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Psychoneuro-oncology: How chronic stress grows cancer

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Abstract Chronic stress is an inextricable part of modern daily living; practically all human diseases, particularly cancer, are negatively affected by it. Numerous studies have shown that stressors, depression, social isolation, and adversity correlate with a worse prognosis for patients with cancer, with increased symptoms, early metastasis, and a shortened life span. Prolonged or very intense adverse life episodes are perceived and assessed by the brain and translated into physiologic responses mediated through relays to the hypothalamus and locus coereleus. This response triggers the activation of the hypothalamus-pituitary-adrenal axis (HPA) and the peripheral nervous system (PNS) with the secretion of glucocorticosteroids/epinephrine and norepinephrine (NE). These hormones and neurotransmitters affect immune surveillance and the immune response to malignancies by skewing immunity from a type 1 to a type 2 response; this process not only impedes the detection and killing of cancer cells but induces immune cells to facilitate cancer growth and systemic spread. It may be mediated by the engagement of norepinephrine to β-adrenergic receptors, which can be partially reversed by the administration of β-blockers.

Introduction

Stress can result from internal aggression; for example, in diseases that course with inflammation, proinflammatory cytokines reach the brain and trigger the activation of the hypothalamus-pituitary-adrenal (HPA) axis; the hypothalamus cannot distinguish between an internal or external aggressor, and the physiologic response is identical.

The stress response (SR) is a survival mechanism that, throughout evolution, has endowed animals, including our ancestors, with the ability to avoid succumbing to external threats.[1] When confronting a predator, they had to activate the "fight-flight" reaction, which includes increased heart rate and blood pressure and diverting the blood flow to the brain and limbs to escape and reduce nonessential vegetative functions such as digestion or reproduction. This SR has been honed through hundreds of thousands of years, allowing our species to survive; the duration of the stressor is usually brief, and the individual either escapes or falls to the predator.

We rarely encounter acute stressors in our daily lives. In modern times, these have been replaced chiefly by persistent lower-level external aggressors that humans confront daily. Household strife, pollution, economic woes, or any negative aspect of modern living gives rise to widespread chronic stress.

Our organisms have not yet adapted and continue to respond with the same HPA axis answer that evolved for acute stressors. In contrast to the acute form, chronic stress is prolonged through time and occurs when environmental demands exceed one's perception of the ability to cope.[2] If acute stress is a survival mechanism, chronic stress has severe deleterious consequences for human health, including life expectancy.[3,4] This concept is in tune with the original descriptions of stress by Hans Selye,[5] who proposed that an organism can adapt to acute homeostatic threats; however, this ability becomes exhausted through time, leading to distress and disease.[6]

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The limbic system processes the presence of environmental stressors (work, home, squalor, war), major life events, or trauma or abuse. Our brain's processing of these events depends on individual differences (genes, experience) and behavioral interpretations. It results in physiologic responses determining whether an individual will adapt (allostasis), develop resiliency, or succumb to stress (allostatic load[7]). Environmental stressors are perceived and transmitted through sensory pathways to different structures in the central nervous system (CNS; reviewed[8]), relaying information leading to the activation of the hypothalamus and the noradrenergic/sympathetic systems. These are activated simultaneously, and although they complement each other, have different physiologic and immunologic courses (Figure 1).

Afferent projections from the limbic, midbrain, and brain stem nuclei activate cells of the paraventricular nucleus of the hypothalamus, inducing the secretion of corticotropin-releasing factor (CRF) and vasopressin, which when acting on the pituitary gland cause the release of ACTH into the circulation. These bind to receptors in the adrenal cortex resulting in the synthesis and subsequent release of glucocorticosteroids (cortisol). Simultaneously, the nerves of the SNS stimulate the adrenal medulla through the locus coeruleus to secrete epinephrine and norepinephrine (NE) circulation.[9]

Axons from neurons in the paravertebral ganglia of the sympathetic trunk innervate peripheral tissue sites; after a stressor, NE is released locally from nerve endings in tissues,

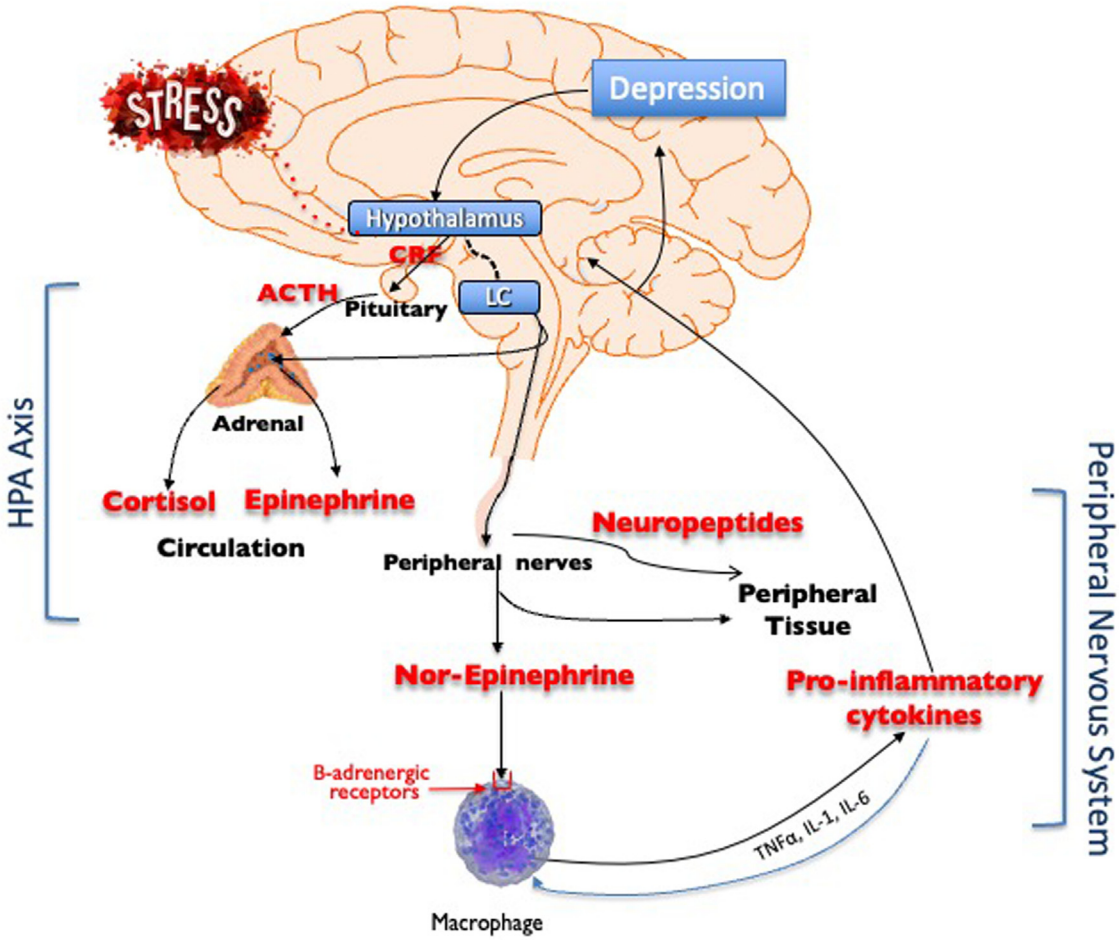

Figure 1 Activation of the stress response. External stressors are processed by the brain leading to the activation of the hypothalamus and the locus coeruleus (LC) noradrenergic/sympathetic systems. The HPA axis consists of the secretion of corticotropin-releasing factor (CRF) by the hypothalamus and the subsequent release of ACTH from the pituitary into the circulation. When it reaches the adrenal cortex, it mediates the synthesis and release of glucocorticosteroids (cortisol). Simultaneously, the LC stimulates the adrenal medulla through the sympathetic nervous system (SNS) to release epinephrine. Axons from neurons in the paravertebral ganglia of the sympathetic trunk innervate peripheral tissue sites releasing nor-epinephrine (NE) into tissues. In the depicted example, NE activates a macrophage to secrete inflammatory cytokines, which, in turn, can activate macrophages further to magnify the inflammatory response. These cytokines pass the BBB and can further activate the HPA axis in a positive feedback mechanism and induce depression.

which upon binding to β-adrenergic receptors has an overall proinflammatory effect.[10] In the depicted example, when acting on macrophages, NE mediates the secretion of inflammatory cytokines such as IL-1, α-TNF, and IL-6, which in turn bind to their receptors on macrophages and through the NFkB pathway can induce a positive feedback mechanism that results in augmented secretion of these molecules. Because epinephrine and norepinephrine are preformed, their effect is immediate (think heart pounding after an acute stressor); subsequently, some 30 minutes later, cortisol is finally released from the adrenal surface, the inflammatory effect is shut down, and the system recovers. Upon repeated or prolonged stress, the secretion of corticosteroids is attenuated, and the glucocorticoid receptors become insensitive to cortisol, allowing the proinflammatory state to persist.

Proinflammatory cytokines can cross the blood-brain barrier[11] and not only stimulate the hypothalamus to trigger further HPA activation but also induce depressive symptoms. During activation of the HPA axis, the secreted cortisol binds to glucocorticoid receptors in the hippocampus, which induces a negative feedback loop on the hypothalamus to stop secreting CRF, thus terminating the stress response. Repeated stressors tend to produce habituation and lower response from the HPA axis; however, the low-grade stimulation of the SNS does not habituate.

Stress and depression

We should comprehend chronic stress as a psychologic construct that includes stress exposure, perceptions of stress, and biopsychosocial responses.[12] If the stressor is of excessive magnitude, prolonged through time, or results in a maladaptive response,[7,10,11] it almost invariably leads to depression.[8,13] Numerous animal and human studies highlight the intimate relationship between chronic stress and depression.[12,13] This author has observed that mice treated with an unpredictable chronic social defeat model develop significant anhedonia and lack of mobility and exploratory behavior (manuscript in preparation); indeed, animals exposed to various chronic stress paradigms clearly show depressive behavior.[14,15] As depicted in Figure 1, stress responses induce the production and secretion to the circulation of proinflammatory cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor alpha (αTNF), and monocyte chemoattractant protein (MCP-1) from cells that express β-adrenergic receptors on their surface; these molecules can, through a positive feedback mechanism, bind to their receptors on immunocytes and induce the secretion of those same cytokines through the nuclear factor kappa B (NFκB) pathway, thus magnifying their production.[13,16-19]

Through the noradrenergic pathway, stressors can flood the circulation with proinflammatory cytokines that can reach every organ. IL-1, IL-6, and TNFα reach the brain through leaky passages of the blood-brain barrier (BBB)[11,16] as well as through an active transport mechanism through saturable transporters[17]; indeed, they additionally induce BBB leakage, triggering neuroinflammation.[18]

The central or peripheral administration of these cytokines activates the hypothalamus triggering HPA activation identically to psychologic stressors creating a neuroinflammatory vicious circle where stressors induce cytokine secretion, which causes further stress response[19] and more cytokines. Studies have shown the correlation between elevated inflammatory markers such as blood C-reactive protein and cytokines and symptoms of depression,[20,21] such as anxiety, anhedonia, and arousal alterations that may result from cytokines affecting the basal ganglia and anterior cingulate cortex of the brain.[17] Numerous studies have reported chronic stress as the most frequent cause of depression. Studies performed in rodents have shed light on the connection between chronic stress and depression.[15] Animals exposed to chronic stress paradigms clearly show depressive behavior. We have observed that mice treated with an unpredictable chronic social defeat model develop significant depressive behavior.[22]

Although not all depressed individuals have elevated proinflammatory markers, depression facilitates inflammatory responses. Inflammation triggers depression; these markers are tightly linked as we approach the influence of the two partners in the initiation and development of cancer.

Stress and Cancer

The effects of chronic stress on the initiation and maintenance of numerous human ailments have been the focus of many studies. Indeed, stress appears to be deleterious to most, if not all, human diseases.[23] The relationship between psychology and neoplasms is not new; it was suggested by Galen of Pergamon in his writings *De Tumoribus* that melancholic patients presenting with fear and despondency were prone to develop tumors.[24,25] Two millennia later, we are beginning to understand the underpinnings of this concept. Studies have shown that patients with cancer frequently have significant chronic stress and depression, and conversely, there is a significant association between these conditions and poor survival.[26]

The question arises whether chronic stressors are able to initiate the development of cancer. A recent study following prospectively 3,015 women found that the degree of stress correlated with a significant overall risk for all cancers[27]; interestingly, stress was also associated with elevated inflammatory markers such as CRP. Numerous other reports confirm that low social support, low social attachment, or depression predicts reduced survival in patients with breast, ovarian, prostate, lung, or skin cancers, among others.[28-30]

Animal studies have significantly contributed markedly to this notion. We examined the effects of chronic stress on mice exposed to the carcinogen ultraviolet light B (UVB)

and found that the stressed animals started developing visible squamous cell carcinomas after only 8 weeks of irradiation compared with their nonstressed counterparts who began at week 21. Not only did it accelerate carcinogenesis markedly, but also, the stressed mice had significantly more tumors.[31] These results were subsequently confirmed by other researchers,[32] who attributed this phenomenon to inhibition of cell-mediated immunity and increased circulating regulatory T cells (Treg).

Stress, cancer, and innervation

During the last 20 years, numerous researchers have demonstrated that metastasis and mortality in patients with cancer are tightly associated with the density of nerves of the autonomic system in or surrounding the cancer tissue.[33] Intratumoral nerve fibers were a prognosticating factor in accelerated death and cancer recurrence in gastric,[34] prostate,[35] colon,[36] breast,[37] biliary, head and neck, cervical, pancreatic, and ovarian cancer.[38] Surgical and pharmacologic sympathectomy decreases prostate tumor growth and lung metastasis.[33] Sensory or sympathetic denervation has also been found to reduce tumors and induce apoptosis in squamous cell carcinomas, melanoma, gastric, and pancreatic tumors,[38] leading to the hypothesis that generating the optimal tumor microenvironment (TM) for cancer growth is highly dependent on innervation.

To this effect, tumors will secrete nerve-attracting molecules, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), to induce axogenesis, resulting in large quantities of norepinephrine, because β-adrenergic transcription control pathways represent key mediators for a favorable pro-tumoral microenvironment. Congruent with this notion, patients with a high-stress burden have tumors with increased levels of this neurotransmitter in the tumor microenvironment, which lead to increased proinflammatory transcription factors.[39]

In patients with ovarian cancer, intratumoral NE correlated to the lack of social support and the advanced stage of the cancer diagnosis at the surgical resection.[40] The amount of NE in the circulation did not vary between patients, whereas the concentration in the tumors and the ascites fluids were markedly elevated. Chronic stress communicates with cancer cells through sympathetic, parasympathetic, and sensory nerves, as well as the products of the HPA-axis activation in the circulation, which will promote or suppress further tumoral growth.

Innervation of cancer tissue and the tumor microenvironment (TM)

Nerves of the sympathetic nervous system (SNS) and sensory nerves reach every organ, including lymphoid organs and individual immunocytes.[41] The tumor microenvironment includes cancer cells, fibroblasts, vascular cells, and immune system cells. To progress, the tumor itself needs to create a hypoxic, low pH favorable milieu that will satisfy its metabolic requirements, create the scenario for escaping immune surveillance, obtain sufficient blood supply, and perforate the basal membranes to spread through lymphatics and the vasculature.[38] Neovascularization and enhanced nerve density are required for cancer development, increasing exponentially as the tumor grows.[42] During the 19th century, there had been a proposal for the ablation of nerves and vessels as a "new treatment for cancer."[43] More recently, there has been a report that the first evidence that neurites will migrate towards prostate cancer cells in culture, proposing that cancers drive neurogenesis.[44] Similarly, host nerve fibers infiltrated tumors derived from human colorectal cancer stem cells grafted into nude mice[45]; furthermore, cancer stem cells were able to differentiate and give rise to neurons; in this manner, cancers may obtain neuronal support by themselves.[45]

Another way in which cancers stimulate axogenesis is through cancer-derived extracellular vesicles, which, once endocytosed or phagocytosed, gain access to the cytosol of the recipient cell. This process is necessary, for instance, for gene silencing or expression induced in the recipient cell by nucleic acids contained inside the EVs, for example, to evade immune-surveillance.[46] These cancer exosomes also contain EphrinB1, an axonal guidance molecule,[47] which can attract neurite growths.

Additionally, they not only attract nerves but induce transdifferentiation and reprogramming from sensory nerves to NE secreting sympathetic nerves.[45]

The most significant agents of nerve-cancer interaction are probably the neurotrophins; nerves that are present in healthy tissue outgrow toward cancers as a result of cancer-derived chemoattractant neurotrophic factors, of which the best studied are nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin 3. They drive nerve axogenesis by binding to the tyrosine receptor family (TRK's) on the surface of nerve end terminals.[48]

Cancers can thus initiate their own innervation in a paracrine fashion through the neurotrophic effect. This process is magnified by immune cells and fibroblasts in the tumor microenvironment, which can also secrete additional neurotrophins.[48] Numerous tumors secrete NGF favoring tumor innervation, which enhances cancer aggressiveness. For example, treatment of pancreatic cancer cells with norepinephrine results in phosphorylation of STAT3, inducing further synthesis of NGF,[38] and elevated levels of NE in the tumor microenvironment can induce the tumor to secrete BDNF,[49] which in turn attracts additional neurites to support the cancer growth. Nerves and neural signals manipulate cancer therapeutic resistance by interfering with apoptotic genes, which lower the effectiveness of the treatments.[50]

Stress, cancer, and adrenergic receptors

The tumor-promoting effect of nerves is mainly mediated by NE binding to the β2- and β3-adrenergic receptors, which activate the cAMP-protein kinase A (PKA) signaling pathway, stimulating tumor angiogenesis and promoting cancer growth through Src phosphorylation, DNA damage, p53 degradation, and the upregulation of vascular endothelial growth factor (VEGF) and the matrix metalloproteinases (MMP-2 and MMP-9).[51] Chronic stress also induces synergistic effects on signaling through adrenergic receptors, leading to DNA damage and promoting the development of breast cancer.[52] Engagement of β-adrenergic receptors by NE secondary to chronic stress has been shown to lead to gastric cancer growth and metastasis by the upregulation of the NF-κB, CREB, and STAT3 pathways,[53] which also mediate strong inflammatory responses.

An important discovery was that the transmission of stress through adrenergic receptors at the early stages of cancer development is through the activation of Src, which induces the production of downstream proteins critical for cell survival, angiogenesis, and metastasis.[54] The role of the parasympathetic innervation of cancers varies according to different organs. In general, it counteracts the adrenergic tumor promotion, for example, in breast cancer, but it has a permissive role mostly in gastrointestinal cancers.[55,56] The growth and progression of breast cancer were accelerated in mice after the stimulation of sympathetic nerves in the tumors, but it ceased after the stimulation of parasympathetic nerves; in humans, a sympathetic increase and the decrease of parasympathetic nerves in the tumoral environment was associated with a bad clinical prognosis and correlated with the increase of "check-point" ligand molecule programmed death-ligand 1 (PD-L1).[55] The latter is a critical participant in the efforts of the cancer cells to evade immune recognition.

NE also produces the generation of tumor-reactive oxygen species (ROS), which promotes DNA damage and interferes with DNA repair,[57] which is magnified by the presence of elevated glucocorticoids.[29] Catecholamines also

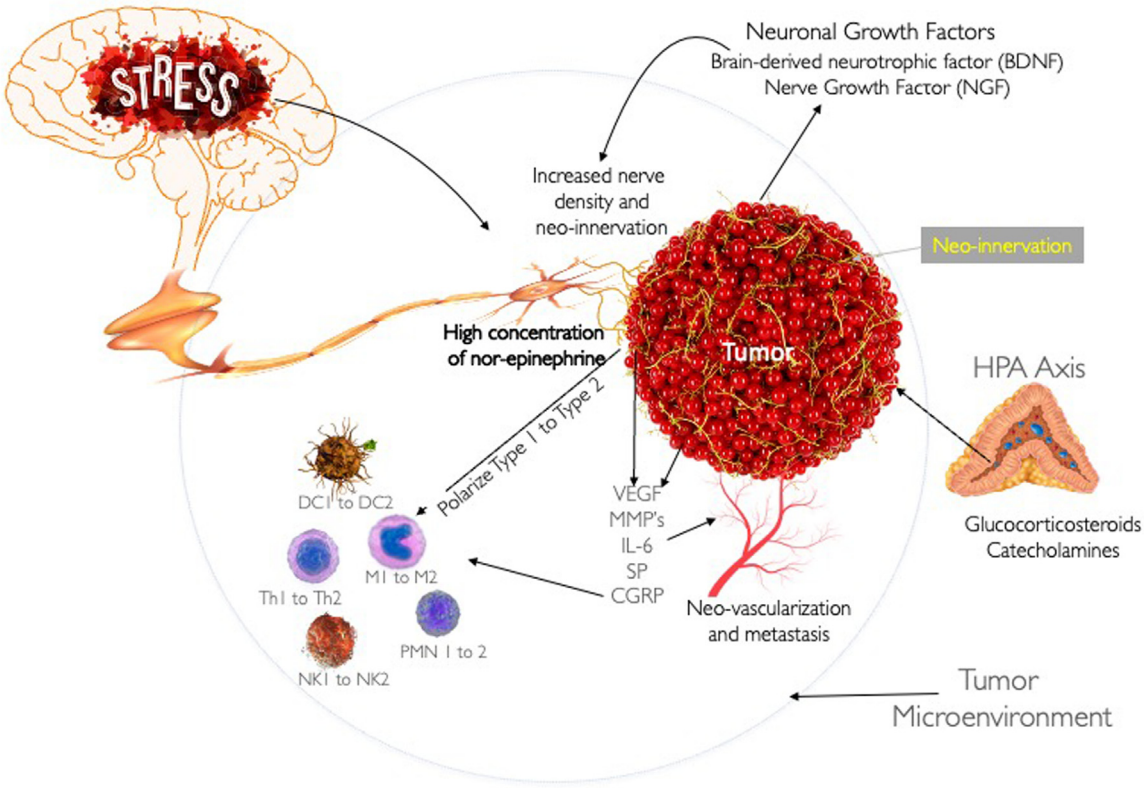

Figure 2 Tumors need nerves. External stressors increase the release of norepinephrine (NE) and neuropeptides from peripheral nerves into the tumor microenvironment (TM), inducing cancer cells to secrete NGF and BDNF; these neurotrophins support axogenesis and neurogenesis, attracting the outgrowth of neurites towards the tumor and release more NE. Under the direction of NE and the tumor, the immune cells that penetrate the TM are reprogrammed from a type 1 profile (to attack cancer) to the pro-tumorigenic type 2 profile. The subsequent interaction between NE and tumor also mediates the release of VGEF and metalloproteinases 1 and 9 (MMPs), facilitating mobility through the basal membranes and metastasis. Additional pro-cancer effects are modulated by CGRP and substance P and adrenal corticosteroids, which prevent apoptosis and inhibit p53-mediated DNA repair.

induce vascular endothelial growth factor (VEGF) and IL-6, which enhance angiogenesis, increasing tumor vascularization and leading to tumor spread.[58] The administration of isoproterenol to mice promoted bone metastasis by stimulating endothelial cells and secreting the proinflammatory cytokines IL-1 and IL-6.[59] The association between behavioral factors and enhanced angiogenesis has been reported in various tumors, an effect that was reversed by β-blockers; also, greater social support was associated with lower secretion of VEGF. The neovascularization promoters VEGF and IL-6 correlate well with better psychosocial support.[60]

The presence of NE in the cancer microenvironment facilitates the tumoral production of metalloproteinases (MMP), which facilitate the breakdown and remodeling of the extracellular matrix, enabling the neoplastic cells to migrate. The worse the depression in patients with ovarian cancer, the higher the levels of tumoral MMP-9, and the latter was associated with a worse clinical prognosis.[61] Similarly, depressed patients with renal cell carcinoma had increased MMPs in tumor tissue.[62] When cells lose contact with the extracellular matrix, they undergo anoikis, a form of programmed cell death that can be inhibited by the presence of catecholamines, allowing the tumor to survive; this process was seen in patients with ovarian cancer that had significant depression.[63]

Stress, cancer, and sensory nerves

Neuropeptides manufactured in dorsal sensory root ganglion cells (DRC) and transported retrogradely through sensory nerve fibers also play a significant role in cancer promotion. Although substance P (SP) and calcitonin-gene-related peptide (CGRP) are primarily proinflammatory molecules, they also participate in cancer growth. The sensory innervation of cancers significantly contributes to cancer progression.[38] Poorly differentiated squamous cell carcinomas have increased substance P positive nerve fibers, and the density correlates with worse outcomes[64]; SP also promotes cell proliferation and metastasis in various cancers.[38]

We examined the CGRP and SP mRNA content in the dorsal root ganglion cells of mice that were subjected to a chronic social confrontation stressor and found that there was a marked upregulation of the production of CGRP and SP,[22] suggesting that these neuropeptides are a conduit to deliver psychological adversity to peripheral tissue. Various studies reported the elevation of CGRP in lung, prostate, and thyroid cancers because many cancer cells possess CGRP receptors on their surface.[65] CGRP also facilitated tumor-associated angiogenesis and tumor growth in mice bearing lung carcinomas, functions that were significantly reduced after the administration of a CGRP antagonist.[66] Overall, CGRP promotes cancer development through metabolic reprogramming, inhibition of antitumor immunity, and vasodilatation.[65]

Stress, cancer, and the immune response

The concept of immune surveillance includes the notion that the immune system can recognize foreign cells as nonself, leading to their destruction. Several immune cells are involved in the destruction of cancer cells. NK cells circulate, policing our organism in search of foreign cells, upon which these are destroyed through the release of perforins and granzymes. This capacity is shared by cytotoxic T cells, whereas T-helper cells produce a variety of cytokines to help orchestrate the antitumor immune response. Macrophages are scavengers and early responders that destroy tumor cells, also serving as antigen-presenting cells to assist in the cytotoxic activities of T cells. DCs are antigen-presenting cells that capture tumoral antigens, process, and present them to naive T cells.[67] This interaction results in the maturation and activation of tumor-specific cytotoxic T lymphocytes (CTLs) capable of migrating to tumor sites and destroying them. In addition, the interaction triggers a response by T-helper cells, which stimulates the antitumor immune response's T and B cell arms.[67]

Chronic stress significantly hinders cell-mediated immunity and favors cancer initiation, growth, and migration. When referring to the removal of cancerous cells, immunity can become a double-edged sword because cells of the immune system can become "highjacked" by a tumor and induced to work for its survival. A critical site for the effect

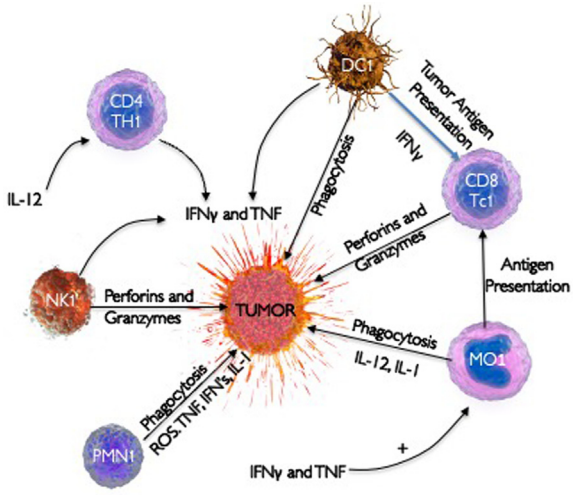

Figure 3 Immune surveillance and tumoricidal properties of immune cells. One of the cell-mediated immune system functions is the recognition, engagement, and killing of tumoral cells; to complete this task, type 1 immune cells are recruited to the tumor environment. Through the concerted effort of $CD4^+$ T cells, cytotoxic T cells, monocyte/macrophages, polymorphonuclear cells, natural killer cells, and dendritic cells, tumors receive a multipronged attack destined to destroy them. These events occur when cancers are early in their development, which is believed to happen frequently and silently.
ROS: reactive oxygen species.

of catecholamines and glucocorticosteroids lies in the area surrounding the tumor, the tumor microenvironment (TM). Cells of the immune system that carry adrenergic and glucocorticoid receptors enter the TM and suffer the transformation into protumorigenic cells, switching their profile from a type 1 to a type 2 cytokine profile, secreting cytokines such as IL-6, IL-10, TNF-α, and MCP-1.[51] Immune cells in peripheral circulation are significantly more effective in detecting and destroying tumor cells than in the TM.[68]

Under the pressure of chronic stress, tumor-associated macrophages, tumor-infiltrating lymphocytes, myeloid-derived suppressor cells, dendritic cells, neutrophils, and NK cells can act on tumor initiation, promotion, and transformation, invasion, and metastasis through mutation, epigenetic modification, and regulation of the tumor microenvironment.[69,70] For example, catecholamines skew macrophages toward the M2 type, inhibit the antigen presentation capacity of dendritic cells, suppress cytotoxic T cells, and activate regulatory T cells (Tregs). They also mediate the resistance of cancer cells to the effects of chemotherapy, impair the function of p53, and promote the secretion of tumor-derived VEGF.[53] Additionally, glucocorticoids inhibit DC activation, migration, and apoptosis.[71]

Important players in pro-tumoral immunosuppressive signaling are myeloid-derived suppressor cells (MDSCs), which are regulated and sequestered in the TM by the effect of catecholamines[72] on their adrenergic receptors. Adrenergic agonists promote metabolic reprogramming of CD8+ T cells, suppressing their activation,[73] and loss of adrenergic input enhances the response of tumors to treatment with immune checkpoint inhibitors[74]; indeed, denervation reduces checkpoint molecules, including PD-1and PD-L1.[55] Stress-induced β-adrenergic activation resulted in macrophage infiltration into the cancer tissue and the switch to the immunosuppressive M2 phenotype, which increased TGF-β, VEGF, and MMP-9, enhancing angiogenesis and metastasis.[75] Depression, chronic stress, or low psychosocial support resulted in low natural killer (NK) cell cytotoxicity, inhibiting CD8-mediated anti-tumor functions and reducing TH1 type cytokine production.[68] As depicted in Figure 2, significant events that result from adrenergic and glucocorticoid stimulation pertain to the reprogramming of the per-

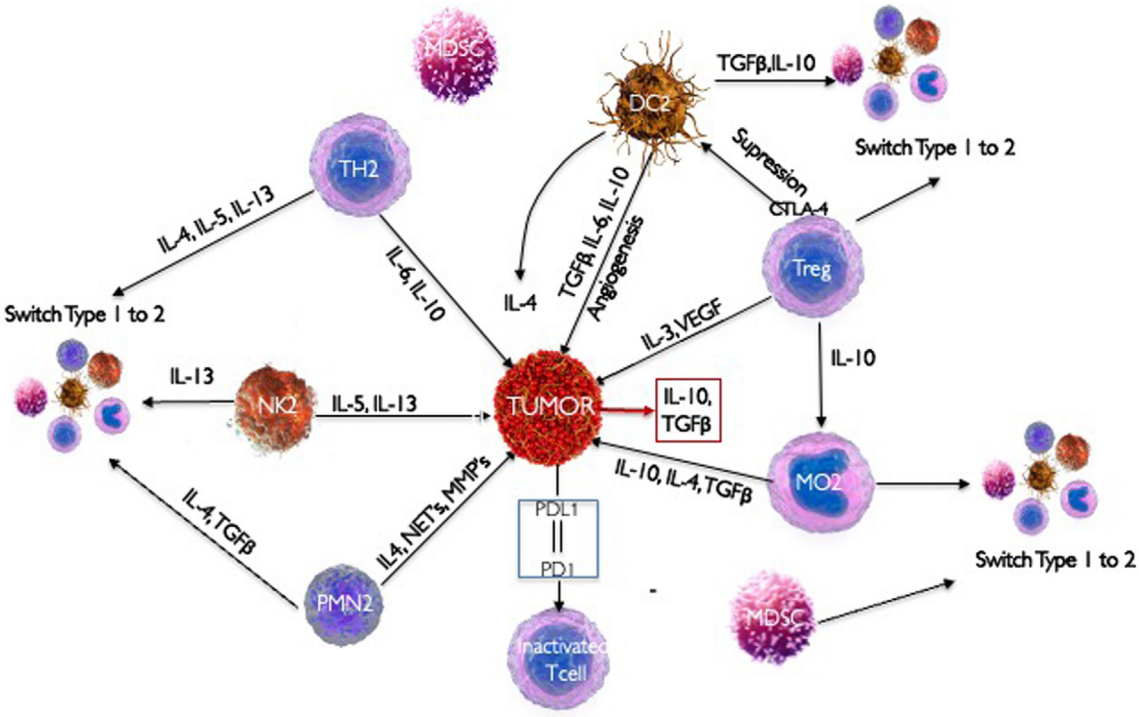

Figure 4 The tumor microenvironment and the hijacking of cellular immunity. As described in the text, with the assistance of peripheral peritumoral nerves, immune cells that reach the tumor microenvironment are reprogrammed to the type 2 immune response and start working to favor cancer growth. The picture changes radically from the one depicted in Figure 3. T cells are inactivated by the engagement of their checkpoint molecule PD1 with the PD1 ligand on the surface of tumoral cells. Myeloid-derived suppressor cells (MDSC) are recruited to dampen local immunity, and TH2 lymphocytes, monocyte/macrophages (MO2), polymorphonuclear cells (PMN2), natural killer cells (NK2), and dendritic cells (DC2) secrete type 2 cytokines and chemokines that not only contribute to tumor growth but also influence other bystander immune cells to switch to the type 2 constellation. The secretion of vascular endothelial growth factor (VEGF) and metalloproteinases (MMPs) contribute to augmenting cancer's potential for metastasis. The expansion of T regulatory cells (Treg) leads to further immunosuppression. *Partly adapted from Hinshaw DC, Shevde LA. The Tumor Microenvironment Innately Modulates Cancer Progression. Cancer Res. 2019;79:4557-4566.*

itumoral immune cells to acquire a type 2 response leading to a permissive environment for cancer development and metastasis by switching from the Type 1 tumoricidal immunesurveillance (Figure 3) to the Type 2 pro-tumor immunity (Figure 4).

Stress, cancer, and countering measures

Tregs, which impair the anti-cancer immune response, proliferated under adrenergic signaling, and this effect was abolished by propranolol.[76] β-blockers have been observed to increase the survival of patients suffering from various cancers,[48,77] in particular in women with breast cancer, liver cancer, melanoma, prostate cancer, colon cancer, and non-small cell lung cancer; these advantages were found in patients taking non-selective β-blockers.[78,79] In a prospective study of 53 patients with stage IB to IIIA melanoma, propranolol intake had an 80% reduction in melanoma recurrence compared with control patients not taking β-blockers.[80] One study reported that the stress from surgical interventions enhanced tumor metastasis in a breast cancer murine model,[81] which resulted from a marked inhibition of NK cell activity field[82] secondary to adrenergic stimulation, which could be prevented by the administration of β-blockers.[83] Similar findings were observed in a model of ovarian cancer, which also was reversed by propranolol.[84] Because patients who have cancer are frequently subjected to the stressors of surgical interventions, which not only have proven deleterious to survival but also mitigate the effects of anti-cancer chemo/radiotherapy, it was proposed that patients receive β-blockers and cyclooxygenase inhibitors during the perioperative period because both adrenergic and eicosanoid mechanisms are simultaneously activated by surgery-induced inflammatory responses.[85]

Numerous biobehavioral interventions have been studied in patients with cancer, showing enhanced well-being, prolonged survival, lower metastasis, and modification of biological tumor-promoting factors.[30,68,79,86,87] Ideally, the biopsychosocial approach to cancer model will include multimodal interventions consisting of pharmacologic and behavioral interventions not only to alleviate symptoms but to prolong meaningful survival.

Conclusions

Overwhelming evidence supports the notion that chronic stress strongly influences cancer development, growth, and propagation. This role is mediated by the activation of adrenergic and peptidergic pathways and, to a lesser extent, glucocorticosteroids. A stress response system that initially evolved to allow humans to escape life-threatening episodes has transformed into a life-threatening agent. Maybe humans will develop adaptative physiologic mechanisms to cope with modern-living chronic stressors in the future, but by then, we may be exposed to unknown novel forms of adversity. On a more optimistic note, biopsychosocial approaches to mitigate chronic stress and ensuing depression can become mainstream and endow patients with weapons to overcome it, live better lives, and maybe be cancer-free.

Declaration of Competing Interest

None.

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