State of the Science: Stress, Inflammation, and Cancer

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Diagnosis with a life-threatening illness such as cancer is almost universally experienced as stressful. The construct of stress has received substantial consideration as a correlate or predictor of psychological and health outcomes (Andersen et al., 2004) and has often been conceptualized within a stress and coping framework (Lazarus & Folkman, 1984). Biobehavioral factors have long been thought to affect many health processes. The relationship between inflammation of stress and cancer originated centuries ago and is now recognized as a facilitating characteristic of cancer (Mantovani, Allavena, Sica, & Balkwill, 2008). In addition, stress and the stress response are probable mediators of the effects of psychological factors on cancer, and specifically on progression of cancer (Powell, Tarr, & Sheridan, 2013). A substantial amount of new research activity has enlightened scientists and clinicians on the neuroendocrine regulatory function of physiologic pathways in cancer growth and progression (Lutgendorf & Sood, 2011). However, in spite of considerable research over the past several decades, inconsistent data remain a challenge in establishing evidence-based pathways between behavioral risk factors and cancer initiation.

The current state-of-the-science article focuses on stress and inflammation in the context of cancer and will address conceptual definitions, physiologic mechanisms linking stress and inflammation to cancer, and elusive measurement issues. In addition, this article describes approaches that may have value as preventive strategies for reducing risks of cancer progression.

Conceptual Definitions and Connections

Although extensively studied, the definition of stress has varied widely. Stress has frequently been defined as the experience of a negative life event or the occurrence of an event without adequacy to effectively cope with it (Lazarus & Folkman, 1984). Stress can further be characterized by psychological and physiologic responses to an event or circumstance that is perceived as threatening, harmful, or challenging, and typically includes an individual's appraisal of a stressor to indicate his or her perceived level of stress (Lazarus & Folkman, 1984; Kemeny & Schedlowski, 2007). As a result, cognitive appraisal is an important component of stress. Stress is normal; however, when the cellular repair mechanisms cannot catch up with damage, major inflammation can occur (Lutgendorf, Sood, & Antoni, 2010; Thaker & Sood, 2008). It has been well documented that stress increases inflammation at the cellular level, which can directly influence responses from the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), as well as contribute to changes in health-related outcomes (Antoni, 2013). Although some stress can be beneficial, excessive stress throughout a long period of time can result in inflammation. Although stress has been described by many terms, "at the cellular level it has been called inflammation" (Xing, 2012, p. C7).

Inflammation is a physiologic reaction generated by the body in response to injury, infection, or irritation (Reuter, Gupta, Chaturvedi, & Aggarwal, 2010). The links between inflammation and cancer can be viewed as two pathways: "An extrinsic pathway, driven by inflammatory conditions that increase cancer risk, and an intrinsic pathway, driven by genetic alterations that cause inflammation and neoplasia" (Mantovani et al., 2008, p. 436). Inflammation can be either acute or chronic. Acute inflammation is an initial stage of inflammation, called innate immunity, which is mediated through activation of the immune system and can help ward off infections (Reuter et al., 2010). If acute inflammation persists for a short time, it can be beneficial. If inflammation lingers over time, chronic inflammation sets in and may predispose the individual to various illnesses, including cancer (Lin & Karin, 2007).

Subsequently, the connection between inflammation and cancer is now regarded as a promoter of cancer (Aggarwal, Vijayalekshmi, & Sung, 2009).

Cancers are considered "inherently complex collections of heterogeneous pathologies that vary by tissue of origin and constellation of genomic, proteomic, and metabolic alterations" (McDonald, O'Connell, & Lutgendorf, 2013, p. S2). Cancer also is a multistage process defined by initiation, promotion, and progression. However, the majority of cancer-related deaths are caused by metastases resistant to current treatments (Armaiz-Pena, Lutgendorf, Cole, & Sood, 2009). The stress response and inflammation play an important role in the steps required for cancer metastasis. Although a diagnosis with cancer is almost always stressful, the way individuals respond to a cancer diagnosis and their recovery from the stress can vary significantly.

As mentioned previously, a wide variety of cytokines and other proinflammatory markers contribute to both the extrinsic and intrinsic pathways of inflammation-associated cancer (Mantovani et al., 2008). Cytokines are proteins that are produced by cells and function as molecular messengers between cells. They influence changes in cellular behavior that are important in a number of physiologic processes, including regulation, immune response, and inflammation (Colotta, Allavena, Sica, Garlanda, & Mantovani, 2009). The action of cytokines can be either proinflammatory (provoke inflammation) or anti-inflammatory (reduce inflammation). Cytokines, such as interleukins (ILs) and tumor necrosis factors (TNFs), have been implicated in a number of inflammation-associated cancer processes (Germano, Allavena, & Mantovani, 2008). The tumor microenvironment contains various proinflammatory mediators that participate in the signaling process and can promote tumor progression (Kundu & Surh, 2008; McDonald et al., 2013). These proinflammatory cytokines turn on various transcription factors by communicating with cell signaling circuits to bring about cellular responses (Colotta et al., 2009).

Physiology and Mechanisms

As mentioned previously, stressful events, in conjunction with the overall stress response, can activate the HPA axis and the SNS, which causes hormones such as catecholamines and epinephrine to be released, causing increased heart rate and quickened breathing in preparation for the fight or flight response (Armaiz-Pena, Cole, Lutgendorf, & Sood, 2013). The HPA response also releases corticotropin-releasing hormone from the hypothalamus, inducing secretion of adrenocorticotrophic hormone from the anterior cortex (Lutgendorf et al., 2010). Other neuroendocrine factors also are modified following stressful events, including dopamine, prolactin, nerve growth factors, substance P, and oxytocin (McEwen, 2007; Thaker & Sood, 2008). A cancer diagnosis and subsequent treatment almost universally causes immediate stress and, later, can lead to chronic stress while living with the uncertainty of treatment options and cancer prognosis (Antoni, 2013). Literature strongly supports the notion that stress increases the release and production of numerous inflammatory markers (Kiecolt-Glaser et al., 2003), and that health is a result of various complex interactions involving many biobehavioral factors (Kang, Rice, Park, Turner-Henson, & Downs, 2010; Lutgendorf et al., 2010). Increased sympathetic adrenal activity appears to play a significant role in immune changes following acute stress. HPA activity and increased release of glucocorticoids, together with the sympathetic mechanisms, are mainly responsible for the inhibition of cellular and humoral immune responses after chronic stress exposure (Glaser & Kiecolt-Glaser, 2005).

Stress and Stress Response

Although studied extensively, words used to describe stress in the context of cancer have not been definitively defined at the cellular level (Lutgendorf & Sood, 2011). Because much of the recent work in this area has involved the neuroendocrine system, this article will focus primarily on the stress-response system. However, the possibility exists that other neuroendocrine hormones may also heavily influence the physiologic processes involved in inflammation and cancer. The physiologic stress response is considered one of the probable mediators of the effects of psychosocial factors on cancer progression (Lutgendorf et al., 2010). The stress response includes two main systems, the SNS and HPA axis (Thaker & Sood, 2008). The HPA axis response results in the release of cortisol, and, in addition, other neuroendocrine factors, such as dopamine and prolactin, are also modulated following stress (Armaiz-Pena et al., 2013). For example, prolactin appears to play a functional role in tumor cell proliferation and promotes survival of breast, prostate, endometrial, and other cancer cells (McEwen, 2007). Stress can be either acute or chronic; however, with chronic stress, the body experiences a hypervigilant state that can eventually have negative effects on the parameters of stress-response and organ systems (Andersen, Kiecolt-Glaser, & Glaser, 1994).

Inflammation

Rudolf Virchow, a German physician, was the first to study pathology on a cellular level, which provided the basis for his future contributions to oncology (Mantovani et al., 2008). Virchow later discovered leukocytes in tumor tissue, prompting him to begin studying different aspects of inflammation and their connection to cancer (Aggarwal et al., 2009). Inflammation can be

defined as a change in tissue homeostasis, which can lead to a chronic inflammatory response that never ends, further promoting tumor growth, angiogenesis, invasion, and metastasis through the activation of surrounding stromal cells and recruitment of different inflammatory cells (Kundu & Surh, 2012). Although acute inflammation can be a protective response to pathogens or injury, chronic inflammation represents a failure of normal host defense mechanisms and is associated in the initiation, promotion, and progression of cancer (Kundu & Surh, 2008). Inadequate resolution of inflammation can cause prolonged chronic inflammation and has been acknowledged as a factor in diseases such as cancer (Aggarwal, Shishodia, Sandur, Pandey, & Sethi, 2006; Kundu & Surh, 2012). Not surprisingly, estimates suggest that about 25% of all cancers are associated with chronic inflammations of broad origin (Balkwill & Mantovani, 2012; Kundu & Surh, 2012).

Chronic Inflammation and Risk for Tumorigenesis

Sustained cellular injuries have long been suspected of causing inflammation (Aggarwal et al., 2009), and the compelling role of inflammation in cancer has become increasingly more evident in recent decades (Balkwill & Mantovani, 2012; Kundu & Surh, 2008). Convincing evidence strongly supports the fact that chronic inflammation precedes tumorigenesis (Kundu & Surh, 2012).

Many scientists believe that, in large part, cancer is now considered to be a preventable disease. According to Aggarwal et al. (2009), "Only 5% to 10% of cancers are caused by genetic factors whereas the remaining 90%–95% has been linked to lifestyle factors and the environment" (p. 425). Both scientific and epidemiologic studies suggest that certain malignancies arise in tissues severely damaged by chronic inflammation (Allavena, Garlanda, Borrello, Sica, & Mantovani, 2008; Mantovani et al., 2008) (see Table 1).

The physiology underlying the strong connection between chronic inflammation and disease is based on the notion that inflammatory and innate immune cells (e.g., mast cells, neutrophils, leukocytes, natural killer cells) often are recruited at the site of infection or inflammation (Kundu & Surh, 2008). In a prolonged stress environment, activated inflammatory/immune cells generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can promote inflammation in cancer (Aggarwal et al., 2009). Therefore, one possible action underlying chronic inflammation and tumor promotion is the generation of ROS and/or RNS, leading to activation of oncogenes and/or inactivation of tumor suppressor genes (Kundu & Surh, 2008). In addition to changes in DNA, epigenetic factors, such as DNA methylation, play a role in the link between inflammation and cancer (Kundu & Surh, 2008).

Table 1. Association Between Cellular Inflammation and Cancer Risk

Malignancy	Inflammatory Stimulus
Bronchial	Asbestos, cigarette smoke
Cervical	Papillomavirus
Gastric	*H. pylori*-induced gastritis
Hepatocellular	Hepatitis virus (B and C)
Ovarian	Pelvic inflammatory disease; talc powder

Note. Based on information from Allavena et al., 2008.

The human body contains numerous and different types of cytokines and other proinflammatory mediators that contribute to both intrinsic (driven by genetic events) and extrinsic (driven by inflammatory processes) pathways of inflammation-associated cancer. Cytokines are regulatory proteins that are released by cells of the immune system and act as intercellular mediators in an immune response. In part, they have a role in modulating HPA axis responses at all levels—hypothalamus, pituitary, and adrenals (Germano et al., 2008). Some cytokines stimulate or even aggravate inflammation, whereas others reduce inflammatory responses by interacting with specific cell surface receptors. These cytokines turn on various transcription factors that comprise cell signaling circuits to bring about cellular responses. Transcription factors and primary proinflammatory cytokines are important regulatory messengers between the intrinsic (genetic) and extrinsic (immunity) pathways (Colotta et al., 2009).

The tumor microenvironment can be defined as the cellular environment in which the tumor exists, including surrounding blood vessels, immune cells, signaling molecules, and other cells. All the different types of cells within tumors—the proteins that surround them and the conditions they create together—are referred to as the tumor environment (Germano et al., 2008). Tumors begin in the microenvironment; therefore, tumors and the surrounding microenvironment are closely related and in constant interaction (Allavena et al., 2008). Psychosocial factors help set the stage for a macroenvironment that can shape tumor microenvironments to be more or less favorable to tumor growth, presenting an opportunity for researchers in the area of epigenetics.

Although several studies have demonstrated that patient-level psychological, neural, and endocrine processes are associated with differences in tumor-level gene expression, most of these studies reflect cross-sectional or longitudinal associations and no experimental data have yet confirmed that psychological or neural/endocrine interactions influence tumor cell gene expression (Cole, 2013). Still, the relationships among social risk factors, neural and endocrine

signaling to the tumor environment, and transcriptional responses by cancer cells may provide insight into the mechanisms and therapeutic approaches for patients with cancer. A major challenge in psychosocial research in oncology is discovering methods to minimize and account for the confounding effects of different disease characteristics and cancer treatments on biobehavioral measures and clinical outcomes (Antoni, 2013).

Future Direction and Opportunities

Growing evidence suggests that stress, inflammation, and other biobehavioral factors likely affect tumor progression and patient outcomes. Meta-analyses and systematic reviews have demonstrated that chronic stress, in association with altered production of cytokines (inflammation), can promote tumor growth and progression (Aggarwal et al., 2009), suggesting that stress factors likely contribute to poor outcomes in patients with cancer. Equally important, behavioral factors may serve as predictors of clinical outcomes, including response to therapy and overall survival (Sood et al., 2006). In spite of recent advances linking biobehavioral factors and tumor progression, more research is needed to completely understand the complex steps of metastatic progression. This type of research will aid in the efforts to develop new behavioral and pharmacologic alternatives for the treatment of patients with cancer. Biobehavioral research supports the use of cognitive, behavioral, and social constructs during active treatment and beyond, which provides the rationale for the use of selected psychosocial interventions for patients with cancer (Antoni, 2013). Although exact mechanisms are still being explored, some evidence suggests that behavioral and psychosocial factors, which activate the neuroendocrine stress response, can alter inflammatory pathways important in the development and progress of cancer.

Strategies and Approaches to Mitigate Stress, Inflammation, and Cancer Initiation or Progression

Management

Research has shown significant differences in the way patients respond to a diagnosis and subsequent treatment of cancer (Antoni, 2013). Psychosocial adaptation interventions often use cognitive behavioral approaches to modify mood; enhance outlook; appraise stress and coping with cognitive behavioral therapy (CBT); and behaviorally reduce tension, anxiety, and distress through relaxation training, mindfulness, hypnosis, yoga, and other techniques (Chandwani et al., 2012). In addition, these group-based interventions can help to develop and reinforce coping skills, such as aggression and anger management, by providing psychosocial support and modeling good communication. In brief, psychosocial interventions can facilitate relaxation and other anxiety-reducing strategies among patients with cancer, help to modify cognitive appraisals, and develop skills to build and maintain social support (Andersen et al., 2010; Powell et al., 2013).

Because psycho-oncology interventions may significantly influence lifestyle behaviors, such as physical exercise and diet, they play a significant role in creating positive health outcomes in patients with cancer. To what extent these interventions can influence cancer progression and survival is not yet clear. However, evidence exists showing that cognitive behavioral interventions decrease mortality rates in women with breast cancer (Lutgendorf et al., 2010). Stressors associated with a cancer diagnosis and related treatment may have a negative effect on neuroimmune signaling, which may result in the promotion of a tumor (Andersen et al., 1994; Antoni et al., 2006). Substantial evidence demonstrates associations among stress, social factors, and neuroendocrine changes, which can reduce quality of life and promote cancer progression and, perhaps, cancer initiation (Lutgendorf et al., 2010). This evidence suggests the next obvious step is to develop and test the effects of psychosocial interventions, not only on quality of life and cancer progression in general, but on specific parameters of stress factors and HPA activity. Because associations among stress, neuroendocrine changes, and the tumor microenvironment are evident, a necessary extension of human research is testing the effects of psychosocial interventions of quality of life, neuroendocrine parameters, and cancer progression.

Psycho-oncology interventions can be broadly categorized as mind-body, energy-based techniques, natural products, and exercise interventions. The mind-body category includes yoga, mindfulness, CBT, and meditation. These interventions take into account the physiologic, psychic, and spiritual connections between the state of the body and that of the mind. For example, yoga focuses on various postures and breathing techniques, whereas CBT helps patients understand the thoughts and feelings that influence behaviors. Meditation is a practice in which an individual trains the mind or induces a mode of consciousness either to realize some benefit or as an end in itself. Energy-based techniques are holistic healing therapies that focus on manipulating "life force" to bring about balance and wellness. Examples include Reiki, acupuncture, acupressure, and meridian tapping techniques. Natural products refer to vitamins and minerals, botanicals, fish oils, and probiotics. Lastly, exercise broadly consists of walking, swimming, hiking,

bicycling, Zumba (a dance fitness program), and other forms of aerobatics.

Stress-Related Biobehavioral Interventions

Over the past several decades, more than 300 trials of psychological interventions have been conducted in patients with cancer (Antoni, 2013). In an early study by Spiegal, Bloom, Kraemar, and Gottheil (1989), women with metastatic breast cancer received a 12-month, group-based intervention that focused on emotional expression, social support provision, encouraging acceptance of mortality, and decreasing anxiety. Women assigned to the intervention lived twice as long as the women assigned to standard cancer treatment (Spiegal et al., 1989). This was one of the first published reports suggesting that social support improves quality of life in women with breast cancer. Antoni (2013) conducted a meta-analysis of psychological studies (198 studies with total of 22,238 patients), which showed significant small to moderate effects in improving psychological and physiologic indicators. Other trials have shown significant positive effects on psychological adaptation, as well as neuroendocrine and immunologic indicators (Chandwani et al., 2012.)

Fawzy et al. (1990) and Andersen et al. (2008) used psychosocial interventions to affect psychological interventions in patients treated for primary disease and observed increases in the biobehavioral (e.g., cellular immune) process. Patient follow-up was conducted for evidence of intervention effects on disease course (reoccurrence, mortality) for at least 10 years. In Fawzy et al.'s (1990) clinical study of patients with malignant melanoma, participants who were randomized to a group-based, structured, psychosocial intervention arm demonstrated increased coping and decreased negative mood at six weeks, increased interferon-stimulated natural killer cell cytotoxicity at six months, and decreased mortality and recurrence at the 6- and 10-year follow-ups when compared to the usual care group. Although study results at the six-month follow-up did not predict long-term outcomes, findings did show that active coping was associated with positive clinical outcomes.

Similarly, Andersen et al. (2008) conducted a study randomizing postoperative patients to a group-based psychosocial intervention on survival and recurrence and found that the intervention showed a significant reduction in overall and breast cancer-specific mortality rates, as well as a 45% reduced risk of cancer recurrence at a median of 11-year follow-up. Alterations were also noted in several stress-related immune processes that could potentially change disease outcomes, such as increases in cellular immunity measures, decreased stress, and reduced smoking rates. At 12-month follow-up, intervention participants evidenced better health status (Andersen et al., 2008). Other trials have evaluated the effects of stress reduction techniques and have shown positive effects on psychological adaptation and neuroendocrine and immune indicators in patients recruited for study (Andersen et al., 2010; McGregor & Antoni, 2009).

Complementary and Alternative Approaches

The National Center for Complementary and Alternative Medicine (2014) has defined complementary and alternative medicine (CAM) as a group of diverse medical and healthcare systems, practices, and products not usually considered part of conventional medicine. These techniques include mind-body interventions. These modalities have recently been classified as integrative medicine because they are not currently considered an alternative to conventional medicine use (Chandwani et al., 2012). The definition of mind-body includes taking into account the physiologic, psychic, and spiritual connections between the state of the body and that of the mind, and describes the interrelationship between physical and mental health (Chandwani et al., 2012).

CBT is based on principles of psychology and is a type of treatment that helps patients understand the thoughts and feelings that influence behaviors. CBT emphasizes the important role of thinking in how people feel and what people do. Substantial research in this area has shown reduced stress, anxiety, and fatigue, as well as improved sleep in both individuals newly diagnosed with cancer (Doorenbos et al., 2006) and those with advanced cancer (Sherwood et al., 2005).

Meditation is a practice in which an individual trains the mind or induces a mode of consciousness, either to realize some benefit or as an end in itself. Evidence suggests that the categories of meditation, defined by how they direct attention, appear to generate different brainwave patterns. Substantial research has demonstrated that mindfulness therapy benefits patients in oncology settings and is used as a way to reduce stress and improve well-being. Patients report feeling more in control of their thoughts and of their life (Biegler, Chaoul, & Cohen, 2009).

Yoga is an ancient art that began in India as early as 3,000 BC and entered the western world in the 19th century (Buffart et al., 2012). Beginning courses in yoga focus on various postures and breathing techniques. Research supports the belief that yoga may improve health through down-regulation of the HPA axis and SNS (Kiecolt-Glaser et al., 2010). Other research has shown that yoga improves fatigue, sleep, quality of life, and general well-being. A systematic review and meta-analysis of 13 randomized, controlled trials on effects of yoga on physical and psychosocial outcomes in patients

with cancer and survivors found yoga to be a feasible intervention with beneficial effects on physical and psychosocial symptoms (Buffart et al., 2012). However, the majority of studies focused on well-being, fatigue, sleep, or quality of life, and only a few studies investigated the efficacy of a yoga intervention on stress and inflammation (Buffart et al., 2012). One study conducted in patients with chronic inflammatory disease showed a reduction in stress (plasma cortisol and β-endorphin) and inflammation (IL-6 and TNF) from day 0–10 (Yadav, Magan, Mehta, Sharma, & Mahapatra, 2012). In another study, Kiecolt-Glaser et al. (2010) reported that a yoga intervention with 50 healthy women decreased their levels of inflammatory markers significantly and could impact health benefits. In addition, Kiecolt-Glaser et al. (2014) found that breast cancer survivors reported the positive effects of a yoga intervention on fatigue and the inflammatory markers IL-6, TNF, and IL-1B.

Natural products are a thriving business for patients seeking an integrated health program. Commonly used herbal supplements for stress include lemon balm, kava, valerian root, lavender, St. John's wort, and passionflower (Ernst, 2006). Some natural products used include vitamins, minerals, botanicals such as green tea and soy, fish oils, mushrooms, and probiotics. However, minimal research has been conducted in this area and more rigorous research is needed. Other limitations include the lack of product standardization, nonspecific outcome measures, and safety issues concerning side effects and lack of U.S. Food and Drug Administration approval.

Exercise has been established as an effective adjuvant therapy to control adverse consequences associated with cancer and subsequent treatments (Faul et al., 2011; Midtgaard et al., 2005; Mock et al., 1997; Yang, Tsai, Huang, & Lin, 2011). Exercise behaviors can include walking, swimming, hiking, bicycling, and Zumba. Although strong evidence exists that walking is beneficial for patients with cancer, less research has been conducted on other types of physical activity. Walking is the only exercise that has been shown to significantly reduce fatigue and improve sleep and well-being in patients with cancer (Mock et al., 1997; Payne, Held, Thorpe, & Shaw, 2008).

Energy-based techniques are a broad group of holistic-healing therapies focused on manipulating life force to bring about balance and wellness. The use of CAM has increased substantially at the point of cancer diagnosis, during treatment, and following treatment. Those techniques include acupuncture, meridian tapping, acupressure, energy-based polarity therapy, Reiki, massage, mindfulness-based stress reduction, and therapeutic touch (Chandwani et al., 2012). However, many of these studies have methodologic issues including small sample size, various types of disease, lack of randomization, and a variety of psychosocial measures, and few used physiologic measures, therefore limiting generalizability.

Other Preventive Inflammation Opportunities

The plasma or serum levels of inflammatory cytokines are elevated in patients with a wide range of advanced cancers, which is generally considered a poor prognostic sign (Balkwill & Mantovani, 2012). Based on previous cancer-related inflammation research, it appears that anti-inflammatory agents may have potential as cancer preventative agents (Balkwill & Mantovani, 2012). For example, several studies suggest that aspirin reduces the risk of certain cancers, such as colon cancer, solid tumor cancers, and vascular disease (Balkwill & Mantovani, 2012). The cancer-preventive potential of specific antagonists of cytokines is more elusive, as well as the fact that these types of agents can have significant side effects. Agents with potential to suppress inflammation include TNF blockers, such as thalidomide, and COX-2 inhibitors, such as celecoxib. Animal models also suggest a role for TNF in the promotion of early cancers, and the administration of IL-1 to patients with myeloma has been reported to inhibit progression to advanced disease (Lust et al., 2009). Knowledge of cancer-related inflammation has reached the point where researchers can hopefully begin to translate this knowledge into new pharmacologic approaches to reduce inflammation in patients with cancer.

Implications for Practice

Cancer and cancer-related treatment cause stress, which affect the neuroimmune regulation that promotes inflammatory processes, contributing to both symptom exacerbation and recurrence (Antoni et al., 2006). Oncology nurses and physicians recognize that cancer treatment is rapidly moving toward individualized regimens based on parameters that are distinct in each patient. These therapies fall under the term *targeted therapies*. However, the complexity and inherent variability of the human biobehavioral response make it critical to define the behavioral and/or pharmacologic interventions that are most likely to benefit individual patients.

Improvements in psychological adaptation have been linked to an improved physiologic profile during and following treatment, which may increase the chances for disease-free survival (Antoni, 2013). Research suggests that stress, inflammation, and some psychological interventions can influence biobehavioral processes in patients with cancer (Antoni, 2013). Additional research is needed to determine whether these changes can influence the clinical course of these diseases. Future research also will benefit from "parsing out effects of different biobehavioral states such as stress,

depression, fatigue, to determine if there is one common pathway, or to what extent there are discrete biological signatures of these different psychological constructs" (Green, O'Connell, & Lutgendorf, 2013, p. S6). Equally important is determining what the most important intermediate outcome variables are for biobehavioral cancer research. In addition to survival and progression of disease, knowing to what extent genetics, metabolics, and epigenetic changes affect quality of life is an essential outcome for this work.

Biobehavioral approaches in research are essential to understanding the relationships among stress, inflammation, and cancer. The conceptual role of physiologic responses as a moderator will likely be determined by the nature of the inquiry and based on specific research interests. A review of stress and inflammation literature strongly indicates the significance of nurse scientists and the role they need to play in biobehavioral research (Kang et al., 2010). Targeting interventions based on the underlying etiology of commonly experienced stressors and inflammation will be the new paradigm in symptom management. Nurses must develop strong interprofessional collaborations with other disciplines. At the center of these collaborations, nurse researchers can provide their unique knowledge and skills to develop personalized targeted interventions to their patients.

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