Andersen et al. (1) have linked psychologic experience to immunity in patients whose immune systems are already compromised by disease. The question remains whether the immune changes associated with stress have implications for cancer progression and metastasis. If they do, it also remains to be seen whether stress-reduction interventions can ameliorate cancer progression through immune enhancement. The article by Andersen et al. provides an important piece of this fascinating puzzle, but the solution is still a ways off.

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