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Neuroendocrine influences on cancer progression

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ABSTRACT

During the past decade, new studies have continued to shed light on the role of neuroendocrine regulation of downstream physiological and biological pathways relevant to cancer growth and progression. More specifically, our knowledge of the effects of the sympathetic nervous system (SNS) on cancer biology has been greatly expanded by new data demonstrating how the cellular immune response, inflammatory processes, tumor-associated angiogenesis, and tumor cell invasion and survival converge to promote tumor growth. This review will summarize these studies, while synthesizing clinical, cellular and molecular research that has continued to unearth the biological events mediating the interplay between SNS-related processes and cancer progression.

1. Introduction

Biobehavioral factors, such as chronic stress, have long been thought to affect many health processes, including cancer (Antoni et al., 2006). To better understand the effects of chronic stress on human disease, it is imperative to study the biological mechanisms underlying this process. The past decade has produced a substantial amount of new work that has shed light on the role of neuroendocrine regulation of physiological pathways in cancer growth and progression. While there is mounting evidence suggesting that neuroendocrine stress mediators can enhance cancer progression, clinical data have remained largely inconsistent in their support of a relationship between behavioral risk factors and cancer initiation. Here, we summarize current knowledge about the potential influences of stress-induced neuroendocrine responses on key cellular and molecular processes that lead to cancer progression and highlight recent advances in this field (Fig. 1 and Table 1).

2. Stress response

The stress response is a complex process that is largely mediated by the sympathetic nervous system (SNS) and the hypothalamic pituitary adrenal (HPA) axis (Glaser and Kiecolt-Glaser, 2005). Once these compartments are activated, catecholamines and glucocorticoids are released into the bloodstream or directly by neurons into various organs. Epinephrine (Epi) and norepinephrine (NE) act as hormones and neurotransmitters that are able to control physiological responses while mediating the "fight-or-flight" stress response that is responsible for rapid elevation of blood pressure, increased heart rate and release of glucose from energy stores. Conversely, the third catecholamine, dopamine (DA), serves as a neurotransmitter that primarily functions to mediate the body's ability to sense pleasure and pain. Besides catecholamines, glucocorticoids are also involved in the stress response and can control many normal physiological activities such as circadian rhythms, immune function and restoration of homeostasis (Glaser and Kiecolt-Glaser, 2005). Although stress can be divided into many categories such as physical, mental, emotional, social, or biological, it is mainly grouped into two major types: acute and chronic. In this review, we will focus on chronic stress conditions that keep the body in a constant state of "overdrive", leading to deleterious downstream effects, deregulating the stress response and negatively affecting many organs systems (McEwen, 1998).

It is important to note that during chronic stress, NE and Epi remain elevated, while DA levels are quickly depleted following an initial increase in the acute phase (as reviewed in Moreno-Smith et al., 2010). This shift in catecholamine levels can result in a more conducive microenvironment for tumor growth (Antoni et al., 2006). For example, in the rat, it is well known that SNS-induced catecholamine release can play a role in the regulation of peripheral organs, such as the ovary, where stress hormones affect ovarian hormone production and menstrual cycle (Aguado and Ojeda, 1984; Ben-Jonathan et al., 1984). Interestingly, rat ovaries have significantly higher catecholamine levels than those found in

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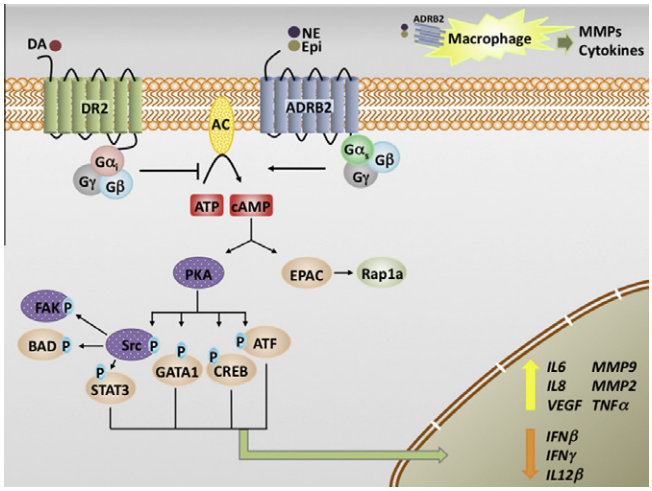

Fig. 1. Overview of catecholamine-mediated signaling pathways in cancer. Norepinephrine (NE) or Epinephrine (Epi) bind to beta adrenergic receptors (ADRB), resulting in increased cyclic AMP (cAMP) levels that induce Protein Kinase A (PKA) activity. PKA can then phosphorylate several proteins, such as CREB/ATF, GATA1 and Src leading to increased activity of several pro-tumoral proteins. Additionally, elevated levels of cAMP also result in the activation of Exchange Protein Activated by cAMP (EPAC) and its associated signaling cascade. Conversely, upon binding to dopamine receptor 2 (DR2), dopamine (DA) can inhibit adenylyl cyclase (AC) function leading to decreased cAMP and downstream pro-tumoral protein levels.

plasma (Ben-Jonathan et al., 1984). Furthermore, rat ovarian catecholamine levels are augmented in response to increased sympathetic activity and this elevation has been associated with the appearance of precystic follicles (Lara et al., 2000). Catecholamine levels are also elevated in the murine bone marrow, as nerve endings and bone marrow cells possess the ability to secrete them into the bone marrow microenvironment (Maestroni, 2000).

3. Effect of chronic stress on animal models of disease

Animal models of human disease are a powerful tool in our effort to understand and study the mechanisms by which biobehavioral factors can promote tumor growth and metastasis. Various approaches have been used to model disease (Frese and Tuveson, 2007). For example, in orthotopic tumor models, human cancer cells are implanted into the organ of origin where they grow and eventually disseminate. Additionally, tumors can be generated by exposure to carcinogens that lead to site-specific disease or they can arise from transgenic or mutant animals carrying insertions, deletions, or mutations in gene sites known to enhance the development of site-specific cancers. Animal tumor models are available for a wide range of cancers, including lung, colon, skin, bladder, mammary, prostate, head and neck, esophagus, ovary, and pancreas. The effect of neuroendocrine factors on cancer have been studied in several of these models by utilizing various types of stressors, including restraint stress, swim stress, surgical stress, social confrontation and hypothermia (Table 1). Restraint stress has been shown to increase norepinephrine, epinephrine and corticosterone levels in various murine-based models (as seen in Thaker et al., 2006), leading to increased inflammatory responses and depressed antiviral cellular immunity (as reviewed in Antoni et al., 2006). Restraint stress has also been consistently associated with elevated interleukin 6 levels (Nilsson et al., 2007). While most of these models have been used in the context of the effects of stress on the immune system, new evidence is suggesting that increased neuroendocrine activity can lead to increased tumor growth by immune independent mechanisms (Armaiz-Pena et al., 2009).

4. Chronic stress and cancer initiation

Several studies have reported that there is no relationship between stressful events (Duijts et al., 2003) or personality (Bleiker et al., 2008) and cancer incidence, while other reports seem to suggest that severe life stressors might induce cancer development (Lillberg et al., 2003; Price et al., 2001). Interestingly, viral infections have been noted to be important co-factors at the initiation stage of several human cancers. Central to this process is the fact that all major human tumor-associated viruses have been found to be responsive to beta-adrenergic receptor (ADRB) or glucocorticoid-dependent signaling cascades. For example, human herpesvirus 8, which induces Kaposi's sarcoma, possesses a cyclic adenosine monophosphate (cAMP) response element in the promoter of an important viral transcription factor (Chang et al., 2005). Additionally, ADRB stimulation of the viral host cell has been shown to increase cAMP response element binding (CREB)-mediated expression of viral oncogenes and growth factors that

Table 1
Representative studies on the effects of stress and stress-associated hormones on cancer.

Experimental condition	Species	Main biological effect	Cancer type	Effect on tumor growth	References
Immobilization stress	Mice	Increased angiogenesis	Ovarian	Increased growth	Thaker et al. (2006)
Enriched environment	Mice	Decreased proliferation	Skin, colon	Decreased tumor growth	Cao et al. (2010)
Restraint stress	Mice	Anchorage-independent survival	Ovarian	Increased growth and metastasis	Sood et al. (2010)
Force swim, surgical stress	Rat	Suppressed NK cell activity	Leukemia, breast	Increased growth	Ben-Eliyahu et al. (1999)
Restraint stress	Mice	Suppressed immune function	Skin	Increased susceptibility to UV-induced disease	Saul et al. (2005)
Restraint stress	Mice	Increased macrophage infiltration	Breast	Increased metastasis	Sloan et al. (2010)
Dopamine administration	Mice, Rat	Decreased angiogenesis	Gastric	Decreased growth	Chakroborty et al. (2004)
Depression	Human	Increased cortisol, IL-6	Ovarian	n/a	Lutgendorf et al. (2008a–c)
Psychological intervention	Human	Increased immune activity	Breast	Improved survival	Andersen et al. (2010)
Social support	Human	Increased immune activity	Ovarian	n/a	Lutgendorf et al. (2005)
Beta-blocker Administration	Human	n/a	Breast	Decreased mortality	Barron et al. (2011)
Stressful life events	Human	n/a	Breast	No association with cancer risk	Duijts et al. (2003)
Personality	Human	n/a	Breast	No association with cancer risk	Bleiker et al. (2008)
Stressful life events	Human	n/a	Breast	Association with cancer risk	Lillberg et al. (2003)
Stressful life events	Human	n/a	Breast	Association with cancer risk	Price et al. (2001)

are known to promote tumor growth, and Epstein-Barr virus and high-risk variants of the human papilloma virus are similarly subject to activation by glucocorticoids (Cacioppo et al., 2002; Glaser et al., 1995). Furthermore, genetic factors have been implicated in stress-mediated cancer initiation. One study identified the genetic status at the interleukin 6 (*IL6)* locus as an important factor in ADRB activation of the transcriptional factor GATA1, potentially explaining how social adversity can affect health risk (Cole et al., 2010; Webster et al., 2002). Even though there are emerging data supporting the role of neuroendocrine factors in cancer initiation, knowledge in this area remains limited and needs further investigation.

5. Effects of chronic stress on the metastatic cascade

The majority of cancer-related deaths are caused by metastases resistant to current treatment regimens. Metastasis is a sequential process in which a cancer cell has to overcome and complete multiple steps in order to colonize distant tissues. For tumors to grow beyond 1 mm, recruitment of new blood vessels has to occur (Fidler, 2003). This new vasculature is needed to deliver the nutrients required to support further growth and to provide a route for the dissemination of tumor cells to distant sites. For this dissemination to occur, the tumor cell must have the capacity to invade through the basement membrane and embolize into the bloodstream. While traveling through the bloodstream, it must then adhere and arrest in capillary beds and extravasate into parenchymal tissues. Once tumor cells have colonized a new site, they must interact with the local microenvironment to grow and develop their own blood supply. Tumor cells must perform these steps while evading immune system surveillance, and the cells that fail in any of these tasks cannot metastasize (Fidler, 2003). New evidence points toward the stress response playing an important role in many of the steps required for cancer metastasis (Armaiz-Pena et al., 2009). In the following subsections, we will summarize the current knowledge regarding these interactions and the underlying mechanisms mediating these effects.

5.1. Tumor growth

Once a tumor is established at the primary site, its growth is determined primarily by nutrient and oxygen diffusion. However, once tumor cells establish a metastatic site, its growth is dependent on the net balance of a multitude of autocrine, paracrine and endocrine signals. Several studies have shown that the effect of stress hormones on cancer cell proliferation varies according to the specific hormone influences and the tumor type studied (as reviewed in Antoni et al., 2006). For example, in a rat model of breast cancer, ADRB activation was associated with increased tumor growth (Marchetti et al., 1991). Downstream mediators of ADRB signaling, such as CREB, have been shown to promote stress hormone-induced tumor cell proliferation, migration and angiogenesis and to inhibit apoptosis in animal models of human disease (Cole and Sood, 2012; Duijts et al., 2003). Conversely, in human melanoma and neuroblastoma cells, catecholamines appear to inhibit tumor cell proliferation, a process that may be mediated by alpha adrenergic receptors (ADRA) (Bleiker et al., 2008; Lutgendorf et al., 2002; Pifl et al., 2001; Scarparo et al., 2004). Additionally, much of the data on the effects of catecholamines on normal cell proliferation indicates that catecholamines are suppressors of cell proliferation, as it has been shown that stress hormones can delay wound healing, mainly by decreasing keratinocyte proliferation (Flaxman and Harper, 1975; Merritt et al., 2008).

It has been shown that NE can inhibit neuroblastoma cell growth, primarily in cells that express the DA transporter (Pifl et al., 2001). Furthermore, in cells that can uptake DA, the proportion of non-dividing cells was significantly increased after treatment with NE. These data point towards a role for DA in inhibiting cell proliferation and counteracting NE-mediated effects. Interestingly, in human prostate carcinoma cells, Epi treatment resulted in epithelial prostate cancer cells acquiring neuroendocrine characteristics (Cox et al., 1999). This process has been associated with poor prognosis in prostate cancer patients. Although these cells have minimal proliferative activity, they provide pro-proliferative paracrine stimuli for nearby cells. Furthermore, it is well known that among epithelial tumors, some decrease in proliferation may be reflective of a more invasive phenotype.

5.2. Angiogenesis

One key to tumoral progression is the development of a new blood supply that can sustain rapid growth and distant metastases. Neovascularization is a multifactorial, complex process that requires the activation of many signaling pathways to induce endothelial cell proliferation and migration. There are several proteins known to induce and promote angiogenesis, including vascular endothelial growth factor (VEGF), interleukin 6 (IL-6), interleukin 8 (IL-8), transforming growth factor alpha and beta (TGF-α and β) and tumor necrosis factor alpha (TNF-α) (Moreno-Smith et al., 2011). Recent studies have examined the relationship between alterations in biobehavioral states and increases in pro-angiogenic factors. Data now demonstrate a clear link between social support and elevated serum VEGF levels in ovarian cancer patients (Lutgendorf et al., 2002). Furthermore, poor social support was associated with higher tumor VEGF levels as well. These results were validated in murine brown adipocytes and human ovarian cancer cells *in vitro* that showed that norepinephrine and the beta agonist isoproterenol were both capable of inducing VEGF expression and that this effect was largely mediated by the ADRB/cAMP/Protein Kinase A (PKA) signaling axis (Fredriksson et al., 2000; Lutgendorf et al., 2003). We have demonstrated that tumor-bearing mice exposed to chronic restraint stress had higher tissue catecholamine levels, as well as greater tumor burden and more invasive disease, than mice not exposed to restraint stress (Thaker et al., 2006). Additionally, it was shown that NE and Isoproterenol increased VEGF levels in mice undergoing chronic stress and that this effect was abrogated by the use of a beta-blocker, which validates the role of ADRB in this setting. Furthermore, restraint stress resulted in increased tumoral microvessel density via the elevated VEGF production (Thaker et al., 2006).

It is well known that IL-6 is a cytokine that plays an important role in tumor progression by inducing angiogenesis, among other functions. Interestingly, ovarian cancer patients who experience distress and poor social support have elevated IL-6 levels, which have been associated with shorter survival in epidemiologic studies (Costanzo et al., 2005; Lutgendorf et al., 2008c). On the other hand, patients with stronger social support had lower IL-6 levels in serum and ascites. We have shown that NE can induce IL-6 production in ovarian cancer cells through a mechanism mediated by the Src kinase (Nilsson et al., 2007).

Other factors are also known to be key mediators in the induction of angiogenesis by chronic stress. Chronic stress can result in the activation of signal transducer and activator of transcription 3 (STAT-3), which increases tumor-associated angiogenesis in an orthotopic model of ovarian cancer (Landen et al., 2007). More specifically, it was demonstrated that NE and Epi can induce STAT-3 activation, leading to its translocation into the nucleus and subsequent binding to DNA to promote transcription of genes associated with angiogenesis, among other processes (Landen et al., 2007).

Additionally, tumor-bearing mice undergoing chronic stress had increased levels of the pro-angiogenic factor, interleukin 8 (IL-8) that were mediated by FosB (Moreno-Smith et al., 2010; Shahzad et al., 2010). Elevated levels of IL-8 were associated with increased microvessel density, all of which were completely abrogated by IL-8 gene silencing (Moreno-Smith et al., 2010; Shahzad et al., 2010).

Alternatively, *in vivo* mouse and *in vitro* studies have shown that DA can abrogate VEGF-induced angiogenesis by reducing the downstream activity mediated by one of its receptors, VEGFR-2 (Basu et al., 2001). Furthermore, studies performed on DA receptor 2 (DR2) knockout mouse models validate these findings as they exhibit more tumor burden, which is associated with increased angiogenesis (Basu et al., 2004). Our group has utilized a mouse model of chronic stress, in which tumoral DA levels are significantly decreased, to show that chronic stress results in increased tumor growth, angiogenesis and metastasis (Moreno-Smith et al., 2011). Recently, we have demonstrated that DA restoration counteracts the effect of chronic stress on tumor growth and angiogenesis through activation of DR2 (Moreno-Smith et al., 2011). Taken together, these studies support a major role for neuroendocrine factors in tumor angiogesis while opening the door for beta-blockers and DR2 receptor antagonists for the abrogation of stress-induced effects on cancer.

5.3. Adhesion

Tumor cell adhesion to the extracellular matrix within the microenvironment is key to the invasion of cancer cells and their spread to distant organs. The extracellular matrix is largely composed of collagen, laminin, fibronectin and other glycoproteins. Tumor cells adhere to these proteins mainly through the interaction of integrins on the tumor cell surface with the extracellular matrix. Even though the mechanisms underlying adhesion to matrix components are not clearly understood, it is well known that cAMP/PKA-mediated pathways are involved in the regulation of guanosine triphosphate (GTP) hydrolysis, Ras homolog gene family member A (RhoA) and Rac, which are important in the cell adhesion process (Mercurio and Rabinovitz, 2001). Recently, it was shown that cAMP, besides targeting PKA, can also signal through exchange protein activated by cAMP (EPAC), a widely expressed exchange factor for the small GTPases Ras-related protein (RAP) 1 and 2 (Mercurio and Rabinovitz, 2001). More importantly, it is well known that EPAC can control a number of cellular processes that were once thought to be exclusively regulated by PKA. For example, cAMP controls cell adhesion through an Epac–Rap1-mediated pathway. Furthermore, it has been demonstrated that isoproterenol can promote ovarian cancer cell movement and adhesion via laminin-5 through an Epac1 dependent pathway (Bos, 2006). Another *in vitro* study reported that isoproterenol can stimulate cell adhesion to fibronectin in a cAMP-mediated Epac–Rap1 pathway (Rangarajan et al., 2003). Taken together, the data demonstrate that stress hormones can promote the attachment of cancer cells to the matrix. Understanding this process is paramount, especially for certain cancers, such as ovarian cancer, in which the cancer cells shed off from the primary tumor and implant at multiple peritoneal sites.

5.4. Invasion

As part of the metastatic cascade, cancer cells have to separate from the primary tumor site, move through the basement membrane, survive the journey through the blood supply, and invade distant organs. Stress hormones can increase the invasiveness of cancer cells, mainly by increasing matrix metalloproteinase protein production and acting as chemoattractants to induce cell migration (Armaiz-Pena et al., 2009). Several *in vitro* and *in vivo* studies have demonstrated that NE can increase the migratory and metastatic potential of several types of cancers by inducing the activation of ADRB-mediated signaling cascades (Voss and Entschladen, 2010). More specifically, we have shown that NE can increase the *in vitro* invasive potential of human ovarian cancer cells and that a beta blocker completely abrogated this effect (Sood et al., 2006). Additionally, several *in vivo* and *in vitro* studies have shown that stress hormones can significantly increase the production of matrix metalloproteinase (MMP) 2 and 9 by ovarian cancer cells through ADRB-mediated pathways (Sood et al., 2006; Thaker et al., 2006). This effect was recapitulated by the use of isoproterenol, which significantly increased tumor cell infiltration into normal tissue, while beta-blockers abrogated this effect. Experiments using human head and neck cancer cells have shown similar results, demonstrating that MMP levels were substantially elevated in response to NE treatment in these cell lines (Yang et al., 2006). Additional studies have provided evidence that pro-tumoral macrophages and other stromal cells in the tumor microenvironment are partially responsible for the release of MMPs. Orthotopic mouse models of breast cancer have shown that chronic stress did not induce primary tumor growth, but did lead to a 30-fold increase in the rate of metastasis (Sloan et al., 2010). Subsequently, it was found that these effects were mediated by ADRB signaling and increased infiltration of protumoral macrophages into the primary tumor site. Furthermore, in human studies, our group has shown that ovarian cancer patients with depressive symptoms and high levels of stress had increased MMP9 in tumor associated macrophages and incubation of monocyte derived macrophages with that hydrocortisone or NE resulted in increased levels of MMP9 (Lutgendorf et al., 2008b). These data now support a role for neuroendocrine factors in the potentiation of tumor cell invasiveness.

5.5. Tumor cell survival and anoikis

To complete the metastatic process, a tumor cell has to evade apoptotic signals. There is now evidence that catecholamines may make cancer cells less sensitive to apoptotic factors (Armaiz-Pena et al., 2009). For example, a recent study has shown that Epi can reduce apoptosis sensitivity in breast and prostate tumor cell lines through activation of ADRB2-mediated pathways. More specifically, when cancer cells were exposed to Epi, ADRB2 activation resulted in the induction of PKA signaling pathways, which led to the phosphorylation of B-cell lymphoma-2 (Bcl-2) associated death promoter (BAD) (Sastry et al., 2007). BAD is known to have pro-apoptotic functions in its unphosphorylated form, but once phosphorylated it releases Bcl-2 and B-cell lymphoma-extra large (Bcl-xL), thereby inhibiting the apoptotic process (Sastry et al., 2007). Even though emerging data support the role of stress hormones in avoiding apoptosis, there are still some models in which NE and DA can induce apoptosis, such as neuroblastoma cells, but this effect was not seen in lung cancer cells (as reviewed in Moreno-Smith et al., 2010). Because DA might largely mediate these effects, our group has examined its role in apoptosis and found that DA can induce *in vivo* and *in vitro* ovarian cancer cell apoptosis through dopamine receptor 2 (DR2) (Moreno-Smith et al., 2011). Furthermore, it has been shown that glucocorticoids can work in concert with catecholamines to aid tumor growth (Herr et al., 2003). In lung cancer cells, cortisol treatment increased membrane-bound ADRB, while potentiating the cellular effects of interleukin-1α, interleukin-1β, and tumor necrosis factor-α (Nakane et al., 1990).

Another process affected by catecholamines in the context of cancer biology is avoidance of anoikis. Anoikis is a cellular process by which normal cells undergo apoptosis once they are detached from the extracellular matrix and neighboring cells. We found that

NE and Epi can protect ovarian cancer cells from anoikis by inducing the activation of focal adhesion kinase (FAK) through an ADRB/PKA/Src dependent pathway (Sood et al., 2010). Furthermore, we showed that NE-induced FAK activation was required for chronic stress-induced tumor growth in a murine orthotopic ovarian cancer model. Moreover, in ovarian cancer patients, our data suggested that both depression and tumor norepinephrine levels were associated with increased FAK activation, which was, in turn, associated with decreased survival (Sood et al., 2010). Collectively, these studies suggest that stress hormones can increase tumor cell survival by increasing the ability of cancer cells to avoid apoptotic processes.

6. Cancer-related immunity

Glucocorticoids and catecholamines have a profound effect on the immune response. In the setting of chronic stress, altered release of glucocorticoids and catecholamines will result in suppression of the immune system, enabling tumor cells to avoid elimination (as reviewed in Antoni et al., 2006). More specifically, it has been shown that natural killer cell function is compromised in tumor bearing animals and cancer patients that underwent surgery. (Ben-Eliyahu et al., 1999; Pollock et al., 1991). Animal models of disease have shown that tumor incidence and progression can be exacerbated by chronic stressors, mainly through the reduction of type 1 cytokines and T cell and natural killer cell activity resulting in impaired antigen presentation and higher numbers of regulatory T cells (Webster et al., 2002). For example, mice exposed to ultraviolet radiation and undergoing chronic stress had an increased incidence of squamous cell carcinoma resulting from the reduction of type 1 cytokines and protective T-cell infiltrates (Saul et al., 2005). While the role of the SNS was not investigated, it is conceivable that such dynamics could play a role in the stress effects on skin immune cell infiltration.

In humans, it is known that states such as chronic stress, loneliness and depression can decrease immune function via mechanisms including adrenergic and glucocorticoid mediated pathways (Antoni et al., 2006). Furthermore, breast cancer patients that underwent surgery demonstrated immune alterations such as lowered T cell mediated secretion of T_H1 versus T_H2 cytokines, a poorer T-cell response to mitogen stimulation and reduced natural killer cell activity (Andersen et al., 1998; Blomberg et al., 2009; Thornton et al., 2007). Advanced breast cancer patients diagnosed with clinical depression exhibit decreased cellular immunity (Sephton et al., 2009). Moreover, in ovarian cancer patients, distress at the time of surgery was associated with decreased natural killer cell activity in tumor infiltrating lymphocytes (TIL) and lower T cell secretion of T_H1 and T_H2 cytokines in peripheral blood mononuclear cells and TIL (Lutgendorf et al., 2005). Conversely, higher social support was associated with increased natural killer cell activity (Lutgendorf et al., 2008a). In summary, there is a substantial amount of research related to the effects of chronic activation of the stress response on the immune system that can lead to increased tumor growth. These effects are mainly due to the disruption of the delicate balance among the central nervous system (CNS), endocrine and immune systems.

7. Clinical studies

Human studies investigating the effects of biobehavioral influences on cancer have focused on two distinct strategies: psychosocial interventions and pharmacological approaches. Although there are promising data relating psychosocial interventions to survival (Andersen et al., 2010, 2008), additional work is needed to understand the efficacy of such interventions and the physiological mechanisms mediating such results. These data are discussed in further detail in another article in this issue.

ADRBs are the key components of the stress signaling pathway, and data now suggest that they also play a major role in protumoral signaling pathways (Cole and Sood, 2012). This convergence allows for the use of clinically available beta-blockers as a viable strategy for disrupting the effects of altered biobehavioral states on tumor growth and progression. At the time of this review, most of the data related to clinical efficacy of beta-blockers have been obtained from non-randomized observational studies. However, some studies have started to shed light on the involvement of ADRBs in cancer risk and survival. For example, an epidemiological study found that patients who used beta-blockers had a reduced risk of developing prostate cancer, which suggests that ADRBs play a role in the development of prostate cancer (Perron et al., 2004). A second study found that the use of beta-blockers by patients with cardiovascular disease significantly reduced their risk of cancer (Algazi et al., 2004). Furthermore, recent studies have reported that beta-blocker use can improve the outcomes of breast cancer patient (Barron et al., 2011; Melhem-Bertrandt et al., 2011; Powe and Entschladen, 2011). We recently analyzed the US Food and Drug Administration's Adverse Event Reporting System (262,262 patients) to examine whether the use of beta-blockers by patients affected cancer related mortality. Our analysis revealed that mortality was reduced by an average of 17% across all major cancer types if patients were treated with beta-blockers (Armaiz Pena et al., 2011). Even though these data suggest a potential role for beta-blockers as adjuvant therapy for cancer patients, additional studies are needed to further examine their protective effects.

8. Summary

In summary, there is strong and growing evidence to suggest that altered biobehavioral states can promote tumor growth and progression, whereas data supporting their role in cancer initiation remain weak. In this light, studies such as, a recent report indicating that chronic stress, through ADRB2-mediated signaling, leads to the accumulation of DNA damage in murine and human cell lines (Hara et al., 2011) suggest that new research strategies may shed light on the question of whether and/or under what conditions biobehavioral states, such as depression and chronic stress, might contribute to cancer initiation. Despite the significant progress seen in the past decade linking biobehavioral factors and tumor progression, more research is required to completely understand how stress hormones affect the many steps of the metastatic cascade. Such research efforts may lead to the development of new behavioral and pharmacological alternatives for the treatment of cancer patients. Animal models of disease have shown that beta-blockers can reduce or substantially eliminate many of the deleterious effects of chronic stress related to cancer. Human studies are now starting to support a protective role for beta-blockers in cancer patients. We have also identified other targetable proteins, such as STAT-3, IL-6, VEGF and FAK that are activated in response to SNS activation. Some of these, such as VEGF and FAK, are already being targeted with drugs either approved for use in the clinic or being evaluated in clinical trials. Furthermore, a rationale exists for the use of antidepressants, owing to their known anti-inflammatory effects in the context of several types of cancer (Moreno-Smith et al., 2010). Another interesting approach could be the use of dopamine analogues since dopamine replacement abrogates chronic stress-induced cancer growth (Basu et al., 2004; Moreno-Smith et al., 2011).

It is well known that chronically elevated stress hormone levels, besides affecting tumor cells and their microenvironment, can alter a variety of important physiological processes that may play a role

in determining the efficacy of chemo- or immuno-modulatory therapy. Additionally, we need to better determine the roles of environmental factors and social support in cancer progression. One study demonstrated that in animal models of colon and skin cancer, an enriched environment decreased tumor growth, and increased tumor remission. Furthermore, this study suggests that hypothalamic brain-derived neurotrophic factor can be selectively upregulated by the enriched environment, while proposing that genetic or environmental activation of this brain-derived neurotrophic factor-leptin axis may have therapeutic significance for cancer (Cao et al., 2010).

Cancer therapy is rapidly moving toward individualized regimens based on parameters that are distinct in each patient. Because of the complexity and inherent variability of the human biobehavioral response, it will be crucial to define the behavioral and/or pharmacological interventions that are most likely to benefit individual patients.

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Conflict of Interest

The authors of this manuscript have nothing to declare.

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