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Review

Insights on neuroendocrine regulation of immune mediators in female reproductive aging and cancer

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Abstract: Neuroendocrine-immune homeostasis in health and disease is a tightly regulated bidirectional network that influences predisposition, onset and progression of age-associated disorders. The complexity of interactions among the nervous, endocrine and immune systems necessitates a complete review of all the likely mechanisms by which each individual system can alter neuroendocrine-immune homeostasis and influence the outcome in age and disease. Dysfunctions in this network with age or external/internal stimuli are implicated in the development of several disorders including autoimmunity and cancer. The existence of sympathetic noradrenergic innervations on lymphoid organs in synaptic association with immune cells that express receptors for endocrine mediators such as hormones, neural mediators such as neurotransmitters and immune effector molecules such as cytokines explains the complicated nature of the regulatory pathways that must always maintain homeostatic equilibrium within and among the nervous, endocrine and immune systems. The incidence, development and progression of cancer, affects each of the three systems by disrupting regulatory pathways and tipping the scales away from homeostasis to favour pathways that enable it to evade, override and thrive by using the network to its advantage. In this review, we have explained how the neuroendocrine-immune network is altered in female reproductive aging and cancer, and how these modulations contribute to incidence and progression of cancer and hence prove to be valuable targets from a therapeutic standpoint. Reproductive aging,

stress-associated central pathways, sympathetic immunomodulation in the periphery, inflammatory and immunomodulatory changes in central, peripheral and tumor-microenvironment, and neuro-neoplastic associations are all likely candidates that influence the onset, incidence and progression of cancer.

Keywords: neuroimmunology; cytokines; tumor microenvironment; neuro-neoplastic associations; norepinephrine; sympathetic innervation

1. Introduction

The crosstalk among the nervous, endocrine and immune systems is responsible for the maintenance of homeostasis; and dysfunctions in this effective crosstalk pave way for the onset and progression of diseases such as cancer. These complex systems interact at multiple levels. Cancer, irrespective of the site of origin, tissue type or aggressiveness, is a disease that affects the body at the systemic level, thereby modulating the neuroendocrine-immune network on the whole to alter homeostasis and fuel its own growth [1]. Although recent studies have shifted their focus to study the dysregulation of the neuroendocrine-immune network in disease conditions such as cancer, rather than individual systems, there are a lot of unanswered questions. Are cancer-associated dysfunctions of the neuroendocrine-immune network causal or contributory to the development and progression of the disease? Most tumors are irregularly innervated by nerve fibers that directly interact with cancer cells through neuro-neoplastic synapses [2–5]. Although the existence of such innervations have been shown by several studies the exact mechanism by which these nerves influence or may be potential therapeutic targets have not been explored yet. Studies have shown that neural mediators can bind to receptors on cancer cells and modulate signaling pathways that may alter proliferation, angiogenesis, progression, invasion, migration and metastasis. Although a few of these pathways have been studied, how these signals may influence tumors of different hormone sensitivities is yet to be explored.

Neurotransmitters released into tumor microenvironment can also suppress immune functions, modulate inflammatory pathways and aid in cancer progression and metastasis [1,6]. Hormone responsive tumors express receptors for endocrine mediators that bind to stress-associated outputs of the hypothalamo-pituitary-adrenal axis, thereby influencing cancer cell metabolism, growth and migration [7–9]. Tumor microenvironment attracts routine immune surveillance during stages of cancer development beginning from the initial cellular level anomalies, and stimulation of angiogenesis; to migration, invasion and colonisation [10–12]. In each stage, cancer cells evade immunosurveillance by modulating their interaction with immune mediators through various mechanisms including: shedding cancer antigens that may be used to target them, releasing immunosuppressive molecules into the tumor microenvironment, using innate immune machinery for promoting angiogenesis and through metastatic movement [13,14]. The endocrine milieu at the cellular level is modulated by cancer-induced direct autocrine secretion of hormones that drive the growth of the tumor itself and suppress or alter immune-cell functions in the microenvironment [15].

It is still unclear how these inflammatory and immunosuppressive processes work in tandem to aid the progression of the disease and if these markers can be altered to influence prognosis.

Centrally, psychological and emotional responses to cancer at the systemic level may trigger the release of stress-associated signals through the HPA axis, ANS or SNS leading to immunosuppressive effects (Figure 1) [16]. Chronic stress can trigger inflammatory responses that may aid tumorigenesis by supporting the tumor microenvironment, enhance neuroinflammatory processes that can impair neural responses to stress and cause selective immunosuppression of type 1 helper T cells (Th1), cytotoxic T cells (CTL) and increase the risk of cancer invasion and metastasis [17–19]. In females and males, the age-associated alterations in gonadal hormone secretion can influence the incidence and progression of certain types of cancers such as cancers of the endometrium, breast and ovary in women and cancer of the prostate in men [20,21]. Hence it is important to explore the role of female reproductive aging, central stress-associated pathways, peripheral immunomodulatory sympathetic innervations, tumor-associated neuro-neoplastic associations, tumor-associated/mediated endocrine secretions and tumor-associated alterations in immune effector cells and molecules in modulating neuroendocrine-immune homeostasis to fuel cancer.

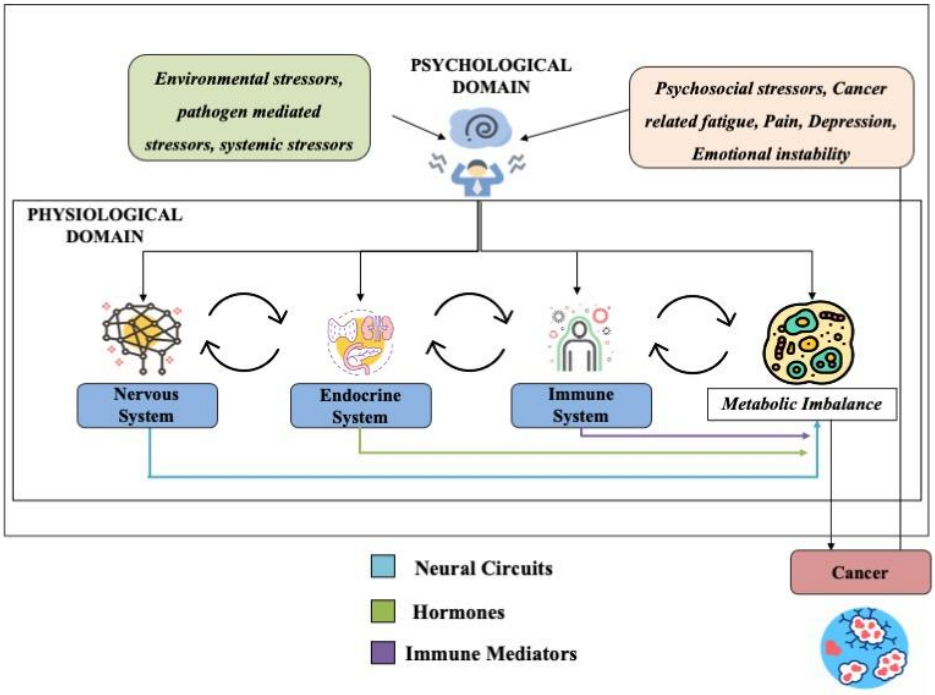

Figure 1. Effective crosstalk among the nervous, endocrine and immune systems maintains systemic, tissue, and cellular homeostasis, which is altered due to dysfunctions in these systems, creating a metabolic imbalance, paving the way to cancer. Factors that contribute to these alterations include: environmental stressors, pathogen mediated stressors, systemic stressors and psychosocial stressors, etc. that aid in the progression of cancer. Conversely, cancer affects the nervous system and thus participates in the development of cancer related fatigue, pain, depression and emotional instability, creating a vicious pattern towards progression of the disease.

2. Female reproductive aging and age-associated cancer

Reproductive aging in female mammals such as humans is characterized by a progressive transition from regular reproductive cycles to irregular cycles, acyclicity and ultimately the loss of follicles and fertility [22]. The reproductive cycle involves two phases: the ovarian cycle (follicular and luteal) and the uterine cycle (menses, proliferative phase, and secretory phase), that prime the uterus for fertilization and is accompanied by a concomitant rise and fall in the levels of associated female sex hormones released during the 28-day period [23,24]. This rhythmic process is tightly regulated by the hypothalamus-pituitary-gonadal (HPG) axis, hence indicating the importance of neuro-endocrine signalling in the maintenance of the reproductive cycles in females [22,25]. Aging in women eventually leads to loss of fertility and is characterized by a slow transition from menarche, regular cycles, perimenopause, to finally menopause, accompanied by alterations in the levels of hormones secreted by the HPG axis [26–28]. Studies from our lab have shown that the bi-directional communication in the neuro-endocrine immune network is altered during reproductive aging [26].

Dysregulation of the HPG axis, following the loss in effective crosstalk between the nervous and endocrine systems, contributes to significant changes in the immune system [24]. This is brought about by alterations in the levels of hormones, such as estrogen and progesterone, released by the HPG axis during reproductive aging [29]. Estrogen exerts immunomodulatory effects by directly binding to estrogen receptors on immune cells and transduces subsequent signalling cascades that alter immune-mediated functions. In the lymphoid organs, estrogen is involved in the regulation of maturation, differentiation, activation and proliferation of lymphoid cells and hence may influence the outflow of cytokines and antibodies [30]. Estrogen also influences T cell maturation (Th2 type) and influences humoral responses to diseases [31]. Estrogen plays an immunomodulatory role indirectly by altering peripheral sympathetic noradrenergic (NA) innervations of the lymphoid organs and by reversing chronic stress-associated adrenergic immunosuppression [27,32–34].

Progesterone shows immunomodulatory effects by binding predominantly to progesterone receptors and to a lesser extent to glucocorticoid and mineralocorticoid receptors on immune cells and mediating downstream signals [35]. Progesterone has broad anti-inflammatory effects including decreased production of TNF and IL-1b cytokines, inhibition of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) pathways, and blockade of TLR and NF-kB pathways in macrophages and dendritic cells, decreased production of IFN-γ via caspase-dependent apoptosis in NK cells, and promotion of Th2 type CD4+ cell response through IL-4, IL-5, IL-10 production in helper T cells [36–41]. Thus, steroid hormones released by the HPG axis play a crucial role in positively modulating immune cell functions in aging women. Studies have shown that the susceptibility to diseases such as cancer, increases with progression of age due to dysregulation of the neuroendocrine-immune network [26,37].

The development of female-specific cancers, such as breast, ovarian and endometrial cancer, can be attributed to the altered outflow of hormones released from the dysregulated HPG axis. The release of hormones estrogen and progesterone has been shown to favour the proliferation of cancer cells despite its immune-enhancive effects [42]. Therapeutic increase in the levels of estrogen and progestogen (synthetic analogue of progesterone) significantly increases the risk of breast cancer, endometrial cancer and ovarian cancer depending on the type of progestogen used [43–46]. However,

treatment with only estrogen has shown to reduce the risk of breast cancer; and the absence of progesterone, backed by the "unopposed estrogen hypothesis", promotes mitotic activity of endometrial cells [47,48]. Despite the roles of female sex hormones produced by the HPG axis in promoting cancers such as breast, endometrial and ovarian cancer, studies have shown that females are less prone to malignancy that males [49]. The role of differences in cancer aetiology including sex differences in hormonal regulation, gene expression, immune function, oxidative damage, autophagy, or a combination of factors that confers protection to females against cancer needs to be explored [50,51]. Additional studies also suggest that estrogen may play a role in upregulating the PD-1 and PD-L1 expression which may contribute to immunosuppression of T cells, B cells, Macrophages and NK cells [53–55]. Studies from our lab have shown that treatment of splenic lymphocytes with estrogen can enhance Con-A-induced proliferation and IFN-γ production dose-dependently and reverse immunosuppression by adrenergic agonists in Con-A-stimulated cells in vitro [56,57]. Middle-aged female rats treated with 0.6mg slow-release pellets implanted at the scruff for 30 days showed significant increase in hippocampal, and splenic NGF expression, TH expression indicating central and peripheral benefits [58,59]. Similarly, women in their follicular phase showed better cell-mediated immune responses compared with luteal and old women indicating that cyclic variations in estrogen and decline with reproductive age influence neuro-immunomodulatory responses and may hence be implicated in the development of female-specific cancers and autoimmunity [60]. Put together, these reports show that the sex hormones, such as estrogen and progesterone, released by the HPG axis in women may play a dual role in the onset and progression of cancers. The role of dose/duration of exposure to hormones and co-stimulatory molecules needs to be explored in animal models of cancer to better understand the synergistic milieu that may cause onset or disease progression.

3. Central stress-associated pathways and cancer

The biological responses to stress are under tight regulation through the combined action of two systems, the hypothalamus- pituitary-adrenal axis (HPA) and sympathetic nervous system (SNS) which releases glucocorticoids and catecholamines, respectively, and both are activated by the central nervous system (CNS) [61]. The stress-related behavioural factors can activate (or inhibit) the HPA and SNS, and the mediators of these pathways can modulate pathological mechanisms in the tumor microenvironment [61]. The key role of the biological circuit is played by paraventricular nucleus of the hypothalamus that recognises any stressful situation, integrating human experiences with physiological signaling and releasing the corticotropin-releasing hormone (CRH) [62]. CRH triggers the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH acts on the adrenal cortex to release glucocorticoids, mainly cortisol, which is released in an inactive form, cortisone. The cortisone is then converted to the active form cortisol and back to cortisone by the enzymes 11-β hydroxysteroid dehydrogenase type 1 (11-β HSD-1) and 11-β hydroxysteroid dehydrogenase type 2 (11-β HSD-2), in the target organs [63]. The production of cortisol is regulated by a negative feedback system via hypothalamus and pituitary gland [64]. The sympathetic fibres play a significant role, by releasing norepinephrine and contributing to potentiation of cancer progression and development of metastases [21]. Both the HPA and SNS pathways maintain the

stress response of the body. However, chronic stress negatively affects the body due to prolonged exposure to stressors, a phenomenon known as allostatic load where the demand exceeds the adaptive capacity of an individual, which contributes to development of the disease [65]. Chronic stress has shown to play key role in cancer progression, due to upregulated levels of glucocorticoids and catecholamines [21,66]. Studies have shown increased levels of circulating catecholamines and glucocorticoids in response to stress, resulting in pro-tumorigenic activities [67,68]. Enhanced expression of β-adrenergic receptors has also been reported in breast cancer [69]. Cancer initiation, progression and metastasis are mediated by sympathetic neural mediators via β-adrenergic signaling, which are also involved in mediating associated psychosocial, noetic and somatic signals [70]. The β_2-adrenergic receptor expression was found to be higher in gastric cancer tissues than normal samples and activation of these receptors was associated with increased malignancy [71]. Adrenergic stimulation of splenic lymphocytes was significantly immunosuppressive, irrespective of receptor subtype [6,56]. Catecholamine-induced β-adrenergic signals have been shown to enhance cancer cell proliferation, as well as tumour growth, through ERK1/2 and promote cancer cell survival, proliferation and angiogenesis through STAT [72,73]. Lymph node metastasis was also associated with higher β2-AR receptor expression [74]. Unpublished data from our laboratory has shown that adrenergic stimulation of ER+ and ER- mammary tumor cell lines differentially altered survival signals in vitro, possibly implicating crosstalk between estrogen and adrenergic signaling pathways. It would be interesting to study how adrenergic immunosuppression would promote the progression of cancers in animal models of the disease.

Various experimental studies have found that chronic stress, as well as significant acute stress, promotes tumor incidence and progression through impairment of antigen presentation, T and NK cell suppression, and enhancement of T regulatory cells [75–78]. The health-related quality of life (HRQoL) of cancer patients is negatively affected by the psychological stressors associated with the diagnosis and treatment of cancer and affect disease prognosis [21,79]. It has been observed that the stigma attached to disfigurement was significantly associated with functional impairments, leading to psychological distress and poor prognosis [80,81]. Although it is clear that cancer affects several brain circuits, it is difficult to determine its effects on the human brain as it might be overlapped by the effect of psychological factors associated with the diagnosis of the disease. This necessitates animal experiments in order to delineate the specific effects of cancer on the brain [82,83].

4. Peripheral immunomodulation, sympathetic innervations, and cancer

The sympathetic nervous system is a part of the autonomic nervous system that keeps the body in a heightened state of awareness for a “fight or flight” response to external and internal stimuli. Sympathetic nerves have been shown to densely innervate the primary (bone marrow and thymus) and secondary (spleen, lymph nodes, etc.) lymphoid organs and hence establish a conduit for possible neural-immune interactions. These nerves primarily release catecholamines, norepinephrine (NE), neuropeptide Y and endogenous opioids such as enkephalins and endorphins, all of which have been shown to affect immunity [84,85]. Sympathetic noradrenergic (NA) circuits that innervate the primary and secondary lymphoid organs are the most widely studied due to the abundance of adrenergic receptors found in the cells of the innate and adaptive immune system [86]. Briefly, the

noradrenergic input to the lymphoid organs is sent via small, unmyelinated post-ganglionic NA fibers along the vasculature. Tracing studies and ganglionectomy have shown that this communication is established through the innervations of axons of pre-ganglionic cell bodies located in the intermediolateral column of upper lumbar and thoracic spinal cord on the post-ganglionic cell bodies present in sympathetic chain or collateral plexuses in conjunction with the great vessels [87]. Thus, the presence of adrenergic receptors on immune cells and the dense sympathetic noradrenergic innervation of the lymphoid organs, provides a gateway for effective communication and signal transduction between the nervous and the immune system. Studies from our lab have shown that dysregulation of the effective bi-directional communication among the nervous, immune, and endocrine systems leads to aging and the onset and progression of age-associated diseases such as cancer [9]. Treatment of splenic lymphocytes with adrenergic agonists significantly decreased proliferation and cytokine expression irrespective of receptor subtype and dose indicating that adrenergic signals may play an immunosuppressive role and aid in the maintenance of naïve cells in the periphery [6,56]. Age associated decline in peripheral sympathetic innervation in the lymphoid organs disrupts neuroendocrine-immune homeostasis, and regeneration of fibers helps to restore homeostasis and check the progression of mammary tumors in animal models [88]. Further, onset of age-associated decline in sympathetic fibers is much earlier in female rats compared to males, suggesting that altered neuroimmunomodulation in the periphery may play a role in female-specific cancers and autoimmunity [34]. Sex-based differences have been shown by our lab on age-associated alterations in cell- and humoral-mediated immune functions, neural-immune mediators, inflammatory markers, trophic factors, and compensatory mechanisms in healthy aging and in rheumatoid arthritis [89,90]. Differences in cellular events that facilitate the crosstalk among hormone receptors and neural mediators and their implications in determining the predisposition to or incidence and progression of age-associated diseases and cancer in males and females is still unclear.

5. Systemic immune interactions in cancer

One way to differentiate a cancer cell from a normal cell is by its potential to evade immune destruction [14]. The immune system strictly prevents cell anomalies that lead to cancer cell formation through the cancer-immunity cycle. This process involves the priming and activation of immune cells upon cancer antigen release, presentation by antigen presenting cells (APC's) and the subsequent trafficking of immune-effector cells such as T cells to perform the required actions to eliminate the anomalies that lead to cancer cell formation [91]. Additionally, the state of cancer is monitored by the process of immunoediting which utilises the functions of cells of the innate and adaptive immune system. This process categorizes that state of cancer into elimination (cancer immunosurveillance), equilibrium (cancer persistence/dormancy) and escape (cancer progression) [92]. From this, it is evident that the cells of the immune system play a vital role in determining the onset and progression of age-associated diseases such as cancer.

Evidence has shown that norepinephrine (released by sympathetic noradrenergic nerves) plays an important role in modulating immune cell response via the adrenergic receptors. These adrenergic receptors bind to norepinephrine and lead to downstream signalling cascades that regulate the activity of immune cells such as T cells and B cells [85,93–95]. A major portion of immune

modulation is brought upon by the stimulation of the β-2 adrenergic receptors (β-2 AR) on immune cells. For instance, NE has been shown to impact T cell development and upregulate the magnitude of Th1 cell-mediated response respectively through the β-2 adrenergic receptor. However, the role that NE plays during Th2 development and/or progression of Th2 cell-mediated response is still unclear [96–98]. Similarly, norepinephrine has also been shown to modulate B-cell mediated release of IgG1 and IgE antibodies through the stimulation of the β-2 adrenergic receptor. Studies shows that β-2 AR stimulation in a B cell that is activated in the presence of IL-4 may induce the activation of two distinct signalling pathways in a B cell to regulate the level of IgG1 and IgE produced and may also upregulate CD86 expression on a B cell to participate in mediating the antibody increase [84,86,99]. In summary, the nervous system might directly affect immune modulation of processes related to cancer through sympathetic noradrenergic innervations which is crucial for maintaining homeostasis at cellular levels. In support of this, it was shown that in the absence of noradrenergic input there is increased anti-inflammatory effects and lytic activity of CD8+ cells through sympathetic activation [10].

6. Modulation of neuroendocrine-immune functions in the tumor microenvironment

Apart from the abovementioned systemic alterations in neuroendocrine-immune functions, crucial changes occur within the tumor microenvironment that warrant close study. Specific changes in the nature and functions of the immune cells in the tumor vicinity are mediated by the tumor cells themselves to facilitate neoplastic growth. Of special interest are the neuro-neoplastic interactions in the tumor microenvironment and their role in prognosis which has been less widely studied [70]. Finally, the role of tumor associated endocrine secretions and their autocrine and paracrine functions and implications in disease prognosis which also contribute to the tumor microenvironment needs to be studied.

6.1. Immunomodulation in the tumor microenvironment

The tumor microenvironment (TME) encompasses the extra cellular matrix, cellular subtypes such as immune cells, fibroblasts, lymphocytes, neuroendocrine cells, adipose cells, and blood and lymphatic vasculature [100–103]. T cells destruct tumor cells by recognizing and reacting to tumor-associated antigens through their T cell receptors (TCRs). Recent studies have shown that the exhaustion and functional impairment of T cells in the TME is a defining feature of many cancers [104]. The various components of the TME exert adverse effects on T cells limiting their differentiation and promoting cellular dysfunction. The tumor cells within the TME also exhibit immunosuppressive properties through production of toxic metabolites that inhibit T cell responses [105]. Myeloid-derived suppressor cells (MDSCs) play pivotal roles in promoting tumor progression and contribute to immunosuppression through the release of high levels of arginase (ARG)-1, inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS) and cyclooxygenase-2 (COX2) all of which contribute to T cell apoptosis [106].

Tumor-associated macrophages (TAMs) are a class of immune cells present in high numbers in the microenvironment of solid tumors. As crucial drivers of chronic cancer-associated inflammation,

their involvement has been described in every step of cancer progression, from early neoplastic transformation throughout metastatic progression to therapy resistance [107,108]. Macrophages can be either pro-inflammatory (M1 type due to IFN-γ) or anti-inflammatory (M2 type due to IL-4 and IL-13). In the initial stages of carcinogenesis, macrophages show a M1 like polarization that works to eliminate immunogenic cancer cells. With progression of the tumor, the TME draws out the M2 polarization hence making it pro-tumorigenic [108]. Polarization of TAMs is regulated by multiple microenvironmental cytokines, chemokines, growth factors, and other signals derived from tumor and stromal cells [109]. Vascular endothelial growth factor- A (VEGF-A) exhibits pro-angiogenic effects and is also shown to foster cancer metastasis by inducing M2 polarization of TAMs in the presence of cytokines IL-4 and IL-10 [110]. Furthermore, other chemokines such as IL-4, IL-6, IL-13, CCL7, CCL8, CCL9, CCL18, and CXCL12 are also highly expressed in tumors and entail TAM recruitment and polarization [111–114]. Hypoxia, one of the main features of solid tumors, develops due to unprecedented cell proliferation, altered metabolism in cancer cells and tumor angiogenesis, resulting in reduced oxygen and nutrient content for normal cells [115,116]. Various chemokines such as CCL2, CCL5, VEGF, SEM3A, oncostatin M and CSF-1 are invariably induced in hypoxic conditions and are accountable for the activation of TAMs and evading immune destruction in the TME [117]. Due to hypoxic conditions, lactate is predominantly produced in the TME due to anaerobic glycolysis which is shown to be a key inducer of M2 phenotype in macrophages. Enhanced expression of G protein-coupled receptor 132 (Gpr132) has been shown to activate downstream signals and modulate the expression of polarization-related genes in breast cancer patients. Studies have also shown a positive correlation between Gpr132 level and M2 macrophage infiltration and metastasis in mice with breast cancer [118]. Although hypoxia fine tunes activation and M2 polarization, it may not be solely responsible for TAM infiltration and hence warrants further study.

6.2. Tumor-associated neuro-neoplastic associations and cancer

The initiation and progression of cancer is regulated by nerve fibres in the tumor microenvironment, although the sympathetic, parasympathetic, and sensory innervations do not play equal roles in all cancers [119]. Evidences of increased nerve density in many cancers have shown the significance of tumor-associated nerve plasticity [120–122]. The emerging pathological feature of many cancers is the process of perineural invasion (PNI), a distant source of metastatic spread well beyond the extent of local tumors. It is one of the important causes of tumor recurrence, mainly due to synergistic neural-epithelial interaction [123,124]. The PNI have been shown to be a prognostic indicator and an independent predictor of outcome in colorectal cancer [125]. The sympathetic neurotransmitters and their cognate receptors have been shown to modulate several hallmarks of cancer, such as proliferation, immune escape, angiogenesis, and extracellular matrix invasion [21,126]. The expression of neural progenitor doublecortin (DCX^+) from the central nervous system has been found to drive neurogenesis in cancer in mouse models [127]. The neuropeptide Y (NPY) family of peptides, in addition to its many physiological actions, has also been shown to be involved in the modulation of tumor progression in endocrine-related cancers, through NPY receptor expression or NPY-related peptide secretion or both [128]. The association of

NPY with tumor progression is found to be due to the activation of G-protein coupled receptors, Y-Rs such as Y1-R, which modulates the proliferation of tumor cells, and Y2-R which enhances angiogenesis [129]. Cholinergic stimulation has been shown to induce nerve growth (NGF), and the over-expression of this paracrine mediator NGF, promotes carcinogenesis [121,129]. Synthetic monoamine oxidase inhibitors such as deprenyl and desmethyldeprenyl have been shown to reverse age-associated loss of sympathetic fibers, expression of neuropeptides, nerve growth factors and neurotransmitters in the periphery and prevent the progression of tumors [88,130]. It would be interesting to see how these molecules modulate neuro-neoplastic associations within the tumors themselves.

6.3. Tumor-associated/mediated endocrine secretions and cancer

The mitogenic effects of the hormones have been implicated in cancer progression [131]. Studies have shown estradiol (E2) as a contributing factor towards carcinogenesis, and that administration of E2 causes breast cancer [132,133]. An autocrine and paracrine β-catenin independent ligand, Wnt5a, has been found to induce carcinogenic signals, and trigger the migration and invasion of tumor cells [134]. The activation of canonical Wnt pathway and transactivation of EFGR in autocrine Wnt signaling also contributes to tumor proliferation in breast cancer [135]. Transforming growth factor beta-1 (TGFβ-1) regulates cancer progression through endocrine, paracrine and autocrine mechanisms, and enhanced expression is shown to be associated with increased breast cancer risk [136]. It has been found that autocrine and paracrine signaling of TGFβ-1 is also mediated through neuropeptide receptor [137]. The neuropeptides such as bombesin-like peptides, gastrin-releasing peptide (GRP) and neuromedin B (NMB) have been shown to function as autocrine growth factors in lung cancer cells [138–140]. Dispersed sub-population of neuroendocrine cells in cancers have been shown to express variety of bio-active neuropeptides including GRP [141,142]. The autocrine actions of peptides, gastrin and cholecystokinin (CCK) are reported in gastrointestinal carcinomas [143]. The co-expression of gastrin and CCK-B receptors is observed in cultured pancreatic carcinoma cell lines and the growth of these cell lines is inhibited by CCK-B receptor antagonists and gastrin neutralizing antibodies [144,145]. The neuropeptide, neurotensin (NT), provides yet another example of a peptide that serves dual functions as a neurotransmitter or neuromodulator in the nervous system, and a hormone in the periphery. Evidence indicates that NT also serves as an autocrine growth factor in prostate cancer. NT receptors were detected in an androgen-independent prostatic carcinoma cell line and NT stimulated the growth of these cells, indicating that NT could contribute to the growth or survival of prostate tumor cells [146].

7. Inflammatory cytokines in cancer

Inflammation plays a crucial role in the immune system to defend against several pathogens, including viruses and bacteria, and has been shown to mediate the initiation, progression, angiogenesis and metastasis of tumors (Figure 2). Several cytokines and mediators of inflammation are attracted by oncogenic changes, hypoxia, chemokines, and other signalling molecules. Immune cells infiltrate the tumor microenvironment and secrete cytokines, chemokines and growth factors

which contribute to the progression of tumor [147]. There is an increased production of pro-inflammatory cytokines in the TME, however, they lack specific functioning and cannot elicit an immune response [148]. One of the distinct physiological difference among tumor and normal cells is hypoxia which can in turn induce an array of cytokines and chemokines. Tumor necrosis factor (TNF) is a versatile cytokine that exerts its role in cell differentiation, proliferation, survival and death [149]. TNF-α in particular plays a double-edged role; being both proinflammatory and tumorigenic. Studies have shown that the effect of TNF-α depends on both concentration and expression site within the tumor. In non-small cell lung cancer, patients with increased TNF-α production in the macrophages and mast cells show higher survival rates than patients expressing stromal TNF-α [150]. TNF-α exerts its function by activating nuclear factor-κB (NF-κB) and c-Jun N-terminal kinase (JNK) signalling pathways [150]. One of the mechanisms for the pro-tumorigenic effect of TNF-α is through increased production of reactive oxygen and reactive nitrogen species, which can induce DNA damage and facilitate the progression of tumors [151,152]. In breast cancer, TNF-α activates the NF-κB pathway through TNFR1, leading to the upregulation of the oncoprotein HBXIP, which in turn upregulates TNFR1, thereby creating positive feedback loop [153].

Interleukin-10 (IL-10) was initially shown to be produced by T-helper cell type 2 (Th2) cells which inhibits Th1 cell type activation and cytokine production [154]. IL-10 has been shown to exert pro-tumorigenic effects by promoting tumor growth and metastasis. The TAMs in microenvironment produce high levels of IL-10 that could be associated with tumor-mediated immunosuppression, thereby setting the stage for tumor progression [155]. Increased expression of IL-10 by Th2 cells has also been implicated in suppressing immune surveillance against cancer growth, despite no direct evidence [156]. IL-6 supports progression of tumors by promoting proliferation and consecutively inhibiting apoptosis, thereby facilitating two major hallmarks of cancer [14,157]. IL-6 mediates its effects through IL-6 receptor (IL-6R) and coreceptor gp130, which subsequently activate the JAK/STAT pathway [158]. Similar to TNF-α, IL-6 also facilitates tumor development by conversion of normal cells to tumor cells by upregulating Oct4 oncogene through the IL-6R/JAK/STAT signalling pathway [158]. Interestingly, there are reported evidences which show that the cytokines synthesized in the tumor microenvironment might mediate cancer-associated effects in the central nervous system. Cancer-induced hypothalamic inflammation may in-turn play a role in the development of cancer anorexia and cachexia [159].

Increasing evidence shows pro-tumorigenic effects of anti-inflammatory cytokine transforming growth factor β (TGF-β). The role of TGF-β in cancer varies according to the cell type and stage of cancer. In the initial stages, TGF-β is anti- tumorigenic, by suppressing oncogenes and promoting apoptosis. But in later stages it is seen that TGF-β promotes invasion and metastasis by inducing epithelial-mesenchymal transition (EMT) [160]. During cancer induction, TGF-β inhibits cyclin-dependent kinase p21 and upregulates c-myc expression [161]. Studies have shown that the expression of TGF-β mRNA in gastric, colorectal, prostate, breast and bladder cancers positively corelated with the degree of invasion and metastasis [162]. Thus proinflammatory milieu in the tumor microenvironment can aid in the initiation and progression of disease.

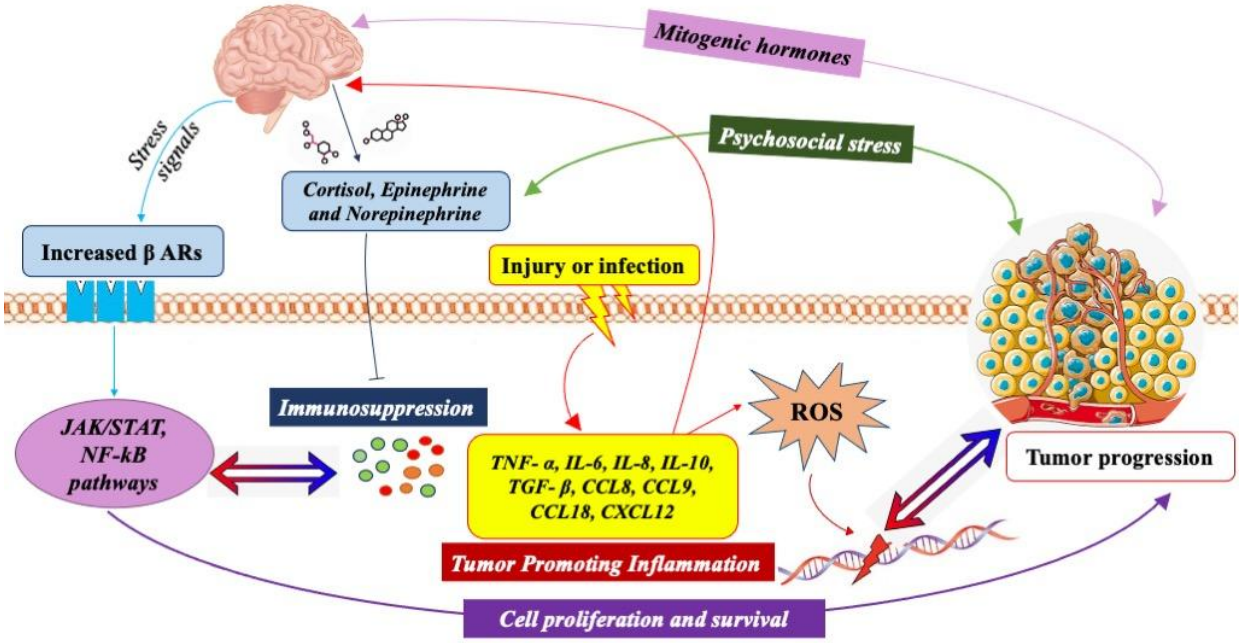

Figure 2. The central nervous system moderates the presence of adrenergic receptors on the surface of cells in response to stress. Increased β ARs on the cell surface leads to activation of JAK/STAT and NF-kB pathways that increase cell proliferation and survival, contributing to tumor maintenance and progression. Due to mechanical damage to cells in the form of any injury or infections, pro-inflammatory cytokines are produced that take two routes: one by contributing to cancer pathways, and other by inducing DNA damage through production of ROS that subsequently aids cancer progression. The TME also produces these cytokines and chemokines for its survival. Psychosocial stressors are also transduced in the form of neurotransmitters and hormones and aid in tumor progression. Mitogenic hormones released due to dysfunctional neuroendocrine-immune homeostasis and autocrine secretion by tumors also promote tumorigenesis.

8. Conclusions

The dysfunctions in the neuro-endocrine immune networks have been shown to set the stage for the onset and progression of various age-associated diseases including cancer. These complex systems interact at multiple levels. Both neuroendocrine (the primary hormonal pathway is hypothalamic–pituitary–adrenal axis) and neuronal (direct sympathetic innervation of the lymphoid organs) pathways are involved in the control of the humoral and cellular immune responses. Chronic activation of sympathetic fibers adversely affects anti-cancer immunity and directly potentiates cancer progression. Stress plays a major role by modulating the HPA axis which sets a series of reactions in motion, and further contributes to the dysfunctional bi-directional communication among the systems. Catecholamines are a major class of neurotransmitters released by the sympathetic nerves in response to stress that modulate immune functions important for tumor immunity, including Th and B cell functions, activation of tumor-associated macrophages, and NK

cell activity. The immune system, in turn, may communicate with the CNS through immune products, primarily cytokines, leading to the direct CNS activation. Production of cytokines and growth factors enhance tumor initiation through inflammation. Initially, tumor growth depends on increased cellular proliferation and decreased cell death, both of which are stimulated by inflammation-driven mechanisms. Peripheral nerve invasion provides another pathway for the spread of cancer cells in the absence of blood and lymphatic metastases, by facilitating tumor-promoting interactions between the tumor microenvironment and the nerve fibres. The nervous system modulates angiogenesis, influences the tumor microenvironment, bone marrow outputs, immune functions and inflammatory pathways to influence metastasis. In addition to these factors, the TME also responds to peripheral signals by producing growth factors, stimulating angiogenesis, evading apoptosis, inducing cytokine storms and expressing other transcription factors that promote invasion and metastasis leading to the progression of cancer (Figure 2).

Thus, the incidence and progression of cancer involves: immunomodulation by neural output, endocrine factors and tumor-associated mediators; neuromodulation by immune effector molecules, tumor microenvironment and associated hormones; and endocrine dysfunctions mediated by stress-associated neural signals, cytokines and autocrine tumor hormones. The loss of regulatory control over the neuroendocrine-immune network and its role in mediating the incidence and progression (associated physiological and psychological manifestations) of age-associated cancers needs further exploration in order to identify possible targets for therapeutic intervention.

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Conflict of interest

The authors declare no conflict of interest.

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