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REVIEW ARTICLE

Host Factors and Cancer Progression: Biobehavioral Signaling Pathways and Interventions

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ABSTRACT

Whereas evidence for the role of psychosocial factors in cancer initiation has been equivocal, support continues to grow for links between psychological factors such as stress, depression, and social isolation and progression of cancer. In vitro, in vivo, and clinical studies show that stress-related processes can impact pathways implicated in cancer progression, including immunoregulation, angiogenesis, and invasion. Contributions of systemic factors, such as stress hormones to the crosstalk between tumor and stromal cells, appear to be critical in modulating downstream signaling pathways with important implications for disease progression. Inflammatory pathways may also be implicated in fatigue and other factors related to quality of life. Although substantial evidence supports a positive effect of psychosocial interventions on quality of life in cancer, the clinical evidence for efficacy of stress-modulating psychosocial interventions in slowing cancer progression remains inconclusive, and the biobehavioral mechanisms that might explain such effects are still being established. This article reviews research findings to date and outlines future avenues of research in this area.

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INTRODUCTION

Throughout history, scientists have pondered connections between psychosocial factors and diseases such as cancer.[1] Epidemiologically established risk factors for carcinogenesis (eg, endocrine, environmental, socioeconomic, and genetic factors) only partially explain the risk for cancer initiation.[2] Whereas evidence for the role of psychosocial factors in cancer initiation is limited and equivocal,[3-6] evidence is stronger for links between psychological factors such as stress, depression, and social isolation and disease progression.[7-9] Thus, this review focuses on literature related to disease progression.

STRESS RESPONSE

The physiological stress response is thought of as one of the probable mediators of the effects of psychosocial factors on cancer progression. The overall stress response involves activation of several body systems including the autonomic nervous system and the hypothalamic-pituitary-adrenal axis. The fight or flight response is elicited by the production of mediators, such as the catecholamines norepinephrine (NE) and epinephrine (E), from the sympathetic nervous system and the adrenal medulla. The hypothalamic-pituitary-adrenal response includes release of corticotropin-releasing hormone from the hypothalamus, inducing secretion of adrenocorticotrophic hormone from the anterior pituitary, resulting in downstream release of glucocorticoids such as cortisol from the adrenal cortex.[10] Additional neuroendocrine factors are also modulated following stress, including dopamine, prolactin, nerve growth factor, substance P, and oxytocin.[11,12] Stress can be acute (ie, short-lived) or chronic (ie, repetitive or occurring over an extended period of time).[13] In chronic stress, the body remains in a constant state of overdrive, with deleterious downstream effects on regulation of stress response systems as well as many organ systems.[14] A variety of stressors, including severe trauma, marital discord, bereavement, as well as depression and social isolation have been associated with dysregulation or alterations in various neuroendocrine hormones, particularly catecholamines and cortisol.[15-19]

STRESS-RELATED MECHANISMS RELEVANT TO CANCER PROGRESSION

Cancer metastasis remains a difficult problem to manage and is responsible for most cancer-related mortality. Metastasis is a complex process that requires several steps to be successful, including angiogenesis, proliferation, invasion, embolization,

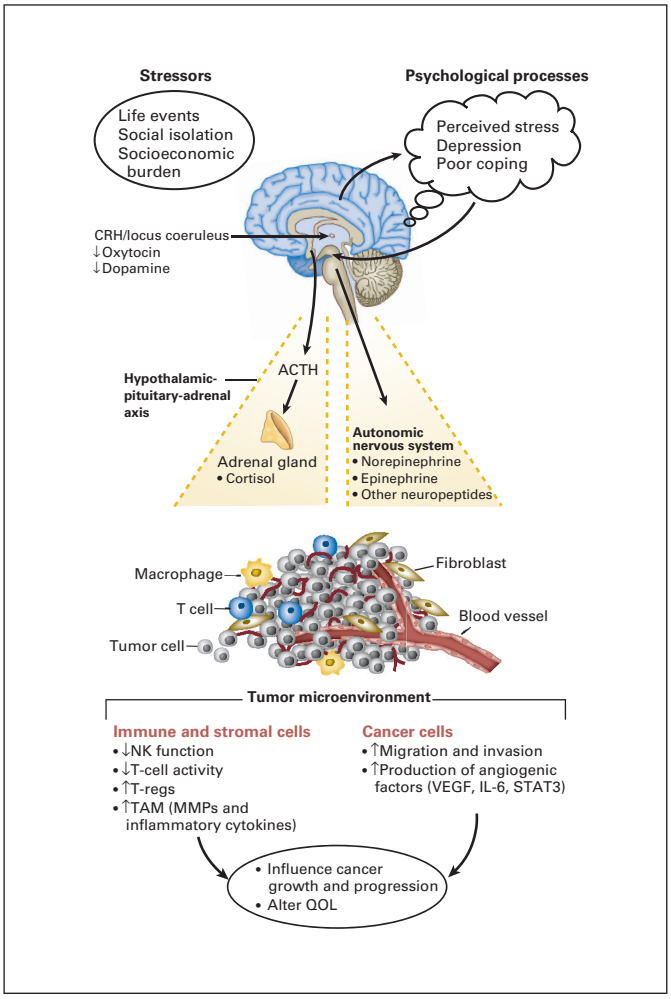

Fig 1. Effects of stress and psychological processes on the tumor microenvironment. The stress response results in activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis. Factors released from these pathways can have direct effects on the tumor microenvironment, resulting in a favorable environment for tumor growth and progression. These dynamics can also adversely affect patient quality of life. CRH, corticotropin-releasing hormone; ACTH, adrenocorticotrophic hormone; NK, natural killer; T-regs, regulatory T cells; TAM, tumor-associated macrophages; MMP, matrix metalloprotinease; VEGF, vascular endothelial growth factor; IL, interleukin; STAT3, signal transducer and activator of transcription factor-3; QOL, quality of life.

and evasion of immune system surveillance.[20] Increasing evidence shows that stress response pathways can affect many parts of this cascade (Fig 1). Here, we examine clinical, animal, cellular, and molecular findings relating psychosocial and behavioral factors (ie, stress, depression, social support/isolation) to processes implicated in cancer progression and metastasis.

Stress and Angiogenesis

Development of a blood supply is critical for tumor growth and metastasis. Many factors promote angiogenesis including vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), transforming growth factor α and β, and tumor necrosis factor α.[21,22] Social support has been shown to be related to lower levels of VEGF among patients with ovarian cancer perisurgically, both in serum[23] and in tumor tissue.[24] In vitro studies have found that NE and the β-agonist isoproterenol were both capable of inducing VEGF expression in ovarian and other cancer cell lines.[25,26] Moreover, using orthotopic animal models of ovarian cancer, chronic restraint stress resulted in increased tumor burden and invasiveness, which was mediated by NE-driven increases in VEGF and angiogenesis.[27] Similar effects were noted with the β-agonist isoproterenol and eliminated by using a β-blocker, thus, verifying the importance of adrenergic receptor signaling in mediating these effects.

Angiogenesis can also be stimulated by a disruption in the balance between pro- and antiangiogenic factors. IL-6 is a prominent angiogenic factor produced by tumor cells that disrupts this equilibrium.[28,29] Clinically, patients with ovarian cancer with poorer social support had higher levels of IL-6 both in plasma and in ascites.[30] Furthermore, NE was responsible for inducing *IL-6* gene transcription through a Src-dependent mechanism, further demonstrating the role of tumor cells in activating stress pathways critical to their growth.[31]

Recent studies have also shown the involvement of signal transducer and activator of transcription factor-3 (STAT3) in promoting stress-mediated tumor-associated angiogenesis. STAT3 is involved in many protumorigenic pathways by activating downstream targets to promote proliferation and inhibit apoptosis. Although STAT3 can be activated by growth factors and cytokines, such as VEGF and IL-6, stress hormones, such as NE and E, can activate STAT3 independent of IL-6, leading to its translocation to the nucleus and subsequent binding to DNA to promote transcription of genes associated with cell survival, angiogenesis, and proliferation.[32]

Effects on Tumor Cell Migration and Invasion

Another key step in the metastatic cascade is the ability of a tumor cell to separate from the main tumor, invade through the basement membrane, and enter the blood supply. Stress hormones can affect these processes by increasing matrix metalloprotinease (MMP) production by tumor cells as well as by acting as chemoattractants to induce cell migration. Stress levels of NE increased the in vitro invasive potential of ovarian cancer cells by 89% to 198%, which was completely blocked by the β antagonist propranolol.[33] Additional in vivo and in vitro studies demonstrated that NE and E significantly increased production of MMP-2 and MMP-9 by ovarian cancer cells through activation of the β-adrenergic pathway.[33] Other studies have reported similar findings in several other tumor types including colon and head and neck cancers.[26,34-36] Clinically, both depression and stress have been related to MMP-9 secretion by tumor-associated macrophages (TAM) in patients with ovarian cancer. As TAM are now known to promote a proinflammatory tumor microenvironment, downregulate cellular immunity, and enhance tumor growth and progression,[37,38] effects of stress on TAM have important implications for tumor progression.[24]

Social support is thought to have direct links to health outcomes, as well as to moderate the effects of stress.[39] For example, individuals with poor social support were shown to have impaired transcription of glucocorticoid response genes and increased activity of proinflammatory transcription control pathways.[40] Social isolation has been related to upregulated mammary gland expression of murine orthologues of several key metabolic genes implicated in human tumorigenesis and to increased tumor growth in a murine breast cancer model.[41] Among ovarian cancers from individuals with high levels of depression and

low levels of social support, more than 200 upregulated gene transcripts were found that were consistent with activation of signaling pathways involved in tumor growth and progression (eg, *CREB*, *NFKB*, *STAT*, and *ELK1*) as compared to histologically and age-matched counterparts with high social support and low levels of depression.[42] Collectively, emerging evidence has shown stress and psychosocial factors to be associated with key elements of the metastatic cascade, in both animal and human models.

Stress and the Immune Response

The cellular immune response has been a central focus of much biobehavioral oncology research because of its role in immunosurveillance and lysis of tumor cells.[43] Experimental studies with animal models have demonstrated that tumor incidence and progression may be aggravated by chronic stress, including surgical stress, by suppressing type 1 (TH_1) cytokines and cytotoxic activities of T cells and natural killer (NK) cells, impairing antigen presentation, and increasing regulatory T cells.[44-47] Psychological states such as chronic stress, loneliness, and depression are known to downregulate the cellular immune response,[48-50] largely via adrenergic and glucocorticoid signaling pathways. Stress has been related to decrements in a broad range of markers of cellular immunity in patients with breast cancer after surgery, including lower T-cell production of TH_1 versus TH_2 cytokines,[51] decreases in T-cell response to mitogen stimulation, and impaired NK cell cytotoxicity.[52,53] Among patients with advanced breast cancer, depression has been related to a reduction in the cellular immune response to a variety of specific antigens.[54] Distress among patients with ovarian cancer at the time of surgery has been associated with poorer NK cell activity in tumor infiltrating lymphocytes (TIL) and lower T-cell production of TH_1 versus TH_2 cytokines in peripheral blood and TIL, whereas social support was related to greater NK activity in both peripheral blood and TIL.[55,56] It should also be noted that inflammatory cytokines have been implicated in cancer-related fatigue and depression.[57-60]

Stress, Neuroendocrine Circadian Dysregulation, and Cancer Progression

There is clinical evidence that stress may disrupt the diurnal secretion of neuroendocrine hormones, such as cortisol, and that such disruption is related to diminished quality of life and poorer outcomes in some patients with cancer. Profound alterations in diurnal serum cortisol rhythms have been reported in animals with tumors and in a variety of patients with cancer.[61,62] It is not clear to what extent these diurnal cortisol dysregulations derive from factors such as stress and depression, or if they are secondary to tumor-produced inflammatory products, or both.[18,59,63,64] Dysregulations in diurnal cortisol have been associated with greater functional disability,[65] fatigue,[66] and poorer survival in women with breast cancer.[67] Direct relationships between glucocorticoids and neoplastic growth have been documented. For example, glucocorticoids directly enhance a survival pathway and inhibit apoptosis of a mammary tumor cell line,[68] downregulate expression of DNA repair genes including *BRCA1*,[69] and decrease paclitaxel-induced apoptosis in a mammary cancer cell line.[70] Patients with advanced breast cancer with higher mean diurnal cortisol concentrations showed suppressed cellular immunity to a number of antigens.[54] Thus, glucocorticoids may have direct effects on tumor growth and development as well as effects on immunosurveillance and on factors related to quality of life.

Summary

These findings highlight the relevance of translational research testing pharmacologic agents on intermediate outcome markers of cancer progression as delineated above (eg, markers of angiogenesis, invasion, and metastasis) as well as more distal outcomes such as recurrence and survival. Potential pharmacologic approaches could include beta blockers, antidepressants, and anti-inflammatory agents as well as molecules specifically targeting the downstream pathways induced by stress. Psychosocial interventions may also modulate stress-related pathways by teaching individuals to behaviorally manage their stress responses.

PSYCHOSOCIAL INTERVENTION AND CANCER PROGRESSION

With evidence for associations between stress, social processes, and neuroendocrine changes that can impair quality of life and promote cancer progression, a logical extension is human research testing the effects of psychosocial interventions on quality of life, neuroendocrine parameters, and cancer progression. More than 300 trials of psychological interventions have been conducted in patients with cancer over the past 50 years.[71-73] Most such intervention trials have been conducted in women with breast cancer.

In previous reviews,[71-73] the consensus has been that different forms of psychosocial intervention that teach relaxation and stress management, help patients ventilate their feelings and anxiety, and provide social support are able to improve quality of life. Salient among these findings are the ability of psychosocial interventions to decrease pain and anxiety in patients with metastatic breast cancer with the most severe symptoms,[74] a finding that has significant clinical implications. More recent studies published after the time of these reviews have generally supported a positive effect for psychosocial interventions on quality of life, depressed mood, distress, and social disruption in patients with cancer.[75,76]

Whether psychological interventions can affect cancer progression and survival has been more controversial. Reviews and commentaries conducted on this topic have produced varied conclusions.[71-73,77,78] In the past 3 years, three trials of 12-month group interventions on cancer recurrence or survival in women with breast cancer have been completed. These trials recruited their cohorts during the 1990s and demonstrated good methodological strength, meeting nearly all of the revised CONSORT criteria.[71] Each trial carefully planned and adequately powered their designs to detect recurrence or survival outcomes (at 80% to 90% power); used appropriate random assignment, follow-up periods, and statistical analyses (eg, survival analyses by intent to treat); delineated primary and secondary analyses from ancillary and exploratory analyses; clearly described stratification procedures, participant characteristics, and decision rules for including covariates; and reported outcome effects and precision (ie, 95% CI).

In one trial, patients with breast cancer with stage 2 to 3 disease were randomly assigned to standard care or 4 months of weekly and 8 months of monthly sessions of group-based cognitive behavioral intervention (eg, relaxation, coping skills training) in the weeks after surgery. Intervention participants showed a significant reduction in

overall and breast cancer–specific mortality rates as well as reduced risk of breast cancer recurrence at a median of 11 years follow-up.[79] Results were not attributable to site of accrual, sociodemographic factors, disease stage, prognostic markers, surgery type, or adjuvant therapies received during the trial nor extra-trial psychiatric medications or counseling received. In two other trials, one in the United States and one in Australia, women with metastatic breast cancer were assigned to a 12-month course of weekly group-based supportive expressive therapy, but neither showed an overall intervention-related survival advantage,[80,81] essentially replicating an equally rigorous prior Canadian trial of supportive expressive therapy in women with metastatic disease published in 2001.[74] Possible explanations for such divergent results include differences in patient populations (eg, metastatic *v* nonmetastatic disease) and covariates employed,[78] and alterations in physiological effects due to variations in the interventions.[82] It has also been suggested that optimizing neuroendocrine and immunologic status may require both psychological and pharmacologic interventions to fully mitigate the deleterious effects of stress biology on tumor growth and progression.[83]

Other recently completed trials reporting the effects of stress reduction techniques have mainly involved cognitive behavioral stress management—combining relaxation-based techniques with cognitive behavioral strategies to change negative thinking and build interpersonal coping skills—and mindfulness meditation-based stress reduction (MBSR) approaches. These two forms of intervention show similar effects on stress/distress and neuroendocrine and immunologic indicators in women with nonmetastatic breast cancer recruited during medical treatment.[84] These effects have included decreases in afternoon and evening serum cortisol levels, increases in the T-cell lymphoproliferative response, and increased TH_1 cytokine production and TH_1/TH_2 production ratio.[85-89] Since the MBSR trials were not randomized clinical trials, caution is in order when interpreting these findings. Nevertheless, the magnitude of the changes in physiological indicators generally paralleled the size of the psychological effects of these interventions.[84] In one randomized clinical trial of cognitive behavioral stress management, distress, social disruption, and cortisol decreases were paralleled by increased confidence in using relaxation as a coping strategy to manage stress,[75,88] findings that mirror those of others conducting trials of cognitive behavioral interventions and MBSR.[87,90]

In addition to alterations in stress responses, it is also essential to consider whether the women who received psychological interventions in these trials successfully changed their health behaviors (eg, more exercise, better nutrition, less alcohol consumption, better adherence to hormonal medications and attendance at follow-up appointments) and actually got more effective medical treatment (eg, cointervention effects),[71] and if these changes conferred greater protection against disease progression and facilitated general health. Nevertheless, such positive side effects of psychological interventions would contribute a net beneficial effect for the care of patients with cancer. Importantly, women assigned to psychological interventions in the Andersen et al[82] trial were more likely to adhere to their chemotherapy regimen and received greater dose intensity than controls.

When designing studies of psychological interventions in patients with cancer, it is also reasonable to consider other stress-related health outcomes beyond survival and disease recurrence, such as the incidence of opportunistic infections during and after the completion of surgical and adjuvant therapy. Stress-related changes in infectious disease processes are well-established.[91-93] Stress reduction interventions showed improved neuroendocrine and immune parameters in persons with HIV,[94] and also decreased the risk of developing persistent squamous intraepithelial lesions in women coinfected with HIV and human papilloma virus. The latter findings suggest that stress reduction may reduce the carcinogenic activity of opportunistic infections in some settings.[95]

FUTURE DIRECTIONS

There is growing evidence from in vitro, in vivo, and clinical studies that stress-related processes can impact pathways implicated in cancer progression, including immunoregulation, angiogenesis, and invasion. Contributions of systemic factors, such as stress hormones, to the crosstalk between tumor and stromal cells appears to be critical in modulating downstream signaling pathways with important implications for progression. Although effects of stress mediators and pharmacologic blockers of stress hormones on tumor progression have been demonstrated in animal models, effects of these pathways on progression of tumors in clinical models has not been well-characterized to date and provide an important avenue for future investigation. As stress mediators not only have effects on tumor growth but have effects on many related physiological processes, examination of how biobehavioral pathways contribute to effectiveness of chemotherapy and immunomodulatory therapies, fatigue, pain, and cognitive sequelae of chemotherapy will be important future lines of research. The role of stress-related immunosuppression in promoting tumor immune escape mechanisms and modulating the effectiveness of immunotherapy programs has been minimally studied and presents a fertile area for investigation.[96,97] Understanding how the biobehavioral pathways outlined here are exacerbated by socioeconomic and cultural stressors and how all these factors interact with dynamics of tumor progression in diverse populations should be examined. The clinical evidence for efficacy of psychosocial interventions in slowing cancer progression remains inconclusive, and the biobehavioral mechanisms that might explain such effects are still being established. As cancer therapy moves toward greater personalization, it will be important to define those most likely to benefit from behavioral and/or pharmacologic interventions blocking the adverse effects of psychosocial factors on patient outcome.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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