



# Neuroendocrine Regulation of Tumor-Associated Immune Cells

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Mounting preclinical and clinical evidence continues to support a role for the neuroendocrine system in the modulation of tumor biology and progression. Several studies have shown data supporting a link between chronic stress and cancer progression. Dysregulation of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis has been implicated in promoting angiogenesis, tumor cell proliferation and survival, alteration of the immune response and exacerbating inflammatory networks in the tumor microenvironment. Here, we review how SNS and HPA dysregulation contributes to disturbances in immune cell populations, modifies cancer biology, and impacts immunotherapy response. We also highlight several interventions aimed at circumventing the adverse effects stress has on cancer patients.

**Keywords:** cancer biology, stress hormones, inflammation, immune cells, tumor microenvironment

## INTRODUCTION

The stress response is a biological process mainly mediated by the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. Activation of the SNS and HPA axis leads to the release of neurotransmitters and hormones, such as catecholamines and glucocorticoids. These molecules mediate many biochemical and physiologic changes (e.g., increased heart rate, rapid breathing, perspiration). Moreover, catecholamines released upon activation of the SNS, such as epinephrine (EPI) and norepinephrine (NE), are capable of binding to receptors on or within immune cells through activation of  $\alpha$  and  $\beta$  adrenergic receptors (ARs) (1). Correspondingly, HPA activation leads to increased glucocorticoid release and activation of glucocorticoid receptors (GR).

Prolonged activation of the SNS and HPA axis, also known as chronic stress (occurring over weeks or years), increases the exposure of the immune system to elevated stress hormone levels. The increased exposure to stress hormones disrupts physiological homeostasis and could serve as a risk factor for the development and progression of many diseases, including cancer (2–4). In contrast to acute stress, which lasts several minutes to hours and is associated with enhanced immunity and resistance to cancer, chronic stress is known to impair immune response and promote tumor growth (5, 6). Multiple studies have correlated stress-induced biobehavioral abnormalities, such as anxiety, depression and chronic stress, with tumor growth, progression, and metastasis (7–11).

A dysregulated HPA or dysfunctional SNS activity due to chronic stress warrants further attention as alterations in these systems can affect immune function in the tumor and ultimately impact its biology and disease outcome (Table 1). One of the primary mechanisms by which chronic stress affects cancer progression is through alterations in humoral and cell-mediated immunity. Chronic stress can lead to variations in the proliferative capacity of lymphocytes

**TABLE 1** | Neuroendocrine regulation of immune cell function in cancer.

Immune cell	Effects of HPA and/or SNS activation on immune cell function	Selected references
T cells	<ul style="list-style-type: none"> <li>• Suppresses APCs and T<sub>H</sub>1 cells promoting T<sub>H</sub>2 cytokine production</li> <li>• Alters distribution, proliferation and apoptosis</li> <li>• Promotes immunosuppression and tumor progression by increasing T regulatory cell activity</li> <li>• Decreases infiltration into tumors</li> <li>• Reduces effectiveness of T-cell targeted immunotherapy by suppressing antitumor CD8+ T</li> </ul>	(12–14) (15–18) (19) (20–23) (24)
Natural Killer cells	<ul style="list-style-type: none"> <li>• Forced swim and administration of Epi or corticosterone inhibited NK cell activity in rats</li> <li>• Elevated levels of stress or depression were linked to decreased NK cell levels and activity, impaired cytotoxicity and altered membrane receptor expression</li> </ul>	(25) (16, 18, 22, 26–28)
B cells	<ul style="list-style-type: none"> <li>• Anxious behavior in mice was associated with increased B-regulatory cell levels and tumor progression</li> <li>• Breast cancer patients that underwent a mastectomy with high levels of stress exhibited decreased T-cell values (cellular immunity) while B-cell values were unaffected (humoral immunity)</li> </ul>	(21) (29)
Dendritic cells	<ul style="list-style-type: none"> <li>• GCs induce apoptosis, represses activation, migration and promotes tolerogenic phenotypes</li> <li>• Dual effect on migration by adrenergic stimulation</li> <li>• Modulates the efficacy of cancer vaccines that use tumor antigen loaded DCs</li> <li>• Inhibits DCs IL-12 production</li> <li>• Immobilization stress in mice lead to induction of VEGF which can lead to DC maturation</li> <li>• Exposure to chronic cold (stressor) temperature was associated to repressed activation of DCs</li> </ul>	(30–32) (33, 34) (35) (3) (7) (36)
Myeloid-derived suppressive cells	<ul style="list-style-type: none"> <li>• Stimulates immune-suppressive activity</li> <li>• High levels of stress correlated with increased levels of MDSCs in breast cancer patients</li> <li>• Chronically stressed mice exhibited increased infiltration into tumor sites and enhanced suppressive activity toward proliferating T cells</li> </ul>	(37, 38) (39) (19, 40)
Granulocytic myeloid derived cells	<ul style="list-style-type: none"> <li>• Influences generation, activity and migration toward the tumor microenvironment</li> <li>• Chronically stressed mice displayed decreased phagocytic activity in neutrophils</li> </ul>	(41) (42)
Macrophages	<ul style="list-style-type: none"> <li>• Contributes to tumor invasiveness by stimulating TAMs to increase gene expression of <i>mmp2</i>, <i>mmp9</i>, <i>mmp12</i>, and <i>ctsl</i> proteases</li> <li>• Promotes transformation from M1 to M2 phenotype</li> <li>• Adrenergic activation increased macrophage infiltration into tumor leading to progression</li> <li>• Catecholamines stimulate macrophage production of pro-inflammatory cytokines</li> <li>• High levels of stress were associated to TAM derived MMP9</li> <li>• Characterization of adrenergic regulated macrophages</li> </ul>	(43) (44, 45) (10, 45) (46–49) (50) (45, 51)

APC, antigen-presenting cell; DC, dendritic cell; T<sub>H</sub>, T-helper cell; GC, glucocorticoid; DC, dendritic cell; IL, interleukin; VEGF, vascular endothelial growth factor; MDSC, myeloid-derived suppressive cell; NK, natural killer cell; TAM, tumor-associated macrophage; Mmp, matrix metalloproteinases; Ctsl, cathepsin.

and suppression of immune activity relevant to cell-mediated immunity [i.e., natural killer (NK) cells, cytotoxic T-lymphocytes (CTLs), dendritic cells, macrophages] (52–54). Likewise, stress-induced immune alterations can enhance the generation and migration of many pro-inflammatory factors, such as interleukin (IL)-6, tumor necrosis factor (TNF- $\alpha$ ) in the tumor microenvironment (6, 15, 21–23, 52). Stress-induced pro-tumoral factors, such as matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF), can significantly influence cancer progression by stimulating tumor cell survival, tumor growth, metastasis, and evasion of the immune system (41, 55–57).

Another key player in tumor-associated immunity is the lymphatic system. In cancer, the lymphatic system is a rich source of chemokines that provides a route for tumor cell escape while enhancing their invasive properties (58). In an orthotopic model of breast cancer, it was shown that chronic stress leads to lymphatic vasculature reorganization in tumors (59). Thus, stress may also enhance cancer progression and provide a route of tumor cell dissemination through the lymphatic vasculature.

Although the effects of chronic stress on tumor cells can vary due to stress mediators released and cancer types, there

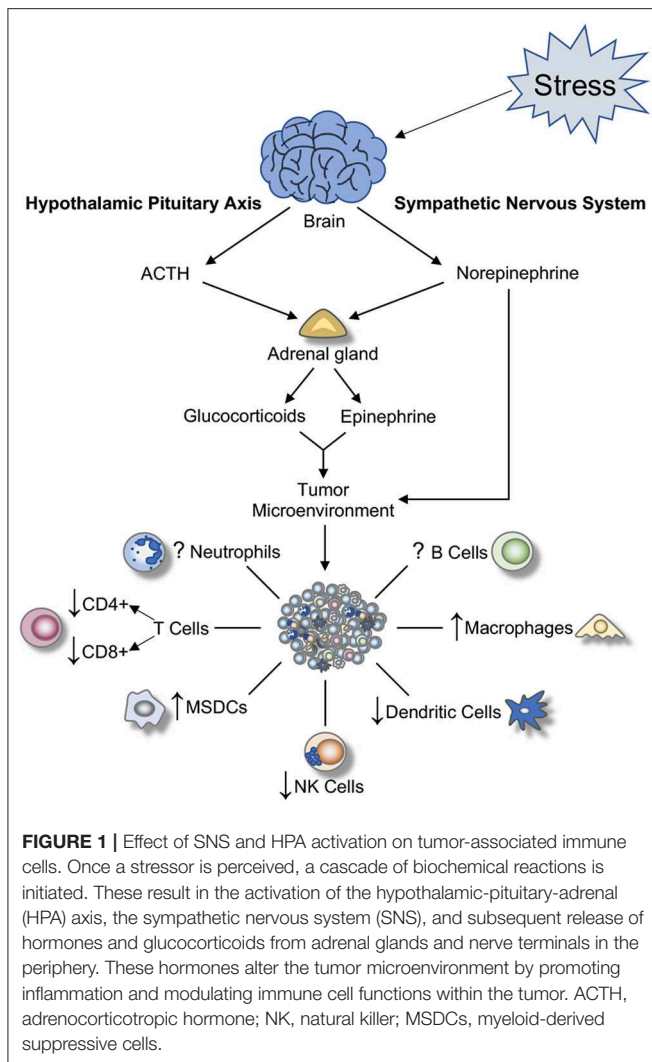
are common pathological effects that arise from prolonged activation of SNS and HPA axis that contribute to cancer progression. Therefore, this review provides an overview of tumor-associated immunity while summarizing components that can be influenced by the stress response (see **Figure 1**). Finally, we discuss interventions for alleviating the effects of chronic stress on cancer patients and possible avenues for future research.

## MYELOID CELLS

### Macrophages

Macrophages are specialized immune cells originating from circulating monocytes and capable of modulating their activity on environmental cues. In tumors, their primary function as scavengers, antigen-presenting cells (APCs) and wound healing are altered and utilized by tumor cells to survive in the host environment.

Macrophages exist in a variety of activation states and can be polarized toward functional subclasses. According to the binary polarization model, there are two primary polarization states M1 and M2 (60). Classically activated macrophages, M1, are activated by IFN- $\gamma$ , lipopolysaccharide (LPS), and toll-like receptor



ligands, produce pro-inflammatory and immunostimulatory cytokines and are involved in  $T_H1$  responses. Alternatively activated, M2, are immunosuppressive and are involved in scavenging for cellular remains, tissue repair and remodeling, and tumor progression. Tumor-associated macrophages (TAMs) are the most abundant immune cell and a vital component of the tumor microenvironment that influences multiple aspects of tumor cell biology.

Interestingly, signals from tumor cells can cause functional alterations in macrophages that can deviate them from the dualistic M1/M2-polarized definition (61). This effect provides evidence that surrounding stimuli can produce TAMs with heterogeneous phenotypes and functions (62). Many studies have evaluated the role of TAMs in the promotion of tumor growth, metastasis, angiogenesis, and maintenance of an immunosuppressive microenvironment. Immune cells and tumor cells both influence and mediate inflammation surrounding the tumor microenvironment.

TAMs promote inflammatory processes at the tumor microenvironment by accelerating angiogenesis, inducing

migration and invasion of tumor cells, and promoting epithelial-mesenchymal transition (EMT) (63). The primary purpose of tumor-associated angiogenesis, the process of creating new vasculature, is to provide cancer cells with nutrients, oxygen, and routes to metastasize. TAMs support this process by secreting proangiogenic factors such as VEGF, and PDGF in the tumor microenvironment. MMP secretion by TAMs serves a dual role in tumor progression, promoting both angiogenesis and metastasis. MMP9 and MMP2 are involved in the induction of the angiogenic switch (64), while an MMP9/VEGF axis controls cancer cell intravasation (65).

Furthermore, MMPs remodel the extracellular matrix (ECM) by degrading ECM proteins such as collagen, and fibronectin (66) disrupting the basement membrane and allowing cancer cells to invade into the adjacent stroma. TAMs are also involved in promoting EMT, where cells change their phenotype to migratory mesenchymal cells and lose cell-cell adhesion proteins and markers. For instance, M2 TAMs promoted EMT in pancreatic cancer cells through the TLR4/IL-10 pathway (67), while TAM-secreted IL-8 activated the JAK2/STAT3/Snail axis in hepatocellular carcinoma (68).

For many types of solid tumors, high levels of intratumoral macrophage infiltration have been associated with poor prognosis (69). In patients with breast carcinoma, macrophage infiltration has been associated with high grade, lack of hormone-receptor expression, basal-like subtype, and poor outcome (70). Furthermore, in ovarian cancer patients, increased macrophage infiltration was associated with decreased overall survival (10). Also, increased macrophage density strongly correlated with poor prognosis in renal cell carcinoma, lung, and hepatocellular carcinoma (71). In addition to poor prognosis, TAM infiltration can affect chemotherapy response in esophageal cancer (72).

Other studies have demonstrated a role for activation of the adrenergic machinery on TAMs in the context of cancer progression. Lamkin et al. investigated how  $\beta$ -adrenergic regulation influenced macrophage polarization and phenotype (45). Interestingly, adrenergic-stimulated macrophages did not fit into one clear category of the M1-M2 binary spectrum but had increased expression of genes involved in M2 macrophage polarization. More importantly,  $\beta_2$ -adrenergic receptors mediated the M2 promoting effects and not  $\beta_1$  or  $\beta_3$  receptors. A recent study found C/EBP $\beta$  signaling mediates the regulation of the M2 transcriptome between  $\beta$ -adrenergic stimulation through expression of Arg1 (51). In malignant melanoma cell lines with high reactive oxygen species (ROS), TAMs increased gene expression of *mmp2*, *mmp9*, *mmp12*, and *ctsl* proteases known to contribute to tumor invasiveness (43). Invasiveness was enhanced by TNF- $\alpha$  TAM secretion. 4T1 mammary carcinoma cells cultured in EPI-treated RAW 264.7 supernatant displayed increased migration and wound-healing (44). Interestingly, this same study found that EPI promoted the transformation of macrophages from M1 to an M2 phenotype. Furthermore, another study showed that NE increased expression of M2 phenotype and pro-metastatic genes in bone marrow-derived macrophages (45). This same study demonstrated that *in vivo* activation of the  $\beta$ -adrenergic system increased macrophage infiltration into breast cancer tumor

parenchyma and triggered a metastatic cascade that resulted in distant tissue metastasis.

Dysregulation of the SNS can exacerbate tumor-promoting characteristics of TAMs. Stress and depression may cause tumor cells to increase the secretion of pro-inflammatory cytokines. For example, after NE stimulation, ovarian cancer cells produced higher levels of IL-6 (8). Catecholamines have been shown to promote macrophage secretion of pro-inflammatory cytokines such as IL-1 $\beta$  and TNF- $\alpha$ , and this might be due to surface expression of alpha and beta receptors (46). In cancer patients, studies have shown that behavioral factors can affect the tumor microenvironment and aid tumor progression. Ovarian cancer patients with high levels of stress, social isolation, and depression demonstrated increased MMP9 production by TAMs (50). Transcriptional pathways regulating inflammation are also influenced by behavioral dysregulation. Bower et al. (73) recently found that breast cancer patients reporting more social isolation exhibited upregulation of genes related to M2 polarization and EMT. Moreover, inadequate inflammatory control, impaired transcription of glucocorticoid response genes, and leukocytes with increased activity in pro-inflammatory transcription were seen in socially isolated adults (74). These studies indicate that stress hormones directly impact tumor cells and TAM while enhancing tumor growth and impairing immune function.

## Dendritic Cells

Dendritic cells (DCs) are a heterogeneous group of APCs that generate antitumor immune responses by stimulating the activation of CD4+ T-cells, CD8+ T-cells, and B-cells (75, 76). Cancer cells can modulate DC activity and promote one of its characteristic hallmarks: evasion of the immune system.

Due to their essential role in capturing, processing, and presenting antigens to T-cells, DCs have been extensively utilized in cancer immunotherapeutic strategies (77). The usual role and function of DCs can be influenced by SNS activation. For instance, glucocorticoids can induce DC apoptosis, suppress DC activation and migration, and promote a tolerogenic DC phenotype (32). Moreover, adrenergic stimulation of DCs may have opposing effects on their migration capacity either by acting as a chemotactic factor and increasing migration (mainly mediated by  $\alpha$ 1-ARs) (33) or by suppressing DC migration mainly through modulation of IL-10 and IL-12 production (mediated by  $\beta$ 2-ARs) (34). Also, it has been noted that activation of  $\beta$ 2-ARs can modulate cancer vaccine efficacy that utilize tumor antigen-loaded DCs, either by boosting antitumor responses or by inducing tolerance, depending on the maturation state of transferred DCs (35). Stress hormones can also inhibit the production of IL-12 in APCs like DCs, leading to reduced T<sub>H</sub>1 responses and stimulation of T<sub>H</sub>2 responses (3).

Additionally, a study that utilized orthotopic mice models of ovarian cancer found that immobilization stress stimulated tumor production of VEGF, leading to increased tumor burden (7). Importantly, VEGF produced by tumors may also promote tumor evasion of the immune system by modulating functional DCs maturation (78). For example, in a chronic cold stress mice model, it was shown that even though stressed tumor-bearing mice had more DCs, mice that were housed at normal

temperatures developed more efficient APC suggesting that stress may reduce DCs activation (36).

A study in ovarian cancer patients found that depressed and anxious mood was correlated with elevated tumor stimulated T<sub>H</sub>2 cytokine response (23). It is known that T<sub>H</sub>2 cytokine responses predominantly stimulate the humoral immune response through IL-4, leading to a reduction in the cytotoxic immune response and sequential tumor growth (79, 80). Under those circumstances, IL-4 is known to block the differentiation of dendritic cells stimulated by cytotoxic precursors (81). In summary, mounting data indicate that SNS plays a significant role in suppressing the immunogenic activity of DCs.

## Neutrophils

Neutrophils represent the most abundant infiltrating white blood cell and are mainly involved in immune surveillance and inflammatory responses. The link between neutrophils and the neuroendocrine system has been well-studied (82–84). However, to the best of our knowledge, there is a gap of knowledge regarding the effects of stress on the neutrophilic response in cancer. Notably, an *in vivo* social stress mice model found that mice that established dominant/submissive relationships had different immunogenic profiles. Submissive mice (comparable to mice undergoing chronic social stress) when compared to dominant male mice, exhibited suppressed neutrophil phagocytic activity and increased melanoma metastasis (42). Interestingly, in a non-cancer setting, the effects of psychological stress on neutrophils are suggested to be dependent on the duration (acute or chronic) and type (i.e., expected or unexpected) of stress. For instance, academic examinations enhance the phagocytic activity of neutrophils while chronic stress suppresses superoxide production leading to decreased phagocytic activity (83).

## Myeloid-Derived Suppressive Cells

Myeloid-derived suppressive cells (MDSCs) are immature myeloid cells with a potent immune-suppressive activity that plays a significant role in cancer immunology. Several studies have found an accumulation of MDSCs in tumors from murine models and cancer patients (39, 85). Several tumor-derived factors (i.e., STATs, C.EBPb, NF-kB, prostaglandin E2) produce the necessary signals for the generation, accumulation, and migration of MDSCs to the tumor microenvironment (86). Because stress responses are known to elevate many of these tumor-derived factors, stress may also stimulate the immune-suppressive activity of MDSCs and promote tumor progression (37, 38). For example, breast cancer patients reporting high levels of stress (based on an Impact of Event Scale questionnaire) had elevated levels of MDSCs (when compared to low-stress patients) (39). Moreover, studies on chronically stressed mice suggest a strong correlation between stress and MDSCs suppression. Specifically, chronically stressed mice exhibited greater tumor burden associated with the infiltration of MDSCs (19, 40) in the tumor tissue and enhanced suppressive activity toward proliferating T-cells (19). Overall, these results suggest that there is a significant link between stress, MDSC-induced immunosuppression, and cancer.



## Other Granulocytic Myeloid Cells

Other granulocytic cells such as basophils, eosinophils, and mast cells are mainly responsible for mediating allergic reactions, and neuroendocrine mediators can modulate their activity. To the best of our knowledge, the effects of stress on the activity of these cells, and how it affects cancer immunity is ripe for future research. However, their activity has been thoroughly studied in a non-cancer setting. It has been shown that stress hormones promote the production of  $T_H2$  cytokines (IL-4, IL-5, IL-10, IL-13) (12–14, 87). Importantly, IL-4 is an anti-inflammatory cytokine that stimulates the proliferation, activation, and migration of eosinophils and mast cells during allergic reaction responses (13, 14). For example, stress that was induced by exposure to pheromones released by footshock-stressed mice leads to an increase in IL-4 production and a decrease in IL-2 cytokine in affected mice (88).

Studies have found that healthy mice caged with tumor-bearing mice displayed elevated serum NE levels that correlated with increased production of pro-inflammatory cytokines (IL-4, IL-5) and increased lung inflammation (89). Specifically, IL-5 has been shown to serve as a chemoattractant for eosinophils in a variety of inflammatory diseases. Thus, stress-induced production of IL-5 may influence tumor immunity through eosinophilic recruitment into the tumor microenvironment.

## LYMPHOCYTES: T-CELLS, B CELLS AND NK CELLS

### T-Cells

T-cells are part of the adaptive immune response and play a significant role in anti-tumoral immunity (90, 91).  $T_H$  cells are classified into  $T_H1$  cells that release interferon-gamma (IFN- $\gamma$ ) and TNF- $\alpha$ , and  $T_H2$  cells that release IL-4, IL-5, and IL-13. Thus, when differentially activated, T-cells can contribute to the immune defense either through regulation of the immune response by recruiting other immune cells or by directly attacking infected or cancerous cells.

Activation of the SNS and HPA axis and subsequent release of glucocorticoids and catecholamines are known to suppress APCs and  $T_H1$  cells leading to a shift in  $T_H2$  cytokine production (12–14) and inhibiting the generation and activity of CTLs (12, 13). Animal models have consistently demonstrated a correlation between stress and T-cell immune dysregulation in cancer (15, 19–21, 92). For example, chronically restrained stressed mice displayed alterations in the T-lymphocyte subset distribution (less  $CD4^+ T_H$ ), proliferation, cytokine secretion, and lymphocyte apoptosis (15). This same study also demonstrated that chronically stressed mice had worse overall survival and exhibited increased tumor growth (15).

In addition to alterations in T-cell proliferation and chemokine/cytokine secretion, chronic stress also leads to increased immunosuppression due to amplified activity of immune cells such as MDSCs and T-regulatory cells (19). Increased immunosuppression of MDSCs and T-regulatory cells can lead to tumor progression (93, 94). A study using sub-thermal temperature housing found that chronic

stress in mice leads to reduced antitumor immune response, enhanced tumor growth, and increased metastasis (20). Also, a UV-induced squamous cell carcinoma model demonstrated that mice that exhibited anxiety-related behaviors displayed increased tumor burden, high corticosterone levels, decreased T-lymphocyte tumor infiltration, increased immunosuppressive activity and a prominent metastatic phenotype (21). Similarly, chronic psychosocially stressed mice exhibited increased immune suppressor cell activity toward proliferating T-cells and enhanced tumor size and weight (19). Additionally, surgically stressed mice displayed suppression of tumor-specific  $CD8^+$  T cells (95).

Clinical studies have also demonstrated that chronic levels of stress can lead to immune impairment in cancer patients (16, 17, 23, 37, 96). For example, studies that recruited surgically-treated breast cancer patients found that patients with high levels of stress exhibited reduced immune function indicated by lower ratios of  $T_H1/T_H2$  cytokine production (96), and decreased T-cell activity (16, 17, 29). Similarly, a study of ovarian cancer patients found a correlation between depression and altered humoral-mediated immunity. These patients showed decreased activity of tumor-infiltrating lymphocytes (TILs), a predominant  $T_H2$  response, and lower  $T_H1/T_H2$  ratios in tumor-stimulated lymphocytes and peripheral blood cells (22, 23). Additionally, another study investigated the effects of depression on immunity in gastrointestinal cancer patients after the completion of the self-rating depression scale (SDS) and self-rating anxiety scale (SAS) questionnaires (18). This study found that patients in the depressed group had higher anxiety levels, poor social support, and a significant decline in lymphocyte count in comparison to non-depressed patients (18). As described in this section, the anti-tumoral activity of CTL and  $T_H$  cells are vital regulators of tumor immunity (90, 91) and thus could play a key role in chronic stress or depression/stress-induced tumor progression.

### B Cells

B-lymphocytes are antibody-producing cells that play an essential role in humoral immunity and immune homeostasis. B-cells exert their function either by direct interaction with surface receptors of other cells or through the release of immunomodulatory cytokines that affect the development and function of a variety of immune cells such as T-cells and DC (97). Antibodies released by B-cells can directly or indirectly influence tumor immunity. For example, B-cell-derived antibodies target cancer cells which then stimulate antigen presentation by DCs. Also, antibodies may indirectly contribute to tumor elimination by encouraging the cytotoxic activity of NK cells (98). B-cells are a key component of the tumor microenvironment, representing up to 60% of all tumor-infiltrating lymphocytes in breast and ovarian cancer patients (99, 100).

Recently, the role of B-cells in cancer immunity has gained more attention due to their possible association with carcinogenesis and progression (98). The ability of B cells to produce specific antibody isotypes may be influenced by the stress-induced shift in  $T_H1$  to  $T_H2$ -mediated humoral immunity. At basal levels,  $T_H1$  cells express higher levels of AR binding sites than  $T_H2$ , while  $\beta_2$ -receptor activation differentially affects cytokine production. For example,  $T_H1$  activation of

the  $\beta_2$ -receptor suppresses the production of IFN- $\gamma$  and consequently, the IFN- $\gamma$ -dependent production of IgG2a by B cells (12). Furthermore,  $\beta_2$ -receptor activation does not affect T<sub>H</sub>2 production of IL-4 nor subsequent IgG1 production by B cells (12).

Stress may also influence B-cell redistribution (21, 101, 102) and affect their survival (103). Notably, B-regulatory cells (Bregs) are capable of mediating pro-tumor immune responses by suppressing T-cells and anti-inflammatory cytokines (57). Recent studies have demonstrated that Bregs play an essential role in promoting tumor progression. For example, soluble factors secreted by tumor cells such as TNF- $\alpha$ , promote Bregs differentiation and enhances their activity (104). Tumor cells indirectly stimulate Bregs by recruiting T-cells that secrete IL-2,1 which induce Bregs differentiation (105). A recent phase II clinical trial in breast cancer patients found that perioperative administration of a  $\beta$ -antagonist and a COX2 inhibitor increased tumor-associated B-cells (106). This finding is especially important since tumor-infiltrating B-cells predict increased survival rates in cancer patients (107, 108). Furthermore, in a preclinical model of squamous cell carcinoma of the skin, it was found that mice exhibiting anxiety displayed T<sub>H</sub>1/T<sub>H</sub>2 cytokine shift and higher levels of Bregs which correlated with increased tumor burden (21). In essence, *in vitro*, and *in vivo* studies demonstrate that the stress-induced shift in T<sub>H</sub>1/T<sub>H</sub>2 immune responses may also modulate B-cell activity.

## NK Cells

NK cells are essential components of the innate immune system specialized in recognizing and attacking virus-infected, malignant, and tumor cells. T-cells and NK cells release IFN- $\gamma$  and TNF, which leads to NK cell activation. NK cells differentiate between host and abnormal cells by recognition of MHC I receptors (109). Tumor cells often downregulate MHC I receptors to prevent recognition by CTLs but are still vulnerable to identification by NK cells (110).

Multiple studies have demonstrated that stress conditions lead to impairment of NK cell function. For example, acute swim stress and administration of EPI or  $\beta$ -agonists in rats, suppressed NK cell activity, demonstrating the involvement of adrenergic signaling in attenuation of immune cell function (111). Similarly, in a leukemia model, forced swim and administration of EPI or corticosterone inhibited NK activity and doubled rat mortality (25). These effects were blocked by the administration of a  $\beta$ -antagonist.

NK function impairment has also been investigated in many clinical studies. In a cohort of breast cancer patients, higher levels of stress were associated with decreased NK cell activity and IFN- $\gamma$  (26). In another study, breast cancer patients with higher stress levels at baseline showed impaired natural killer cell cytotoxicity (NKCC) and decreased NK cell response when stimulated with IFN- $\gamma$  (16). Furthermore, patients with elevated stress symptomatology had NK cells with altered membrane receptor expression (27). In ovarian cancer patients, distress was associated with poorer NKCC in TILs while social support was associated with higher NKCC in both TILs and circulating lymphocytes (22, 23). In addition, surgical stress impaired NKCC

by suppressing IFN- $\gamma$  secretion in colorectal cancer patients (112). These studies demonstrate that biobehavioral effects on immunity can also occur within the tumor microenvironment itself and impair multiple factors involved in NK cell activity. Currently, NK cells are considered a promising tool for cancer immunotherapies due to their role in immunosurveillance and malignant cell recognition. A recent review of the literature on this topic discusses several methods focused on enhancing the activity of NK cells for their potential use in cancer therapeutics (113).

## STRESS, THE IMMUNE SYSTEM, AND POTENTIAL THERAPEUTIC TARGETS

Currently, the incorporation of immunotherapeutic strategies into cancer treatment is steadily increasing. Researchers have a better understanding of the crosstalk between the tumor microenvironment and tumor cells, driving new therapies to target tumor-associated immune cells. For example, TAMs are considered a promising target for tumor therapy because of their capability to modulate different levels of tumorigenesis, such as inflammation, immunosuppression and metastatic potential of cancer cells (114). Preventing macrophage recruitment by pharmacological inhibition of chemoattractants, such as CCL2 (MCP-1), has proven successful in ovarian cancer (115), and pancreatic cancer (116). Macrophage depletion through induction of apoptosis, immunotoxin-conjugated monoclonal antibodies, and activating T cell-mediated recognition of TAMs are currently under study (117, 118). Zoledronic acid, a bisphosphonate currently used in metastatic breast cancer, eliminates MMP9-producing TAMs (119) and prolongs cancer patient survival (120). Another study showed that clodronate-mediated macrophage depletion reverts angiogenesis, tumor growth, and metastasis (121, 122). T cell-targeted therapies such as anti-PD-1 nivolumab (123) and anti-CTLA-4 ipilimumab (124) have shown great promise in clinical trials. Improved formulations of already established immunotherapies, such as recombinant IL-2 (125) and adoptive T cell therapy, for enhancing antitumor immune responses continue to demonstrate clinical benefit in various cancers (126, 127). The adverse systemic effects of chronic stress on immune cells, such as immunosuppression, might impair the positive therapeutic responses and benefits seen by current immunotherapies, highlighting the need to address SNS activation on tumor biology. For instance, ongoing stress can impair the efficacy of therapies based on immune stimulation (24, 128).

Several studies have proposed beta-adrenergic blockers to improve therapeutic outcomes in cancer patients due to the influence of the SNS in tumor biology (129). An existing body of work supports the harmful effects of adrenergic stimulation on cancer patients.  $\beta$ -adrenergic antagonists are suggested as a potential therapeutic strategy since they are widely available and used to treat conditions related to increased SNS activation, such as anxiety and hypertension. Recent clinical trials have begun studying the effects of including  $\beta$ -blockers in cancer patients' treatment regimens (NCT01308944, NCT02013492,

NCT01847001). Interestingly, a clinical trial in MD Anderson Cancer Center (NCT01902966) combined relaxation and guided imagery sessions with propranolol to target both behavioral and molecular effects of SNS in cervical cancer. Multiple studies have shown that the use of beta-adrenergic antagonists improved the survival of cancer patients (130, 131), although others have reported no benefits with this treatment (132). A recent prospective pilot trial in epithelial ovarian cancer patients showed that chemotherapy in combination with propranolol improved depressive symptomatology, anxiety, quality of life, and decreased expression of pro-inflammatory genes (133). Although the known side effects of  $\beta$ -adrenergic blockers might limit their widespread use in cancer patients, preclinical, and clinical data support their use to abrogate the deleterious effects of chronic stress on cancer patients.

## CONCLUSION

Stress reduction programs have established social support networks for cancer patients while psychological therapy has also been utilized as a complementary approach to improve quality of life and clinical outcomes in cancer patients. Studies have shown that psychosocial interventions and psychological therapy in cancer patients have proven to be beneficial in reducing depression, anxiety, and improving quality of life (134, 135). However, some studies report mixed effects (136, 137). A combination of these strategies with immunotherapies and currently available chemotherapeutic treatments could significantly benefit patients under emotional stress and decrease

the harmful consequences of neuroendocrine disruption. Further research is required to understand the complex interactions between neuroendocrine signaling pathways and tumor-associated immune cells. A comprehensive understanding of this process will facilitate the development and clinical application of targeted cancer immunotherapies.

## AUTHOR CONTRIBUTIONS

CC-E, RL-C, and GA-P contributed to the conception and design of this review. CC-E and RL-C wrote the first draft of the manuscript. AA-A wrote sections of the manuscript. GA-P wrote sections of the manuscript and provided oversight. All authors read and approved the final manuscript.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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