Biobehavioral Approaches to Cancer Progression and Survival

Mechanisms and Interventions

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Over the last decade, there have been groundbreaking strides in our understanding of the multiple biological pathways by which psychosocial and behavioral factors can affect cancer progression. It is now clear that biobehavioral factors not only affect cellular immunity but both directly and indirectly modulate fundamental processes in cancer growth, including inflammation, angiogenesis, invasion, and metastasis. There is also an emerging understanding of how psychological and behavioral factors used in interventions can impact these physiological processes. This review outlines our current understanding of the physiological mechanisms by which psychological, social, and behavioral processes can affect cancer progression. The intervention literature is discussed, along with recommendations for future research to move the field of biobehavioral oncology forward.

Keywords: biobehavioral oncology, inflammation, metastasis, intervention, psychological

Epidemiologic and psychological studies have examined relationships between psychosocial factors and both cancer initiation (development of cancer in patients who have no previous disease) and progression (disease that has increased or spread following definitive treatment or the same disease diagnosed following a disease-free period). As the focus of this article is on progression, we mention findings on psychosocial factors and cancer initiation here only briefly. Data supporting a potential role of psychological factors in cancer initiation have been relatively equivocal, with well-done studies demonstrating both positive and null relationships (e.g., Bleiker, van der Ploeg, Hendriks, & Adèr, 1996; Duijts, Zeegers, & Borne, 2003). The strongest evidence in this area has shown associations between cancer incidence and severe life events such as death of a spouse or child, severe distress, Holocaust survival, long-term depression, or the combination of a severe life event and lack of social support (e.g., (Chida, Hamer, Wardle, & Steptoe, 2008; Fang et al., 2011; Lillberg et al., 2003). Mechanistically, there is growing evidence supporting a relationship between stress and tumorigenesis. For example, stress has been shown to increase the down-regulation of p53, an important tumor suppressor gene (Feng et al., 2012). Additionally, links have been demonstrated between stress or stress hormones and potentially carcinogenic DNA mutations such as impairment of DNA repair (Flint, Baum, Chambers, & Jenkins, 2007; Glaser, Thorn, Tarr, Kiecolt-Glaser, & D'Ambrosio, 1985). Readers interested in stress and cancer initiation are referred to several reviews on this subject (Butow et al., 2000; Duijts et al., 2003; Garssen, 2004; Nielsen & Grønbæk, 2006).

Links Between Psychosocial Variables and Cancer Progression and Death

More consistent associations have been documented between psychological and biological processes in patients who already have cancer. The psychological processes that have most consistently emerged as relevant for cancer-related outcomes include lack of social support, depression, distress, and trauma history. Across a range of environments and health conditions, social relationships predict mortality for both men and women, with those having fewer ties showing poorer outcomes. These findings remain even after adjustments for other risk factors (House, Landis, & Umberson, 1988). Studies among cancer populations have focused on various aspects of social support, including quality of support, size of social network, and presence of a partner. A meta-analysis by Pinquart and Duberstein (2010a) examined associations of these three groupings and cancer mortality and considered 87 studies, sampling more than 10 million individuals. Having high levels of perceived social support, having larger social networks, and being married were associated with decreases in the relative risk of cancer mortality of 25%, 20%, and 12%, respectively.

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Depression is common among cancer patients, with meta-analyses showing the point prevalence for major depressive disorder to be 12.5% among cancer patients, four times the rate (3.3%) in the general population (Wu & Andersen, 2011). For all mood disorders, the point prevalence is 23.2% in cancer patients. Depression, stress, and trauma have been associated with poorer survival in multiple cancer populations, (e.g., Chida et al., 2008; Cohen et al., 2012; Palesh et al., 2007; Satin, Linden, & Phillips, 2009; Steel, Geller, Gamblin, Olek, & Carr, 2007), with risk ratios for survival among patients with clinical depression in the range of 1.22 to 1.39 (Pinquart & Duberstein, 2010b; Satin et al., 2009). Depression has not been universally associated with cancer survival, however; for example, in ovarian cancer patients, neither a current nor a past history of major depression was associated with survival (Lutgendorf et al., 2012). When early stressors (prior to age 5) are considered, data suggest their later effects include poor health and premature mortality (Miller, Chen, & Parker, 2011). Early life stressors have also been associated with decreased survival times in women with metastatic breast cancer (Palesh et al., 2007), but literature on this topic is limited to date.

Stress Response Systems That Impact the Tumor Microenvironment

The experience of the cancer patient includes multiple stressors from the time of suspected cancer, through diagnosis, treatment, and survivorship. Individuals differ in their vulnerability to stress, which may be modified by resources such as coping abilities, attitudes, affect, and social support. Central nervous system (CNS) processing of threat or challenge is translated into a physiological stress response, with downstream activation of multiple pathways, including the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis is governed by the hypothalamus and ultimately results in secretion of the hormone cortisol from the adrenals. The sympathetic nervous system (SNS) secretes norepinephrine (NE) at nerve terminals, and both NE and epinephrine (E) are secreted by the adrenal medulla. Other stress hormones and neuropeptides (e.g., oxytocin, dopamine) are also released as part of the stress response (Weiner, 1992). This CNS-mediated "macroenvironment" exerts a profound influence on the tumor microenvironment that we describe below. Our discussion of mechanisms focuses on the SNS and the HPA axis, as most biobehavioral oncology research has examined these stress response systems; however, other neuroendocrine hormones and neuropeptides likely influence tumor biology as well.

Stress Biology and the "Hallmarks of Cancer"

The development of cancer and its spread have been characterized by 10 specific biological capabilities that tumors acquire during their development, described as the "hallmarks of cancer" by Hanahan and Weinberg (2011). These include the ability to avoid destruction by immune cells, promote inflammation, induce angiogenesis, activate invasion and metastasis, and resist cell death. Additionally, host factors, such as the immune response, particularly its cellular arm, are intimately involved in surveillance and destruction of tumor cells, especially in the early stages of disease. Initially, biobehavioral oncology research predominantly focused on how psychosocial factors influenced the immune response and thus shaped a more (or less) permissive environment for tumor growth. Over the last 10 years, both clinical and preclinical (in vitro and animal) research has expanded to reveal how stress-related processes can directly modulate many of these hallmark tumor characteristics in addition to effects on the host. Below, we focus on *direct* stress effects on tumor activities and then discuss the role of biobehavioral factors in modulating the host response, particularly immune and inflammatory responses to tumors.

Stress Effects on Tumor Growth: Angiogenesis and Invasion

The process of metastasis, which involves dissemination of tumor cells from the primary site to other parts of the body, is the usual cause of cancer death. The mechanisms underlying metastasis have been well characterized, involving sequential steps such as angiogenesis (the development of vascularization to the tumor), local tumor growth or proliferation, invasion of the surrounding matrix, embolization and travel of tumor cells via lymph or the blood supply to other sites, and development of a tumor in a new secondary site (Fidler, 2003). Stress-related pathways have now been shown to influence the signaling and outcomes of many of these steps.

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Biobehavioral Effects on Angiogenesis

Early in development, tumors receive most of their nutrients via passive diffusion, which permits only very slow growth. At the size of about 2 cm they start to develop a vascular system that allows utilization of nutrients from blood and is accompanied by accelerated growth. This process, called angiogenesis, is controlled by complex signaling from tumor cells as well as host cells in the tumor microenvironment (Folkman, 1990). Key factors promoting angiogenesis include vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6) (Spannuth, Sood, & Coleman, 2008). Associations between biobehavioral factors and angiogenesis have been documented in both preclinical and clinical studies using a variety of tumor types. (For a review, see Armaiz-Pena, Cole, Lutgendorf, & Sood, 2013). Associations of greater social support with lower levels of VEGF have been reported in ovarian and colon cancer, in both peripheral blood (Lutgendorf et al., 2002; Sharma, Greenman, Sharp, Walker, & Monson, 2008) and tumor tissue (Lutgendorf, Lamkin, Jennings, et al., 2008; Nausheen et al., 2010), while controlling for relevant clinical variables. Similar findings have been observed with IL-6, a pleiotropic cytokine (molecules involved in cell signaling and regulation) produced by many cell types, including tumor cells and macrophages. IL-6 is involved in the stress response and depression, as well as tumor angiogenesis and invasion. Advanced ovarian cancer patients reporting low social support showed elevated IL-6 in both plasma and ascites (malignant effusions in peritoneum; Costanzo et al., 2005). Moreover, ovarian cancer patients with poorer social support had higher NE in both tumor and ascites, suggesting that effects on angiogenic cytokines may be mediated by adrenergic signaling (Lutgendorf et al., 2011).

These clinical findings have been paralleled by in vitro experiments in cell lines from tumor types including ovarian, melanoma, myeloma, and nasopharyngeal. Such mechanistic approaches have demonstrated that stress-related effects on angiogenesis are beta-adrenergically mediated (Armaiz-Pena et al., 2013). In animal models, stressors such as chronic restraint stress or surgical stress increased ovarian tumor weight and invasiveness via beta-adrenergically mediated effects on angiogenesis that were completely blocked by propranolol (for a review, see (Armaiz-Pena et al., 2013). Social isolation also has been shown to promote tumor growth and invasion in animal models of ovarian and breast cancer (e.g.,Williams et al., 2009).

Biobehavioral Influences on Tumor Invasion and Metastasis

Following vascularization, metastasis proceeds when tumor cells invade through the basement membrane and enter the vascular system, enabling spread to other parts of the body. The process of invasion is facilitated by enzymes called matrix metalloproteinases (MMPs), which promote the breakdown of the cellular matrix surrounding the tumor. MMPs are secreted by both tumor and host cells in the tumor microenvironment. Stress hormones (e.g., NE) increase MMP production in vitro in a variety of tumor types, including those in colon, head and neck, and ovarian cancer, and increase the invasive potential of ovarian cancer cells in vitro. These effects are blocked by the nonspecific beta-blocker propranolol, indicating sympathetic mediation (Armaiz-Pena et al., 2013).

Stress effects on macrophages in the tumor microenvironment can also support tumor invasiveness. Macrophages are immune cells that act as scavengers and early responders—they identify and destroy tumor cells and other pathogens and also orchestrate inflammation and wound healing. Tumor-associated macrophages (TAM) can have both anti-tumor and "pro-tumor" phenotypes and are capable of producing cytokines that can destroy or support tumors. In the presence of the pro-inflammatory tumor microenvironment, TAM often lose their anti-tumor phagocytic properties and instead begin to produce mediators that support angiogenesis, invasion, metastasis, and inflammation, along with cytokines that down-regulate cellular immunity (Sica & Mantovani, 2012). Animal studies have highlighted beta-adrenergic effects of stress on TAM in promoting metastatic spread of mammary cancer (Sloan et al., 2010). In ovarian cancer patients, higher levels of depression and/or stress are associated with elevated TAM production of MMP-9, an MMP associated with tumor invasiveness and with poorer survival (Lutgendorf, Lamkin, Jennings, et al., 2008). As TAM infiltration is also associated with poorer survival (Tsutsui et al., 2005), these findings may have clinical implications.

Normally, if cells other than hematopoietic cells become detached from the extracellular matrix (ECM), they are not able to survive and they enter a process of programmed cell death called *anoikis*. Tumor cells develop the ability to resist anoikis, thereby enabling them to migrate and colonize new locations. Catecholamines increase the

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ability of ovarian cancer cells to resist anoikis (and thus survive) when detached from the ECM, in both in vitro and animal models (Sood et al., 2010). Similarly, ovarian cancer patients with elevated depressive symptoms and those with higher levels of tumor NE showed higher levels of an activated molecule that promotes resistance to anoikis and is linked to poorer overall survival (Sood et al., 2010). There is a paucity of psychosocial studies investigating effects on mechanisms of tumor invasion; understanding this area more thoroughly is an important frontier for future research.

Stress Effects on Hematopoietic Cancers

In addition to effects on solid tumors such as those described above, chronic stress has also been shown to accelerate progression of hematopoietic cancers, such as acute lymphoblastic leukemia, in an animal model. Although beta-adrenergic signaling was involved in the stress effects on tumor growth, these effects were not direct; rather, they were thought to act via indirect influences on other host cells such as immune cells or the bone marrow microenvironment (Lamkin et al., 2012).

Biobehavioral Factors and Inflammation

As noted above, inflammation is one of the hallmarks of cancer and serves to both initiate and promote tumor growth (Hagemann, Balkwill, & Lawrence, 2007). Inflammation is mediated by tumor cells, as well as by tumor-associated macrophages, both of which are potent producers of pro-inflammatory cytokines. Stress-related factors are known to enhance the production of pro-inflammatory cytokines (Kiecolt-Glaser et al., 2003). Several studies using genome-wide transcriptional profiling of either white blood cells (leukocytes) or tumor tissue have now shown associations of biobehavioral states and transcriptional regulation of pathways relevant to inflammation. Cohen and colleagues (2012) found that depression was linked with shorter survival in a group of 217 patients with renal cell carcinoma. Molecular analyses were performed on leukocytes of a subsample of 31 patients. Patients with elevated depressive symptoms showed greater leukocyte expression of genes mediating inflammation, oxidative stress, and immune activation. Promoter-based bioinformatics demonstrated increased activity of several important transcription factors, including the pro-inflammatory transcription factor Nuclear Factor Kappa B (NF-κB). Similar patterns were observed in tumors of ovarian cancer patients with high biobehavioral risk (low social support and elevated depressive mood) versus low biobehavioral risk (high social support and low depressive mood), matched for relevant clinical variables such as stage, grade, age, and histology. Tumors of high-risk patients showed over 200 up-regulated gene transcripts, many of which orchestrated transcriptional pathways involved in tumor growth and progression. Promoter-based bioinformatics showed increased activity of beta-adrenergically regulated transcription factors including CREB (cAMP response element-binding protein) and NF-κB (Lutgendorf et al., 2009). Taken together, these findings demonstrate patterns of gene expression and signaling supportive of tumor growth in both blood cells and tumors in patients with high psychosocial risk in two independent studies of cancer patients.

Inflammation, including tumor-derived inflammation, is also known to have effects on the central nervous system and may have significant psychosocial sequelae in cancer patients. Depression in cancer patients, including major depressive disorder (MDD), has been associated with higher IL-6 (Howren, Lamkin, & Suls, 2009; Jehn et al., 2006; Musselman et al., 2001), although some reports have indicated that IL-6 is more closely linked with vegetative rather than affective symptoms of depression (Lutgendorf, Weinrib, et al., 2008; Schrepf et al., 2013). Inflammatory cytokines such as IL-6 are known to induce neurovegetative symptoms in the central nervous system (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008), and thus, the associations noted between IL-6 and depression may be secondary to central effects of tumor-derived IL-6. Interested readers are referred to a comprehensive review of this literature by Bower and Lamkin (2013).

Stress-Related Effects on Host Cells

Intricate signaling patterns between tumor and host help shape the microenvironment and determine tumor growth and spread. Biobehavioral factors can have indirect effects on tumor progression by influencing signaling of host cells that subsequently modulate tumor growth. A striking example of the tumor-promoting effects of stress on bone cells was recently demonstrated in an animal model of breast cancer. Bone marrow metastases are painful, increase risk for fracture, and have no cure. Stress-induced sympathetic activation was found to induce molecular changes in bone marrow osteoblasts, resulting in increased migration of breast cancer cells to the bone marrow, thus promoting bone marrow metastases (Campbell et al., 2012).

Biobehavioral Risk Factors and Cellular Immunity

A variety of immune cells are involved in orchestrating an anti-tumor response. Commonly studied parameters include number and activity of natural killer (NK) cells, number and activity of T-helper and cytotoxic T-cells, and presence or activity of a variety of cytokines. NK cells identify and lyse tumor cells and are involved in surveillance for and destruction of tumor cells. Cytotoxic T-cells also destroy tumor cells, while T-helper cells produce a variety of cytokines to help orchestrate the immune response. Macrophages are immune cells that act as scavengers and early responders—they identify and destroy tumor cells and other pathogens and also orchestrate inflammation and wound healing. They also serve as antigen-presenting cells to assist in the cytotoxic activities of T-cells (Owen, Punt, & Stranford, 2013).

Immune cells bear both adrenergic and glucocorticoid receptors, and psychological effects on the immune response are largely mediated by the SNS and the HPA axis.

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Research in the field of psychoneuroimmunology over the last 30 years has demonstrated robust associations of negative psychosocial states such as chronic stress, depression, and lack of social support with down-regulation of the cellular immune response. Chronic stress is known to decrease cellular immunity and immunosurveillance and to increase inflammation (for reviews, see Glaser & Kiecolt-Glaser, 2005; Reiche, Nunes, & Morimoto, 2004; Segerstrom & Miller, 2004). In contrast, acute stress may temporarily enhance immunity (Dhabhar, Malarkey, Neri, & McEwen, 2012).

Andersen and colleagues (1998) studied a large sample ($N = 116$) of Stage II and Stage III breast cancer patients who subsequently underwent an intervention. Following surgery and before adjuvant chemotherapy, patients with greater stress at baseline showed, after controlling for relevant confounders, blunted natural killer cell cytotoxicity (NKCC), a poorer NK cell response to stimulation with lambda interferon (IFNγ), and a decreased T-cell proliferative response, findings that are consistent with diminished cellular immunity (Andersen et al., 1998). A follow-up study of a subset of these patients ($n = 17$), found altered receptor expression and impaired signaling ability in the NK cells of high-stress patients (Varker et al., 2007). Among patients in the control group who did not participate in Andersen's subsequent intervention, trajectories of immune changes paralleled changes in stress; for example, women reporting an early decline in perceived stress postsurgery showed a rapid recovery of NK cell activity at this time (Thornton, Andersen, Crespin, & Carson, 2007). Similar relationships have also been documented in metastatic breast cancer patients; specifically, those with higher levels of distress had a poorer cellular response to specific antigens (Sephton et al., 2009). Social support, or lack thereof, has also been shown to have links to cellular immunity. For example, in early-stage breast cancer patients, poor social support following surgery was associated with impaired NKCC concurrently (Levy, Herberman, Maluish, Schlien, & Lippman, 1985) and three months later (Levy, Herberman, Lippman, & D'Angelo, 1987). Although stress-related immune decrements have been seen in many laboratories, not all findings have been consistent in this literature (e.g., (Von Ah, Kang, & Carpenter, 2007), and they may be dependent on the type of stress assessment used (e.g., Mundy-Bosse, Thornton, Yang, Andersen, & Carson, 2011).

A more mechanistic understanding of distress-related immune changes has emerged with demonstration of epigenetic changes in peripheral blood cells from distressed breast cancer patients at diagnosis. Alterations in acetylation and phosphorylation of specific histones were associated with reduced NKCC; these epigenetic alterations returned to normal following completion of cancer treatment, when both NKCC and mood improved (Mathews et al., 2011).

Other studies have highlighted immune correlates of positive psychological characteristics in cancer patients. For example, among women with early-stage breast cancer–one to two months postsurgery, optimism, positive reframing, and perceived social support were associated with a greater T-cell proliferative response to a monoclonal antibody to T-cells (McGregor et al., 2000), while greater positive mood was associated with greater stimulated production of IFNγ and IL-12, cytokines that serve to enhance cellular immunity (Blomberg et al., 2009).

Data on relationships between psychosocial factors and cellular immunity, as indexed by assays of peripheral blood, are particularly relevant for understanding the extent of immune surveillance throughout the body. These measures may not, however, reflect immunity in the tumor microenvironment. It is the case that immune cells in peripheral circulation are substantially more effective in detection and destruction of tumor cells than are those in the tumor microenvironment. The complexity of interactions between immune cells and tumor cells is considerable, as tumors regularly alter their cell surface markers, down-regulate local immune cells and interfere with their signaling, and thereby escape from immune-mediated detection and destruction (Khong & Restifo, 2002). A recent study of ovarian cancer patients demonstrated that biobehavioral influences still appear to function within the tumor microenvironment. In these patients, social support was related to higher levels of NKCC both in circulating lymphocytes and in tumor-infiltrating lymphocytes (TIL), whereas distress was related to poorer NKCC in TIL and poorer TH_1 (Type 1 T-helper) cytokine production in all cells, controlling for prognostic indicators (Lutgendorf, Lamkin, Anderson, et al., 2008; Lutgendorf et al., 2005).

Associations between psychosocial factors and immunity in the tumor environment were also observed in a study examining life stress and tumor messenger RNA coding for specific immune factors relevant to basal cell carcinoma (BCC) progression and regression. (Messenger RNA enables the DNA's genetic information to be translated into the creation of proteins.) Among BCC patients with high levels of life stress, those who suffered from maltreatment as children showed a poorer immune response than those without a history of adversity, but in patients without life stress there was no relationship between immune response and early life adversity (Fagundes et al., 2012). Such findings highlight associations between psychosocial risk factors and the cellular immune response in the tumor microenvironment and also highlight the potential role of early life stress in influencing trajectories of vulnerability and disease.

Although there appears to be promising evidence of links between psychosocial factors and cellular immunity in the context of cancer, it is not clear to what extent the magnitude of variability in immune markers associated with psychosocial factors is clinically important or predictive of disease course. Although Steel and colleagues (2007) found that depression in hepatobiliary carcinoma was related to lower NK cell numbers and shorter survival, and that NK cell number mediated the relationship between depression and survival, this type of mediational finding tends to be the exception rather than the rule (e.g., Fawzy et al., 1993; Levy, Herberman, Lippman, D'Angelo, & Lee, 1991), and the importance of stress-related changes in the

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immune response for recurrence and survival is still unclear. It is likely that immune factors operate in concert with a host of other substances to modulate tumor growth; thus examination of mediation may need to include multiple factors. Studies that are specifically powered to answer such mediational questions will be need to be undertaken. An appreciation of the pro-metastatic role of immune cells such as macrophages is also an important consideration.

Glucocorticoid Influences on Cancer Progression

Although we have highlighted adrenergic pathways so far in this discussion, it is important to note that glucocorticoids also have significant effects on several hallmarks of cancer and also have the ability to inhibit the immune response, thereby weakening host surveillance and cytotoxic abilities. Glucocorticoids stimulate the growth of prostate and breast cancer cells (Moran, Gray, Mikosz, & Conzen, 2000), enhance survival of mammary and other cancer cells, inhibit tumor cell apoptosis (Volden & Conzen, 2013), and inhibit the destruction of tumor cells by chemotherapy (Zhang et al., 2006). Glucocorticoids can also alter the tumor microenvironment by modulating transcriptional activity in cells such as tumor-associated fibroblasts and adipocytes to support tumor growth and progression (Volden & Conzen, 2013). Glucocorticoids also downregulate DNA repair activities (Antonova & Mueller, 2008). HPA dysregulation, including flattened diurnal cortisol slopes and elevated nocturnal cortisol (Bower & Lamkin, 2007; Weinrib et al., 2010), has been reported in a variety of cancer populations. For example, nocturnal cortisol in ovarian cancer patients presurgery was 51% higher than that of healthy women (Schrepf et al., 2013). These cortisol elevations are hypothesized to reflect a hypothalamic response to the high levels of inflammatory cytokines secreted by solid tumors and tend to decline over time with successful treatment, at least in ovarian cancer (Schrepf et al., 2013). Distress has been associated with altered cortisol patterns in some of these studies (e.g., Giese-Davis, Sephton, Abercrombie, Duran, & Spiegel, 2004). Moreover, flattened cortisol slopes have been associated with poorer survival in patients with breast, lung, and renal cell cancer (Cohen et al., 2012; Sephton, Sapolsky, Kraemer, & Speigel, 2000; Sephton et al., 2013), suggesting the importance of glucocorticoid-related processes and of cortisol as a biomarker.

Stages of the Cancer Continuum and Biological Processes

Although many of the processes described above can occur at any time in an individual's survivorship, some biological processes may be more or less relevant at different stages of the illness. For example, cellular immunity may have a more salient role in the early stages of tumor development and progression, for attacking primary tumor and for monitoring of tumor cells that have escaped into general circulation and could seed metastases in distant organs. Thus it may be less relevant to examine cellular immune outcomes in studies examining metastatic cancer patients than in studies of early-stage cancer patients or those undergoing surgery.

Different psychological processes may be more salient at different times in the cancer continuum as well. Stress peaks at diagnoses, both initial and recurrence diagnoses (Andersen, Shapiro, Farrar, Crespin, & Wells-DiGregorio, 2005). Though studies vary in estimates of emotional distress, the point prevalence estimates for cancer patients have been estimated to be 20.7% for any mood disorder, 10.3% for anxiety disorders, and 19.4% for any adjustment disorder (Mitchell et al., 2011). By comparison, the National Institute of Mental Health reports 12-month prevalence estimates as being 9.5% for mood disorders and 18.1% for anxiety disorders (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). It must be noted that upwards of 50% of cancer patients do well, manifesting remarkable resilience at diagnosis, treatment, and thereafter. But even when psychological responses during active treatment are satisfactory, a subgroup will still be vulnerable to later distress (Helgeson, Snyder, & Seltman, 2004).

In light of the evidence reviewed above detailing the multiple ways in which psychosocial factors impact physiological mechanisms relevant to cancer progression, we now summarize data regarding the ability of psychosocial interventions to modulate some of the physiological pathways described above and the potential implications of these interventions for survival.

Psychological Interventions and Biobehavioral Outcomes

Thirty years of randomized clinical trials (RCTs) have shown that psychological interventions can consistently reduce patients' stress and enhance their moods (Andersen, 1992, 2002; Osborn, Demoncada, & Feuerstein, 2006; Sheard & Maguire, 1999). A variety of psychological interventions have been employed, many of them multimodal, with the core elements of stress reduction, information, and social support; variable use of cognitive change or other cognitive behavior therapies techniques (e.g., assertive communication); and, infrequently, health behavior components. We make the case, however, that accumulated knowledge regarding endocrine and immune responses, tumor-related processes, disease progression, and biobehavioral factors is sufficient to warrant further scientific investigation, including the study of tumor growth mechanisms.

Since our review does not include correlational or contrasted group designs and instead summarizes experiments—RCTs—with repeated measures, the strength of the evidence is strong. In these trials, patients were randomly assigned to a control condition or a psychological treatment designed to reduce stress, distress, and/or anxiety, and some studies included other outcomes as well. Studies that are noted in this section found Group × Time interactions showing, first, a psychological effect and, second, a biological effect.

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Intervention effects on biological outcomes are of variable reliability and magnitude (for a review, see Antoni, 2012). Findings are nuanced. Variance comes from the heterogeneity of sample sizes (*N*s are noted below), analyses of subgroups within larger trials, intervention components, and differential rates of follow-up, among other factors, which makes generalizations difficult. The majority of trials noted below studied breast cancer patients, and there are only limited data from patients with other types of cancer (i.e., ovarian, Lekander, Fürst, Rotstein, Hursti, & Fredrikson, 1997; prostate, Cohen et al., 2011; melanoma, Fawzy, Kemeny, et al., 1990; cervical, Lutgendorf et al., 2011).

We first note significant outcomes. Positive outcomes reported have included increases in cellular immune response, including stability (in contrast to declines) or elevations in T-cell blastogenesis (Andersen et al., 2004; McGregor et al., 2004) and stability or improvements in NKCC (Cohen et al., 2011; Fawzy, Cousins, et al., 1990; Fawzy, Kemeny, et al., 1990; Witek-Janusek et al., 2008). Significant effects for cytokine outcomes consist of greater production of stimulated or unstimulated TH_1 cytokines such as IL-2, IL-12, and IFN-γ (Antoni et al., 2009; Cohen et al., 2011; Witek-Janusek et al., 2008) and decreases in TH_2 cytokines such as IL-4 and IL-10 or reductions in helper:suppressor ratios (Witek-Janusek et al., 2008). Reductions in cortisol or normalization of diurnal cortisol patterns have also been reported (Antoni et al., 2009; Carlson et al., 2013; Cruess et al., 2000; Phillips et al., 2008; Witek-Janusek et al., 2008). In some of the above trials (e.g., Andersen et al., 2004; Antoni et al., 2009), effects were found for some indicators but not others. However, "matching" need not occur across indicators, considering both the specificity of cell functions and the specificity of responses to stress (see Thornton, Andersen, Crespin, & Carson, 2007, for an example). In contrast, some RCTs testing for biological effects found none (N = 23, Larson, Duberstein, Talbot, Caldwell, & Moynihan, 2000; N = 47, Richardson, Post-White, Grimm, Moye, Singletary, & Justice, 1997; N = 23, van der Pompe, Duivenvoorden, Antoni, Visser, & Heijnen, 1997), and other RCTs found psychosocial improvements correlated with immune changes but showed no specific intervention effects (N = 50, Nelson et al., 2008).

Antoni and colleagues (2011), in secondary analyses, have recently demonstrated that a 10-week group stress management intervention among early-stage breast cancer patients (vs. an active control group) produced changes in leukocyte gene expression observable six and 12 months following the intervention. Specifically, patients in the intervention arm showed altered expression of important regulatory genes, including down-regulation of genes modulating pro-inflammatory and metastatic processes and increased expression of genes relevant for cellular immunity. Promoter-based bioinformatics indicated down-regulation of NF-κB and of the globin transcription factor (GATA) family (related to sympathetic activation), accompanied by increased activity of genes involving the glucocorticoid receptor, which controls inflammation, thus indicating decreased inflammation and greater inflammatory control in intervention participants. These findings were the first from an RCT to indicate that a psychological intervention could have an effect on gene expression in cancer, and they highlight the need to further understand the implications of these dynamics.

In contrast to the literature on psychological outcomes, there have been few trials designed a priori to test for an impact on disease endpoints (e.g., Goodwin, Leszcz, & Ennix, 2001; Kissane et al., 2004, 2007; Küchler, Bestmann, Rappat, Henne-Bruns, & Wood-Dauphinee, 2007; Spiegel et al., 2007), and only three included biomarkers. Fawzy and colleagues (Fawzy, Canada, & Fawzy, 2003; Fawzy, Kemeny, et al., 1990) reported increased stimulated NK cell activity at six months, and significantly longer survival after 6 and 10 years of follow-up, in early-stage melanoma patients who had participated in a six-week coping intervention. In an interim report, Spiegel and colleagues (Sephton et al., 2000) reported analyses of diurnal cortisol slopes and NKCC as predictors of survival in women with metastatic breast cancer (N = 104); analyses were collapsed across study arms. Both flattened slope and lower NKCC predicted lower survival; however, only slope remained predictive when both were entered into the proportional hazards model. A later article on disease outcomes for the entire sample (N = 122) reported no survival differences between groups (Spiegel et al., 2007).

Andersen and colleagues reported increased T-cell blastogenesis for those breast cancer patients randomized to the intervention arm at the end of both the intensive (Andersen et al., 2004) and the maintenance (Andersen et al., 2007) intervention phases. In their examination of maintenance outcomes, intervention effects at four months were tested as predictors of 12-month health outcomes (nurse-rated symptoms, functional status), and it was study arm and distress reduction, rather than immune enhancement, that predicted 12-month health improvements. After a mean of 11 years of follow-up, breast cancer patients in the intervention arm were found to have a reduced risk of breast cancer recurrence (hazards ratio [HR] = 0.55, p = .034; Andersen et al., 2008). Among the patients in both arms who did have a recurrence, intervention-arm patients had a reduced risk of breast cancer death (HR = 0.41, p = .014; Andersen et al., 2010).

Considerations for Future Research

It is important to consider a "second wave" of trials to significantly move the intervention literature forward. Here we discuss characteristics of patients and treatments that could create the conditions that would optimize study of mechanisms and disease endpoints.

Patients

What psychological or behavioral characteristics covary with biological variables *and* disease endpoints? The data suggest three candidate variables: stress, depressive symptoms, and social factors. Their association with biological processes relevant to tumor progression was discussed earlier, as each covaries with disease progression and cancer

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death (Chida et al., 2008; Pinquart & Duberstein, 2010a, 2010b). In many of the biomarker studies described above, it was the social support component of attachment that covaried most strongly with physiological markers and/or with survival (discussed in Lutgendorf et al., 2012; see also Weihs, Enright, & Simmens, 2008). To date in intervention trials, investigators have accrued "all comers," with few exceptions (e.g., Nezu et al., 2003). For example, only nine of hundreds of intervention trials conducted thus far have had significant numbers of patients with MDD (Hart et al., 2012). None of the studies, however, included biobehavioral data. The only available data come from a subset of breast cancer patients with significant depressive symptoms accrued to a larger intervention trial (Thornton, Andersen, Schuler, & Carson, 2009). Data showed that reductions in distress achieved with the intervention were found to be a mechanism for subsequent reductions in pain, fatigue, and inflammation (Thornton et al., 2009). Considering disease characteristics, those with disseminated disease or those with poor treatment profiles (e.g., lung, pancreatic, or ovarian cancer) are vulnerable to higher levels of distress as well (Clark, Loscalzo, Trask, Zabora, & Philip, 2010; Price et al., 2010).

Focusing on the types of patients described above—having at least moderate psychological, biological, and disease progression risk—has implications for the design of intervention trials. These are patients with the potential to show large treatment effects, in contrast to the small to medium effects seen in the majority of the RCTs conducted to date (Schneider et al., 2010). Accrual of patients with at least moderate levels of distress would increase power and increase the likelihood of finding biological or endpoint effects.

It should be noted that psychological or behavioral factors may have direct effects on physiology related to tumor growth and development but may be associated with other behavioral disruptions that also have negative effects, such as disruptions in sleep (Irwin, Olmstead, Ganz, & Haque, 2012), exercise (Scully, Kremer, Meade, Graham, & Dudgeon, 1998), nutrition (Wing, Matthews, Kuller, Meilahn, & Plantinga, 1991), or adherence to medical regimens (Greer, Pirl, Park, Lynch, & Temel, 2008). Other health risks arising from behavioral factors, such as obesity (Parekh, Chandran, & Bandera, 2012), may also have downstream effects on tumor physiology and disease course (Connolly et al., 2002).

Interventions

Few trials have been designed a priori with hypotheses that psychological and behavioral changes from an intervention will "move the biology" and/or alter the course of disease. To embrace the latter goal necessitates a different realm of intervention development and research design. Doing this successfully, however, provides experimental data to confirm or disconfirm correlational findings regarding cellular immunity, tumor growth and spread, and disease course.

If at-risk patients, such as those described above, are accrued, a more intensive treatment will likely be required. This is certainly the case if patients are accrued at the maximally stressful time, that is, at diagnosis and treatment initiation. It is at this time that interventions have their strongest effects, as distress declines steadily thereafter (e.g., Helgeson, Snyder, & Seltman, 2004) with or without an intervention. Efficacious treatments such as cognitive behavior therapy for depression and anxiety exist, as do psychosocial and stress management interventions to treat cancer stress. In the case of depression, a combination treatment—one that treats cognitive dysfunction *and* cancer stress—might be more efficacious than either of two separate treatments alone (see Brothers, Yang, Strunk, & Andersen, 2011, and Hopko et al., 2011, for examples). Moreover, components addressing health behaviors, particularly physical activity, may also be needed. Health behaviors should be measured and monitored as potential mediators of psychological and biological outcomes. Alterations in health behaviors also may be chosen as targets for interventions along with changes in mood. In addition to an intensive treatment, a second phase of therapy involving maintenance (Andersen, Golden-Kreutz, Emery, & Thiel, 2009) or booster sessions (e.g., (Teasdale et al., 2000) may be important to achieve durable change.

Biological Outcomes

The majority of studies to date investigating biobehavioral factors and cancer have examined cellular immunity. At this point, direct and indirect links between biobehavioral factors and many key processes associated with tumor progression have been documented. Thus, linking biobehavioral factors with biological outcome variables implicated in tumor progression in clinical and preclinical settings, as well as in intervention studies, is critical. When feasible, tumor-related biological outcome measures should be assessed in the tumor microenvironment as well as in the periphery. These might include markers of tumor invasion, metastasis, and inflammation, particularly those factors known to be associated with progression of the specific type of tumor being investigated. Research targeting effects of biobehavioral factors and interventions on outcomes of clinical importance is needed as well, for example, on recovery from hematopoietic stem cell transplant (Costanzo, Juckett, & Coe, 2013), recovery from surgery (Neeman & Ben-Eliyahu, 2013), augmentation of immunotherapy or targeted therapies, and others.

Summary

The evidence available to date from both animal and clinical research demonstrates strong links between biobehavioral factors and many of the fundamental biological processes involved in tumor progression. This work is still in its early stages, and delineating relationships of biobehavioral factors with additional "hallmarks of cancer" represents an important task for future research. Work to date points to mediation of many effects by the HPA axis and the SNS, but potential mediators yet to be explored include effects of substances such as oxytocin and of the parasympathetic nervous system. Effects of interactions between biobehavioral pathways and metabolic pathways have been minimally studied in cancer and may be important for

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future research. It is not yet known whether there are stress/depression/social isolation thresholds that set an individual on a positive or negative physiological trajectory or whether there are specific windows during oncology treatment in which patients are most sensitive to biobehavioral effects. A more nuanced understanding of types of psychological stressors, moderating psychosocial factors, and points within the cancer trajectory at which patients are most vulnerable will advance our comprehension of the psychological factors that may be most relevant for cancer outcomes. Effects on physiology have been demonstrated from biobehavioral interventions; however, examination of molecular mechanisms is in the early stages of development. We have argued for a "second wave" of biobehavioral intervention trials focusing on vulnerable patients and clinically relevant markers. Determining the clinical importance of biobehavioral relationships in oncology is one of the important tasks for future research.

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