Abstract

Although the last decades have provided ample evidence for deleterious effects of stress on immunity and on cancer development and suggested mediating mechanisms, no psychoneuroimmunology (PNI)-related intervention has become a standard of care in conventional cancer treatment. We believe the reasons for this include the unique nature of cancer evolvement and interactions with the immune system, and the many conceptual and technical obstacles to studying stress effects on immune activity and their implications for human resistance to malignancy. However, the numerous and diverse interactions between malignant tissue and immunocytes are now better understood, and suggestions can be made with respect to certain critical periods to be investigated in cancer-PNI research. Animal models of cancer progression are instrumental in suggesting neuroendocrine and immunological mediators of stress effects on specific aspects of cancer progression, especially with respect to the role of NK cell activity. The ultimate clinical relevance, however, must be tested in cancer patients. Recent animal studies suggest a role for the sympathetic nervous system in mediating biologically relevant stress effects on immunity and on tumor progression. Related interventions can now be tested in patients to support or refute the promise of such studies.

1. Introduction: the unique nature of the disease and the challenges

A major theme in psychoneuroimmunology (PNI) has been the promise of clinical interventions for immune-related diseases, of which cancer has been paradigmatic. PNI, through numerous publications in *Brain, Behavior, and Immunology* (BBI) and other journals, has showcased observations of stress effects on cancer and on immune processes, and has looked with anticipation for breakthroughs in cancer immunology that would bring its various elements together. However, cancer differs in several respects from most diseases and pathogens that interact with the immune system, providing special challenges for both tumor immunologists and PNI researchers.

1.1. The unique nature of the disease: cancer immunology

Cancer cells evolve from normal cells by acquiring numerous genetic mutations that eventually foster unchecked proliferation, increased mutation rates, and reduced sensitivity to apoptotic signals and cytotoxicity by immunocytes. In the process, surface antigens presented by transformed cells become altered in a variety of ways that initially promote immune responses, but at the final stages of tumor evolvement enable some malignant cells to escape from immune recognition. Accordingly, the stringency of immune surveillance for cancer cells varies considerably through the stages of tumor development and spread. Newly transformed tissue is initially exposed to immunocytes only when it attracts blood capillaries and emits various danger signals (Fuchs and Matzinger, 1996). At this stage, the malignancy commonly expresses sufficient mutations to become immunogenic. This initiates an “evolutionary” process through which selection pressure by the immune system upon malignant cells, if not
eradicating the evolving tumor, increases the proportion of resistant malignant cells. Remaining malignant cells continue to mutate intensively, acquiring additional escape mechanisms that can yield an immune-resistant malignancy. In the clinical cancer patient, the primary tumor has already outmaneuvered the immune system. However, the survival prospects for an individual transformed cell in a healthy individual are unknown but, fortunately, are likely to be poor.

The process of malignant initiation, selection, and metastatic formation in humans may span years to decades, depending on cancer type. Eventually, successful primary tumors exhibit a host of mechanisms to escape the broad range of processes used by the immune system to recognize and destroy malignant cells (Pawelec, 2004). However, when cancer cells metastasize, they are subjected to a more intense immune selection pressure. Metastasizing single tumor cells are not protected by immunosuppressive ligands released by primary tumors, and often encounter new populations of leukocytes in new host microenvironments. Not surprisingly, malignant cells at “established” metastatic foci commonly exhibit escape mechanisms that are more elaborate than those of the primary tumor (Shakh and Ben-Eliyahu, 2003).

1.2. Implications for PNI research

Cancer-PNI research occurs in the context of the prolonged cancer auto-evolutionary process described above. The complex course of cancer evolvement alongside immune responses identifies unique points of interest. As the operational challenges of research design in this field are daunting, research models focusing on such critical points present an advantage, and are only now beginning to be developed.

Clearly, the relationships between immune competence and tumor initiation and progression are multifarious. Not only are the pathophysiology and natural history of various tumors heterogeneous, but also the consequences of host–tumor interactions will vary as a function of the unique conditions associated with different points in tumor progression. It has been considered almost a truism that the earlier a tumor is detected, the less elaborate are its escape mechanisms and the greater the chances for effective immune surveillance and treatment. Cancer types that are more readily detected early in their “evolutionary” process, such as some melanomas, HPV-associated malignancies, and breast cancers, may be more susceptible to immune effects and to modulation by stress and psychological factors. Developments in cancer immunology call attention to other scenarios as well. For example, although a competent immune response may favor eradication of malignant foci, the increased selection pressure may also yield more aggressive and resistant tumor cells. By contrast, suppressed immune competence permitting tumor growth may favor less sophisticated tumor escape mechanisms, rendering the malignancy susceptible to improved immune responses at later stages. Indeed, studies indicated that malignancies that develop in immuno-deficient animals exhibit fewer and less elaborated escape mechanisms (Shakh and Ben-Eliyahu, 2003). Thus, alterations in immune competence may affect tumor incidence and progression in specific relation to the kinetics of the immune–cancer interactions. In the research agenda, PNI effects would be expected to occur either when induced immune alterations (e.g., suppression) are sustained for a prolonged period overlapping with tumor development, or when acute immune alterations are synchronized with critical periods in immune–cancer interaction. Such critical periods would include the initial vascularization of malignant foci (the first immune interaction with cancerous tissue) and initial phases of the metastatic process in which single tumor cells are accessible and vulnerable to destruction by leukocytes.

The history of cancer-PNI may be viewed largely as an accumulation of research studies that, in the early phases, sought to establish links between stress and cancer in humans and animals, largely focused on cancer incidence (rather than progression), and had limited power to investigate pathophysiologic mechanisms concurrently. Potential mechanisms were considered in a separate line of studies investigating stress effects on immune processes considered relevant to tumorogenesis (e.g., NK cells). This approach is ultimately limited by its inability to study PNI mechanisms within the specific neoplastic process, and specific interventions to alter the course of disease would tend to be based on speculative extrapolations. As noted above, putative stress effects on cancer in such models would best be detected using stressors that are sustained over extended periods and, therefore, likely to be present during the “unseen” critical periods of tumor development. Indeed, Lutgendorf et al. observed that stressful life events that are sporadic in nature may not, in general, be demonstrably associated with cancer incidence, in contrast to prolonged conditions of immune change, such as with depressive disorders or bereavement (Lutgendorf et al., 2007).

Acute effects, however, would be detectable in animal models that could isolate critical points in tumor growth. One such point, which has been used as a model in one line of recent research (see below) is the surgical intervention for removal of a primary tumor. Surgical stress promotes a shift toward a pro-angiogenic balance, and the surgical procedure causes ample release of growth factors and the shedding of tumor cells to the circulation. At this high risk period for the outbreak of dormant or new metastases, immune status may become a prominent factor in determining long-term recurrence (see Fig. 1). Importantly, psychological and physiological stress responses were suggested to suppress cellular immunity in the peri-operative context (Greenfeld et al., 2007), and this suppression could be a target for PNI interventions. Another critical period for cancer development, which may provide useful future models, is pregnancy, during which pro-angiogenic and growth factors are in excess and may promote...
vascularization of dormant malignant foci. Third, scheduling stress to coincide with the exact period of environmentally induced carcinogenesis (e.g., by UV light) may show impact even on tumor initiation (Saul et al., 2005).

1.3. The challenges

Questions posed for the cancer-PNI researcher may be grouped into three categories:

(1) Phenomenological questions: (a) what types of stressors or psychological states affect tumor initiation and tumor progression? (b) to what degree do such potential modulating effects of stress interact with genetic makeup, personality traits, and cancer types? and (c) do such stressors suppress anti-cancer immune functions, including NK activity?

(2) Mechanistic questions regarding neuroendocrine and immunological mediators of stress effects: (a) which neural and neuro-endocrine responses (e.g., systemic catecholamine secretion by the adrenal medulla) impact specific aspects of cancer immunity? (b) which immunologic perturbations alter critical aspects of tumor immunity (e.g., reduced dendritic cell release of IL-12 leading to reduced NK activity)? and (c) most challenging: can we demonstrate that suppression of a specific immune index by stress underlies tumor initiation or progression? This ultimately requires distinguishing PNI from non-immunologic stress-related processes in tumor progression such as stress hormone promotion of DNA damage (Flint et al., 2007), secretion of pro-angiogenic factors by human tumor cells, and increased tumor invasiveness (Antoni et al., 2006; Thaker et al., 2006).

(3) Therapeutic relevance: can we develop psychological and physiological interventions to overcome the deleterious effects of PNI processes on immunity and tumor progression? Such interventions may include psychological/behavioral-cognitive approaches, or pharmacotherapies (e.g., benzodiazepines or β-adrenergic blockers) to modulate stress responses.

The following sections will highlight some of the work in this field published both within BBI and elsewhere, in the context of the above themes, and will further elaborate on technical and conceptual obstacles conducting these studies.

2. Before 1987: looking for effects (and finding some)

Early studies of stress effects on cancer and the role of NK and other immune factors were summarized in a thoughtful 1978 news article in Science (Holden, 1978). The state of the science and art at the time (and some might say, even today) might be described as a combination of hopeful anticipation, unbridled speculation, and scientific skepticism. Classic papers in the “psychosomatic” literature had reported that certain stressors and certain depressive reactions to stressful events were more common in patients bearing malignancies, including cancers of the cervix and breast (Katz et al., 1970; Schmale and Iker, 1966), and an epidemiologic study suggested that psychological depression predicted increased cancer risk over the long-term (Shekelle et al., 1981). Animal studies found that stressors could increase tumor growth (Riley, 1981), that similar stressors could suppress in vitro immune measures, including lymphocyte proliferation and NK activity, and that these effects, as further described below, were not strictly related to secretion of corticosteroids (Keller et al., 1983; Shavit et al., 1987). Studies in humans showed the effects of stress, bereavement, and depression on in vitro immune measures (Lutgendorf et al., 2007). Enthusiasm for curing cancer through psychological strategies ran high in certain clinical circles, engendering a scientific backlash supported by studies failing to detect associations between psychological factors and tumor development. Among the “highlights” was an editorialized article in NEJM emphasizing the failure to detect psychosocial correlates of progressive malignant disease (Angell, 1985). As the following decade opened, several landmark but still controversial studies in humans found beneficial effects of structured group therapy interventions on the course of breast cancer and malignant melanoma, the latter associated with concurrent enhancement of the NK cell system (Fawzy et al., 1990; Spiegel et al., 1989). While far from convincing the skeptics (and not having replication), such studies provided some support for the hypothesis that behavioral interventions could influence the course of neoplastic disease, and that immune system changes might play a mediating or modulating role.

3. 1987–1997: attempts to identify mechanisms of NK suppression in the context of methodological obstacles

Shortly after following description of the phenomenon of stress-induced NK suppression, the search for mediating
neuroendocrine mechanisms began. Several candidate mediators were identified, most notably corticosteroids and opioids (Shavit et al., 1984; Sundar et al., 1990; Tseng et al., 2005), however, evidence supporting an in vivo role for these factors was not compelling. Although corticosteroids are potent in vitro suppressors of NK activity, physiological stress levels of these steroids were not shown categorically to suppress NK activity in vivo (Gatti et al., 1987; Irwin et al., 1988), and some studies provided evidence refuting such claims (Bodner et al., 1998; Wrona et al., 2001). With opiates, exogenous ligands including morphine and fentanyl were shown to suppress NK activity and increase cancer susceptibility (Shavit et al., 1987, 2004), however, these effects commonly occurred following pharmacological doses that also elicit other stress responses (including sympathetic nervous system (SNS)) that can directly suppress NK activity (Gan et al., 2002). The systemic release of endogenous opioids by stress has not been implicated in biologically significant suppression of NK activity, although brain opiate and CRF mechanisms may be important mediators of stress or brain-stimulation effects on NK activity (Irwin et al., 1987, 1990; Shavit et al., 1986; Weber and Pert, 1989).

The study of in vivo functions of NK cells and their activity against autologous cancer cells was hindered at the time by several major obstacles. Most of these obstacles remain relevant today and are hard to overcome in humans, but several are surmountable. First, recognition and response of NK cells to autologous malignant cells are based on a balance between numerous intracellular signals delivered by activating and inhibiting NK receptors that specifically interact with certain tumor determinants. Thus, the in vivo impact of these factors on NK activities may not be reflected in the in vitro assessment, unless they are “remembered” through some cellular mechanisms. Although NK cells can retain some information, many in vivo effects on NK cells were shown to be transient (Breznitz et al., 1998). Such effects should not be expected to be truly reflected in an ex-vivo approach following prolonged procedures that delay the testing and do not maintain the in vivo milieu.

Last, NK activity is often assessed without assessing the numbers of NK cells in the tested samples. In such cases, it is impossible to determine whether alterations in NK activity reflect altered cytotoxicity per NK cell, or result from altered numbers of NK cells. Moreover, a number of PNI studies in humans have found that effects on NK activity and on the number of circulating NK cells are often dissociated (Schleifer et al., 2006). Numbers of circulating NK cells fluctuate quickly and dramatically in response to stress hormones (including steroids and catecholamines) as a result of NK cell redistribution among the different immune compartments (Benschop et al., 1997; Dhabhar et al., 1995). Also, total host numbers of NK cells change in response to apoptotic and growth signals, although over days rather than minutes. Accordingly, observations of altered circulating NK activity is difficult to interpret without considering fluctuations in NK numbers and in NK activity in other immune compartments.

By the close of the decade, the shortcomings of studies using ex-vivo approaches were quite apparent and led to the adoption of in vivo approaches that assessed NK activity using various tumor models (Ben-Eliyahu and Page, 1992). Such approaches have their own limitations, but have begun to serve as important complementary strategies to the ex-vivo approach, as will be discussed in the following sections.

4. 1997–2007: PNI and NCI and the need for more systematic study

On February 28 and March 1, 2002, NCI sponsored a multidisciplinary scientific meeting to review the state of the science of PNI and its applicability to cancer control through the “Biological Mechanisms of Psychosocial Effects on Disease (BiMPED) Cancer Core Committee”.

Papers and commentaries from the meeting were published in a special issue of BBI in February, 2003. Future scientists may, perhaps, in retrospect, come to view this conference and its publication in BBI as a watershed in PNI cancer research. The papers presented largely addressed the physiological mechanisms associated with psychoneuroimmunologic effects on cancer, including neural and...
neuroendocrine processes, and also considered biobehavioral factors such as stress characteristics, conditioned immune responses, sleep, and individual behavioral differences. The bidirectional character of brain–immune interactions was further emphasized, as were the implications of such interactions for cancer therapies.

While the various components of cancer-PNI were well evidenced, PNI investigators attending the meeting (including SBE) came away with an uneasiness that not infrequently emerges from interactions with scientists from other fields. It seemed that, at the conclusion of the meeting, little progress had been made in dispelling the skepticism concerning PNI among tumor immunologists and oncologists. An all too common criticism of the field has been the paucity of sustained lines of research that are able to “drill down” from the phenomenology (e.g., of stress-cancer effects and stress-immune effects) to the systemic mechanisms involved and specifically into the cell itself and its molecular biology. We suggest that a response to that critique can be developed using specific in vivo research paradigms with the power to track behavioral effects through immunologic mechanisms, to specific effects on tumor growth (which can be brought to the cellular level), and then tested using specific therapeutic interventions based on the same PNI model. Some of us (Sood et al., Dhabhar et al., SBE & GGP, and others) have been developing such paradigms over the past decade with systematic research programs that have found a supportive home in the pages of BBI and other journals.

In a series of studies in rats, Ben-Eliyahu and Page have shown that endogenous systemic release of catecholamines and prostaglandins (PGs), following stress or surgery, suppresses circulating and marginating-pulmonary NK activity per ml blood, per lung, and per individual NK cell. This suppression was also shown in vivo and was causally related to increased susceptibility to metastasis of the MADB106 mammary adenocarcinoma and other syngeneic tumor lines in the F344 rat (Ben-Eliyahu et al., 2000, 1999; Shakhar and Ben-Eliyahu, 1998; Stefanski and Ben-Eliyahu, 1996; Yakar et al., 2003). Pain and its associated stress responses were implicated as some of the mediating mechanisms (Bar-Yosef et al., 2001; Franchi et al., 2007; Page et al., 2001). Addressing the potential clinical implications of these finding, the NK suppressive and tumor promoting effects of stress and surgery were shown to be attenuated or abolished using a treatment based on a combination of a β-adrenergic blocker and a PGs synthesis inhibitor (Melamed et al., 2005). These interventions have now been successfully tested employing drugs that are in common clinical use (Benish et al., submitted for publication). This approach is currently being tested and is yielding positive findings in animal models of clinical relevance, including survival following exposure to the CRNK leukemia (in the F344 rat), and in the context of spontaneous metastasis following excision of the B16 melanoma in C57BL mice. Because these drugs are already in clinical use in the surgical setting for other indications, and may reduce cancer progression though other mechanisms as well (Antoni et al., 2006), we believe that this approach can and should now be tested clinically and need not remain yet another promissory note.

Related developments in this decade were associated with the realization that immunity can have a critical role in controlling metastasis even when it fails to control the primary tumor. While it had become evident that the majority of cancer patients harbor micrometastases and circulating malignant cells following the removal of the primary tumor (Yamaguchi et al., 2000), recurrence still occurs only in a small portion of this population, suggesting a role for immunity in eradicating such minimal residual disease (MRD). Indeed, patient leukocyte cytotoxicity (Uchida et al., 1990) or proliferative response (McCoy et al., 2000) to the autologous tumor during the perioperative period have been shown to be the best independent predictors of metastasis-free long-term survival (better than tumor stage and grade). Such observations support the clinical potential for PNI studies in relation to metastasis and MRD.

5. 2007 and beyond

Animal models that permit elucidation of immunologic mechanisms in the course of specific tumor initiation and metastasis help overcome some major hurdles of cancer-PNI in humans: the unknown period of malignant initiation, the prolonged process of tumor development, and the silent initiation of metastatic processes. Animal models have shown the potential to assess immune–cancer interactions and design therapeutic interventions at specific critical periods that can then be extrapolated to the clinical condition. Nevertheless, the use of animal tumor models for studying cancer and PNI-cancer interactions has been justifiably challenged. Even the most advanced tumor models do not simulate the prolonged process of immune–cancer interactions and cancer “ontogenetic evolution” in humans. In our opinion, tumor models have clear but limited value in providing answers concerning the clinical significance of the effects of stress on tumor progression. Tumor models can be very efficient in: (a) simulating specific aspects of tumor progression (e.g., malignant cell extravasation) and the impact of stress on such processes, (b) studying immune anti cancer activities in vivo (including NK activity), (c) elucidating mediating neuroendocrine mechanisms of the impact of stress on immune competence and tumor progression, and (d) testing potential pharmacological and immunological in vivo interventions before using such interventions in cancer patients. Such models, however, are ultimately limited. In the end, it becomes necessary to test for possible beneficial effects of PNI-based interventions in humans. As noted above, we believe that, for some such interventions, the animal data now justify clinical trials.

In designing such trials, it should be remembered that not all stress responses are maladaptive with respect to
immunity and cancer progression (Viswanathan and Dhabhar, 2005), and researchers might best focus on attenuating maladaptive responses with large demonstrated effects on cancer progression. Researchers should employ specific interventions to reduce the impact of undesirable stress responses and, within patients, assess clinically relevant measures of immunity as well as cancer progression. Such studies should be conducted only after ensuring sufficient statistical power to demonstrate effects that could be reasonably expected. Whereas the current status of cancer-PNI in the conventional treatment of malignancies is somewhere between non-existent and informal ("support groups can do no harm"), one of our greatest challenges will be to integrate cancer-PNI interventions, as appropriate, within the broader array of conventional cancer treatments.

Acknowledgments

We apologize to those who have made significant contributions in the areas discussed in this mini-review but whose work was not cited due to page and reference limitations. The work of SBE (R01-CA73056 & 2005331) and GGP (NR07742) has been supported by grants from NIH and from the US-Israeli Binational Science Foundation (BSF).

References


