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Stress, Metabolism and Cancer:

Integrated Pathways Contributing to Immune Suppression

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Abstract

The potential for immune cells to control cancers has been recognized for many decades, but only recently has real excitement begun to spread through the oncology community following clear evidence that therapeutic blockade of specific immune-suppressive mechanisms is enough to make a real difference in survival for patients with several different advanced cancers. However, impressive and encouraging as these new clinical data are, it is clear that more effort should be devoted toward understanding the full spectrum of factors within cancer patients, which have the potential to block or weaken antitumor activity by immune cells. The goal of this brief review is to highlight recent literature revealing interactive stress and metabolic pathways, particularly those mediated by the sympathetic nervous system, which may conspire to block immune cells from unleashing their full killing potential. There is exciting new information regarding the role of neurogenesis by tumors and adrenergic signaling in cancer progression (including metabolic changes associated with cachexia and lipolysis) and in regulation of immune cell function and differentiation. However, much more work is needed to fully understand how the systemic metabolic effects mediated by the brain and nervous system can be targeted for therapeutic efficacy in the setting of immunotherapy and other cancer therapies.

Keywords

Adrenergic signaling; immunosuppression; metabolism; stress

The immune system is a combination of both prosecutorial activity designed to kill or limit pathogens, virally infected or otherwise abnormal, defective cells and defensive activity designed to curtail the potential for unlimited destructive power of immune responses. Maintaining a proper balance between these 2 arms of immunity is important both for prevention of infections or malignant cells and for protection of normal cells and tissues from collateral damage such as that caused by autoimmunity. In the case of antitumor immunity, it has now been well established that cancer cells provide a rich array of genetic and epigenetic changes that should be sufficient to generate a strong and long-lasting

antitumor-adaptive immune response. If this is the case, why does the immune response so often fail to control or prevent tumor growth?

What is now clear is that ultimately the efficacy of the antitumor immune response is regulated by a balance between stimulatory and inhibitory (i.e., immune checkpoint) signals that, under normal physiological conditions, are critical for the maintenance of tolerance and prevention of autoimmunity.[1] Several of these inhibitory molecules have been identified including CTLA-4, programmed death 1 (PD-1/B7-H4), T-cell immunoglobulin and mucin domain-containing protein 3 (Tim-3), and lymphocyte activation gene 3 (LAG-3). These various checkpoints are natural brakes that protect normal tissues from being damaged when the immune system is actively engaged in destruction of pathogens. Recent research has confirmed that naturally occurring checkpoint inhibitors can be expressed by tumor cells to protect themselves from the destructive capacity of cytolytic T cells. Excitingly, checkpoints have turned out to be excellent targets for new, antibody-based therapies. These novel classes of cancer drugs are not designed to kill tumor cells directly; instead, they target immune cell receptors or their ligands (which can occur on tumor cells) to promote antitumor immune cell activities.[2] Antibodies targeting 2 of these checkpoints are currently in the clinic.[3] During T-cell activation, CTLA-4 is up-regulated and subsequently binds to the activating ligands B7.1 and B7.2 with greater affinity than the costimulatory molecule CD28, thus interfering with T-cell activation at an early point in the antitumor immune response. Anti–CTLA-4 has Food and Drug Administration approval for renal cell carcinoma and non–small cell lung carcinoma. Once in the tumor microenvironment, exposure of T cells to PD ligand 1 expressed on other immune cells or often by tumor cells themselves induces T-cell inhibition and/or death.[4] Antibodies to both PD-1 and PD ligand 1 are currently in clinical trial.

Despite the enthusiasm surrounding the initial clinical trials testing these drugs and the fact that some of these new immunotherapies are now Food and Drug Administration approved, having shown remarkable rates of durable tumor responses in several cancer types, most patients still do not respond to these new therapies, and nearly all patients with certain types of cancer (i.e., pancreas and colorectal tumor) do not respond. Nevertheless, the success associated with these new approaches has opened new investigations addressing several questions: Are there other factors that may be blocking, even temporarily, the cytolytic function of T cells and other effector immune cells critical to tumor control? Can the microenvironment of tumors be altered to improve the efficacy of checkpoint inhibitors? Can we predict or select ahead of time which patients will respond to checkpoint inhibition[5] and those in which other modifications of the tumor micro-environment must be made ahead of time in order to improve checkpoint inhibitors or other therapies? The goal of this brief review is to highlight new research that is pointing to a surprising role for nerves in the growth of tumors and in control of antitumor immunity, and this is due in part to changes in cellular and systemic metabolic pathways regulated by adrenergic signaling. Importantly, these adrenergic signaling pathways may be increased in patients experiencing pain or anxiety and other forms of stress, which increase upon a diagnosis of cancer and during progression. We conclude that modification of adrenergic signaling pathways, which are involved in tumor cell proliferation and apoptosis and metastasis and also impact the

immune response and metabolic pathways, will be essential for optimization of immunotherapy efforts.

The Physiological Stress Response Pathway: The Basics

The stress response is 1 of the most highly conserved and fundamental biological processes in living creatures. Many different types of signals, including anxiety, depression, pain, fear, and thermal stress, can activate stress response pathways that originate largely in the brain (limbic system, hypothalamus, medulla, and pituitary gland) and can generate a myriad of physiological responses, which in turn stimulate afferent signals from the periphery back to the brain to return the system to homeostasis. Several neurotransmitters and hormones mediate behavioral and physiological changes, including the well-recognized "fight-or-flight response" to acute and serious threats. Two major arms of the nervous system regulate the response to stress: the autonomic nervous system and the hypothalamic-pituitary-adrenal axis. These are initiated by stimulation of spinal cord and preganglionic and postganglionic neurons in the sympathetic nervous system, which innervate multiple peripheral tissues and cells. The catecholamines, norepinephrine (NE) and epinephrine (Epi), originate from sympathetic nerves of the autonomic system (NE) and also from the adrenal medulla and other cells, whereas corticosterones are produced in the cortex of the adrenal glands.[6,7] Catecholamines mediate the acute stress response by binding to α- or β-adrenergic receptors, which are a class of 7-pass transmembrane, G-coupled protein receptors.[8–11] Norepinephrine and epinephrine regulate overall metabolism by influencing blood pressure, heart and respiratory rate, and body temperature (nonshivering thermogenesis) by binding to α- and β-adrenergic receptors on tissues.[12] The wide range of physiological responses which are generated by stress signaling depends on the specific receptor and function of the target cell to which the neurotransmitters bind. In addition, several of these molecules also play a significant role in maintaining homeostasis even during unstressed states. For example, these molecules can activate multiple intracellular signal transduction pathways that influence survival or apoptosis, protein production, and cellular replication. Importantly, the development of numerous pharmacologic agents with which to target these adrenergic receptors (e.g., β-blockers and agonists) has provided valuable medications for use in both the clinic (largely for diseases such as hypertension or asthma) and in the laboratory.

Growing Recognition of a Role for Systemic Stress Response Pathways in Immunology and Cancer Biology

From the early recognition of research linking chronic psychological stress with impaired immunity, i.e., "psychoneuroimmunology," there has been a growing, interdisciplinary appreciation of the importance of interactions between the nervous system, endocrine organs, and the immune system.[13–16] A more recent recognition of how environmental pressures force a balancing act between evolutionarily essential functions (such as growth, reproduction and thermoregulation) and other lower priority but energy-costly processes such as the immune response has led to the emergence of a field known as ecological immunology (ecoimmunology).[17] Recently efforts are being made to identify the overlapping concepts within both of these fields in order to identify common mechanistic pathways linking stress to immune function.[18]

A major mechanism by which stress regulates the immune system is via cellular signals mediated by receptors on the surface of immune cells. Both lymphoid and myeloid cells possess receptors known to respond to stress molecules including catecholamines and corticosteroids. It is generally accepted that acute stress stimulates myelopoiesis and increases release of mature immune cells from the bone marrow into the blood to enhance immune function to provide defense against infections which could occur during injury.[19–21] On the other hand, it is recognized that chronic exposure of immune cells to stress hormones can significantly diminish their activity and even induce immune cell tolerance or death.

Glucocorticoids have well-characterized mechanisms by which they impair the immune response, and for over 60 years, they have been used as immunosuppressive agents in the treatment of autoimmunity and inflammation.[22] Recently, we are beginning to appreciate the impact of the sympathetic nervous system on the immune system. But, as with the glucocorticoids, there are data showing that immune system, cells can be significantly impaired by stimulation of adrenergic receptors by catecholamines.[23,24] Postsurgical analysis of cancer patients shows that of catecholamines following surgery significantly increases the risk of cancer recurrence. Experiments performed in rat models that were also treated with β-blockers and anti-inflammatory cyclooxygenase (COX) inhibitors revealed a vast improvement in long-term tumor-free survival in these animals, indicating that major drivers of this relapse were the stress hormones.[25] Other studies[26–28] show that natural killer cell impairment is also associated with the catecholamine-driven impaired immunity seen in the postsurgical period. Together these could facilitate the reestablishment of remaining tumor cells.

Other data demonstrating the immune-suppressive potential of NE exist and are briefly summarized here (Fig. 1). For example, major histocompatibility complex class II expression on astrocytes has been shown to be reduced by NE.[29] As mentioned earlier, NE production is increased by physical stressors including exposure to cold temperatures during which NE drives metabolic heat production (thermogenesis).[30] An intriguing study shows that the increased production of NE in brown adipose tissue during cold stress is associated with a skewing of macrophage differentiation toward an M2 phenotype as characterized by the expression of arginase, the scavenger receptors, MRC1, and the lectin receptor, CLEC10A.[31] These macrophages are themselves an additional and major source of catecholamines; depletion of these cells (through the use of knockout mouse models) resulted in impaired ability to maintain body temperature.[31] Other studies from our own laboratory show that when mice are mildly cold stressed (which occurs under standard housing conditions) they are not able to control tumor growth as well as mice housed under thermoneutral temperatures, i.e., 30 °C (when NE-driven thermogenesis is minimized).[32] The improved control of tumor growth at thermoneutrality was determined to be dependent on CD8+ T cells, which exhibited improved functional markers, including an increase in glucose receptors, and was increased within the tumor microenvironment. Additionally, we also observed a decrease in immunosuppressive cells such as regulatory T cells (T_{regs}) and myeloid-derived suppressor cells (MDSCs) in mice that were not cold stressed, which could definitely play a major role in promoting tumor growth by suppression of the anti-tumor immune response. These studies by Nguyen et al[31] and Kokolus et al[32] provide strong evidence that chronic stress deriving from suboptimal physical environments generates

signals that can significantly influence subsequent immune function. In this regard, it will be interesting to determine whether in response to cold-stress, TAMs also serve as a source of NE in the tumor microenvironment.

Defining the Mechanism of Stress-Induced Immunosuppression

Guereschi and colleagues[33] have shown that activation of the β_2-adrenergic receptor on cells expressing FoxP3^{+} enhances their suppressive properties by increasing cell surface expression of CTLA-4, a molecule that promotes Treg suppressor function. In addition, this study demonstrated that β_2-adrenergic signaling on CD4^{+} FoxP3^{−} cells induced expression of FoxP3 in CD4 cells, suggesting that stress could actually result in additional skewing of the antitumor immune response toward an immunosuppressive phenotype. However, the situation is likely to be highly complex and dependent on precise immunological settings. That T_{regs} could also be inhibited by signals from the sympathetic nervous system was shown in mouse studies involving systemic blockade of catecholamine release from nerve endings.[34] While these studies on the role of adrenergic signaling on T_{regs} were not done in the setting of tumors, or antitumor immune responses, they do highlight the fact that T_{regs} are definitely sensitive to signals from the nervous system, which could play a role in altering the anti-tumor immune response given physiological and psychological stress in patients diagnosed with cancer.

Other cells which can suppress anti-tumor immune effector cells include myeloid derived suppressor cells (MDSC) dendritic cells (DCs), and tummor associated macrophages (TAMS). Sloan et al[35] and Madden et al[36] have shown, ominously, that stress can lead to the recruitment of tumor-associated macrophages to tumors where they can produce numerous proinflammatory and proangiogenic factors including vascular endothelial growth factor and metastasis-enhancing matrix metalloproteinases. Earlier work by Bernard et al[37] using a murine model of trauma demonstrated that catecholamines facilitate the production of arginase from macrophages which then could contribute to the immune suppressive tumor microenvironment.

Work by several groups has demonstrated that tumor-derived factors can induce the development of MDSCs, which can suppress CD8^{+} T-cell function.[38–40] However, Jin and colleagues[41] show that stress itself can lead to the accumulation of CD11b^{+}GR1^{+} cells, which are phenotypically defined as MDSCs, and that these cells also produce nitric oxide and arginase. Patients diagnosed with cancer are known to experience increased levels of various forms of stress, and therefore, studies by Mundy-Bosse and colleagues showing a strong correlation between stress and immune suppression in breast cancer patients are highly suggestive of a role for stress signaling–induced MDSC accumulation.[42]

Dendritic cells, which are critical for generating adaptive immune responses, can also be greatly influenced by stress. Both glucocorticoids and catecholamines have profound suppressive effects on DCs. Many reports indicate that dexamethasone impairs DCs' ability to activate T cells[43–45] and prevents DCs from maturing in response to inflammatory stimuli, resulting in immature DCs that promote T_{reg} differentiation and production of the suppressive cytokine IL-10.[43] Catecholamine stimulation of DCs causes similar suppressive

effects by hindering IL-12p70 production, which favors an immunosuppressive T_H2 response.[46] Our own recent work demonstrates that mild cold stress can impair DC activation of T cells.[47] Taken together, these new studies indicate that stress can lead to significant dysregulation of immune cell function and potentially contribute to a protumorigenic environment in patients by suppressing host immunity.

Other aspects of adrenergic signaling may also be critical for modulating the degree of immune function. For example, lymphocyte recruitment and trafficking through secondary lymphoid organs are critical for immunosurveillance and effector function. Recent studies demonstrate a critical role for adrenergic signaling in control of lymphocyte egress from lymph nodes.[48] Also, modulation of cytokine production and proliferation in CD8 memory T-cell function has been shown to be regulated by NE.[49]

Is Cancer Progression Regulated by Systemic Adrenergic Stress Modulation?

Recent retrospective analysis of patients taking β-blockers (which suppress signaling through β-adrenergic receptors) for treatment of problems unrelated to their cancer diagnosis (i.e., most commonly for hypertension and anxiety) has found that the patients have significantly lower rates of several cancers as well as increased long-term survival, reduced metastasis, and improved therapeutic responsiveness compared to patients not taking these medications.[50–53] Moreover, use of both β-blockers and the α_1-adrenergic antagonist, prazosin, which is prescribed for the treatment of benign prostatic hypertrophy, in mouse tumor models has been shown to inhibit proangiogenic cytokine production, decrease cell proliferation, and increase apoptosis.[54,55] Finally, studies reveal that taking β-blockers before surgery improves outcome.[56] This work takes on increasing significance as the immunomodulatory impact of stress, as well as the effect of stress on tumor cell biology, is beginning to be revealed.

Adrenergic Stress and Tumor Cell Biology

Adrenergic receptor signaling can regulate apoptosis, proliferation, and angiogenesis—all of which are critical for survival of tumors. Thus, the fact that many tumor types have been found to express functional, cell surface adrenergic receptors should be alarming in the context of increased stress in cancer patients. Several studies have revealed the expression of adrenergic receptors on various murine and patient tumor cells, including carcinogen-induced mammary tumors,[57,58] melanoma,[59,60] pituitary tumors,[61] pancreatic tumors,[62] lung cancers,[63] breast cancers,[64] and prostate cancer cells,[65] as well as an analysis of several other human cancers (including Ewing sarcoma, neuroblastoma, rhabdomyosarcoma, lymphoma, and other pediatric tumors).[66,67] Recent data have demonstrated that stimulation of these receptors can have dramatic effects on cancer cell biology, particularly metastasis. This work has been done using both pancreas and prostate cancer models. Work in pancreatic cancer cell models shows that blockade of adrenergic receptors leads to significantly better responses to specific therapeutic agents and a decrease in the activation level of pathways regulating survival. These include decreases in the expression of Bcl-2, which correlates with increased killing by gemcitabine.[68] Zhang and colleagues[62,69] showed

that the β-adrenergic receptors regulate cyclin expression, nuclear factor κB activity, and Akt/Erk1/2 pathways. The use of a β₂-adrenergic receptor antagonist alone significantly decreased the expression of all these molecules and reduced metastasis.

Studies in both transgenic and xenograft models of prostate cancer have demonstrated a highly enriched expression of adrenergic receptors, and there has been a detailed analysis of the signaling pathways associated with these receptors. Sastry and colleagues[70] demonstrated that β₂-adrenergic receptor signaling in prostate tumor cells led to phosphorylation of BAD and increased survival.

Our recent work[71] has demonstrated that cool housing temperature–induced sympathetic nerve activity is sufficient to increase therapeutic resistance of several different pancreatic tumor models to several cytotoxic and targeted therapies. This effect was correlated with differences in NE expression, with cold-stressed mice expressing significantly greater levels of NE. Importantly, mice that were cold stressed also expressed higher levels of prosurvival molecules including phosphorylated BAD. The up-regulation of intracellular apoptotic pathways in response to adrenergic signaling would also be expected to protect tumor cells from effector immune cells. Thus adrenergic signaling induces resistance of tumor cells to apoptosis as well as suppressing effector cell function.

Adrenergic signaling has also been recently studied for its role in facilitating metastasis, both at the level of the cancer cells and at distant sites. Recent work has demonstrated that catecholamines can protect cells from apoptosis, which normally occurs when these cells lose contact with the extracellular matrix, i.e., anoikis.[72] Other studies show that the expression of vascular endothelial growth factor and matrix metalloproteinases is increased in response to adrenergic signaling.[73] Moreover, elevated levels of IL-6 and IL-8,[74,75] in combination with vascular endothelial growth factor and matrix metalloproteinases, are thought to be major components of the "metastatic switch" controlled by adrenergic signaling.[35]

In very exciting new studies, Magnon and colleagues[76] have shown a remarkable role for recruitment of sympathetic nerves in the initial engraftment of prostate tumor cells in immunodeficient mice. Moreover, Campbell et al[77] observed that catecholamines induced the production of osteoprotegerin in the bone marrow, which facilitates the dissemination of breast tumor cells to these sites. These data draw attention to the fact that while growing, tumors, to support their growth and progression, recruit autonomic nerves to the TME. These same nerves likely are directly involved in immunosuppression of the anti-tumor immune response. This underlines an additional mechanism by which tumors escape immune surveillance. Collectively, these data strongly support additional study on the role of neurogenesis and stress signaling in cancer progression.

Relationship of Stress to Metabolism and Tumor Immunosuppression

Overall, the evolutionary role of adrenergic signaling is to convert rapidly a system generally at rest to one that is activated and capable of escaping danger. Thus, the fundamental effect of the fight-or-flight response is to increase oxygen consumption to cardiovascular and musculoskeletal systems and other organs, as energy is expended, to help

overcome a dangerous situation. In the case of immunity, the system acts preemptively to help prevent infections that might occur as a result of injury, producing and releasing more immune cells to the periphery. However, in addition to being involved in the escape from immediate danger, the same pathways and transmitters, such as catecholamines, are activated by many other forms of stress, including emotional grief, anxiety, and pain. As this review and others emphasize, chronic activation of this pathway and the continued production of catecholamines have profound ramifications for cancer progression.[78,79]

However, while there is much more work that needs to be done, there are other aspects of adrenergic signaling and metabolic changes that may overlap with those metabolic pathways that influence cancer progression and the antitumor immune response. For example, there is now clear evidence that lymphocyte activation is a bioenergetically challenging process and that available nutrients and oxygen can become rate limiting for activation.[80] In fact, the competition between tumor, immune suppressive cells and immune effector cells for limited resources present in the TME are known to contribute to immune suppression. Thus, any systemic drain of energy stores by chronic adrenergic stress responses, particularly those that may modify availability of oxygen or the activity level of mitochondria, could limit immune function. Another area of systemic modulation of metabolism by chronic adrenergic signaling involves lipolysis and the increased release of free fatty acids needed to fuel functions driven by stress pathways. However, in the setting of cachexia, the muscle wasting and release of amino acids and activation of acute-phase response proteins and changes in the rate of tumor glycolysis in cancer patients[81] could also limit the full activation of immune cells in the tumor microenvironment.

Conclusions and Implications

Although relatively little research has explored the role of catecholamines (and adrenergic signaling) on immune cells and cancer progression in comparison to the many decades of work on corticosteroids, it is clear that there is significant potential for targeting the interaction of nerves with immune cells to improve antitumor immunity (Fig. 1). New immunomodulatory agents aimed not at the tumor cells but toward the host immune cells have shown tremendous clinical promise. In particular, the successes of ipilimumab (anti-CTLA4) and nivolimumab (anti-PD-1), which prevent the engagement of molecules on T cells that induce anergy and exhaustion, have spurred excitement in the field and highlight the enormous potential that the host immune response alone has in controlling tumor growth.[82] Yet, these treatment strategies are still dependent on T-cell functionality and limited by suppressive factors in the tumor. Therefore, any means of optimizing the host environment to prevent T-cell dysfunction or death and to reduce the degree of immunosuppression could have profound effects on the therapeutic response in patients. As described here, the growing epidemiological evidence hints toward the possibility that α-and β-blockers may be a method of safely improving therapeutic response by targeting multiple adrenergic pathways in the tumor and the host.

While catecholamines are seen to modulate and impair the function of cells which are critical for antitumor immune responses, most of these studies have not yet been conducted in the setting of tumor models. On the other hand, there is a growing appreciation of the

impact of adrenergic signaling on tumor growth and therapeutic responsiveness. The demonstration[75] that nerve recruitment (neurogenesis) facilitates tumor growth reveals the importance of adrenergic signaling to tumor cell survival. The exact mechanism of how stress hormones affect immune cells in the setting of cancer is not completely understood because of the complex signal transduction pathways and responses that can be elicited through adrenergic receptor activation and much more work is needed. While there are significant effects of adrenergic signaling on metabolic pathways that are known to intersect with those needed by the tumor for its survival (and which can modulate immune activity), there is still a major gap in the field regarding the metabolic changes in tumor cells stimulated by sympathetic nerve–driven pathways. An important question is how adrenergic signaling pathways may alter tumor metabolism, e.g. glycolysis. How adrenergic signaling in tumor cells may alter this microenvironment remains to be clarified. As patients who are newly diagnosed with cancer or who are undergoing cancer treatment are under considerable emotional and physical stress, the data presented here indicate that there is high potential for this increased adrenergic stress to actually promote tumor growth and metastasis, reduce therapeutic efficacy, and impair antitumor immunity. Fortunately, the wide assortment of inhibitors, β-blockers and α-blockers, developed for the routine treatment of hypertension and other disorders provides an opportunity for immediate translational research.

Acknowledgments

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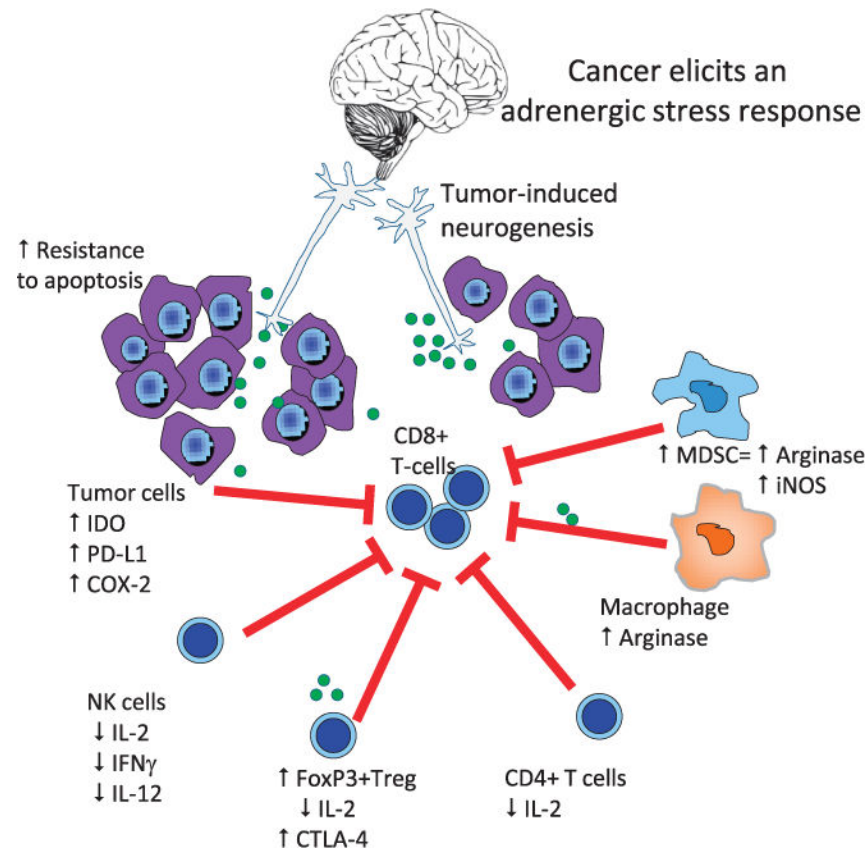
FIGURE 1.

Adrenergic stress impacts the tumor microenvironment in multiple ways to inhibit antitumor immunity. In a process analogous to angiogenesis, neurogenesis of autonomic nerves takes place in growing tumors. Tumor cells and multiple immune cells express β-adrenergic receptors and respond to the neurotransmitter NE (○) released by sympathetic nerves in the tumor microenvironment. Adrenergic signaling promotes resistance of tumor cells to apoptosis. Importantly, multiple immune cell types express the β-adrenergic receptor and respond to NE in ways that result in suppression of the CD8^{+}-mediated antitumor immune response as described in the text.