npj | precision oncology

Review

Published in partnership with The Hormel Institute, University of Minnesota

https://doi.org/10.1038/s41698-025-00957-y

Autonomic modulation of the immune response and implications for CNS malignancies

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While the central nervous system (CNS) has long been known to regulate global physiologic processes, its role in regulating immune responses has only relatively recently been appreciated. Specifically, CNS input via the autonomic nervous system (ANS) is increasingly emerging as a crucial modulator of immune responses in numerous pathologies, though understanding of the role of these pathways in malignancy is limited. Herein, we provide an overview of CNS-immune signaling pathways, outline the evidence of ANS inputs to immune organs, provide a detailed description of the impact of ANS signaling on immune cell functions, and consider the implications of ANS-immune regulation for the antitumor immune response and CNS inflammation, with a specific focus on how these factors coalesce to impact the antitumor immune response in intracranial malignancies. This review concludes by highlighting the need to better understand cancer neuro-immunology, the tripartite interactions of malignancy and immune cells within the unique niche of the nervous system.

The central nervous system (CNS) is responsible for the coordination of global physiologic responses and maintenance of homeostasis. While the role of the CNS in regulating more obviously dynamic organ systems has been studied extensively, CNS control of the immune response has become an area of exploration relatively recently. Increasing evidence is accumulating regarding CNS regulation of immune responses to a variety of stimuli, contributing to an increasingly complex and nuanced understanding of CNS-immune interactions. The CNS modulates immune responses via both the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS). In this review, we provide a brief overview of these brain-body communication axes and subsequently focus on ANS-immune regulation, outlining ANS anatomy with a specific focus on immune organs and a detailed description of the functional impact of ANS signaling on immune cells. Finally, we consider the implications of ANS-dependent immune regulation for antitumor immune responses, both overall and in the context of CNS malignancies. Ultimately, experiments to understand the complex interplay between tumor, nervous system, and immunity—so called "cancer neuro-immunology"—are desperately needed.

ANS regulation of physiology

The autonomic nervous system

The autonomic nervous system (ANS), consisting of the sympathetic (SNS), parasympathetic (PNS), and enteric nervous systems (ENS), encompasses an unconscious neural network that links the central nervous system (CNS) to nearly all anatomic locations and physiologic functions (Fig. 1)[1,2]. This review will focus on the SNS and PNS, as the ENS predominantly acts to regulate gastrointestinal processes outside the intended scope. In brief, the SNS and PNS represent largely parallel webs of two-neuron pathways (termed pre-ganglionic and post-ganglionic neurons) originating from the central nervous system and ending at target tissues throughout the body. The SNS and PNS are controlled by centers within the brainstem and hypothalamus and act both together and independently to dynamically allocate resources and adapt responses to the needs dictated by the body's interpretation of stimuli[2,3].

The SNS is colloquially responsible for the "fight-or-flight" adaptive framework, generally geared towards preparing the body for the identification of and response to dangerous environments and stimuli. Beyond this acute transient extreme, its baseline action maintains homeostatic function

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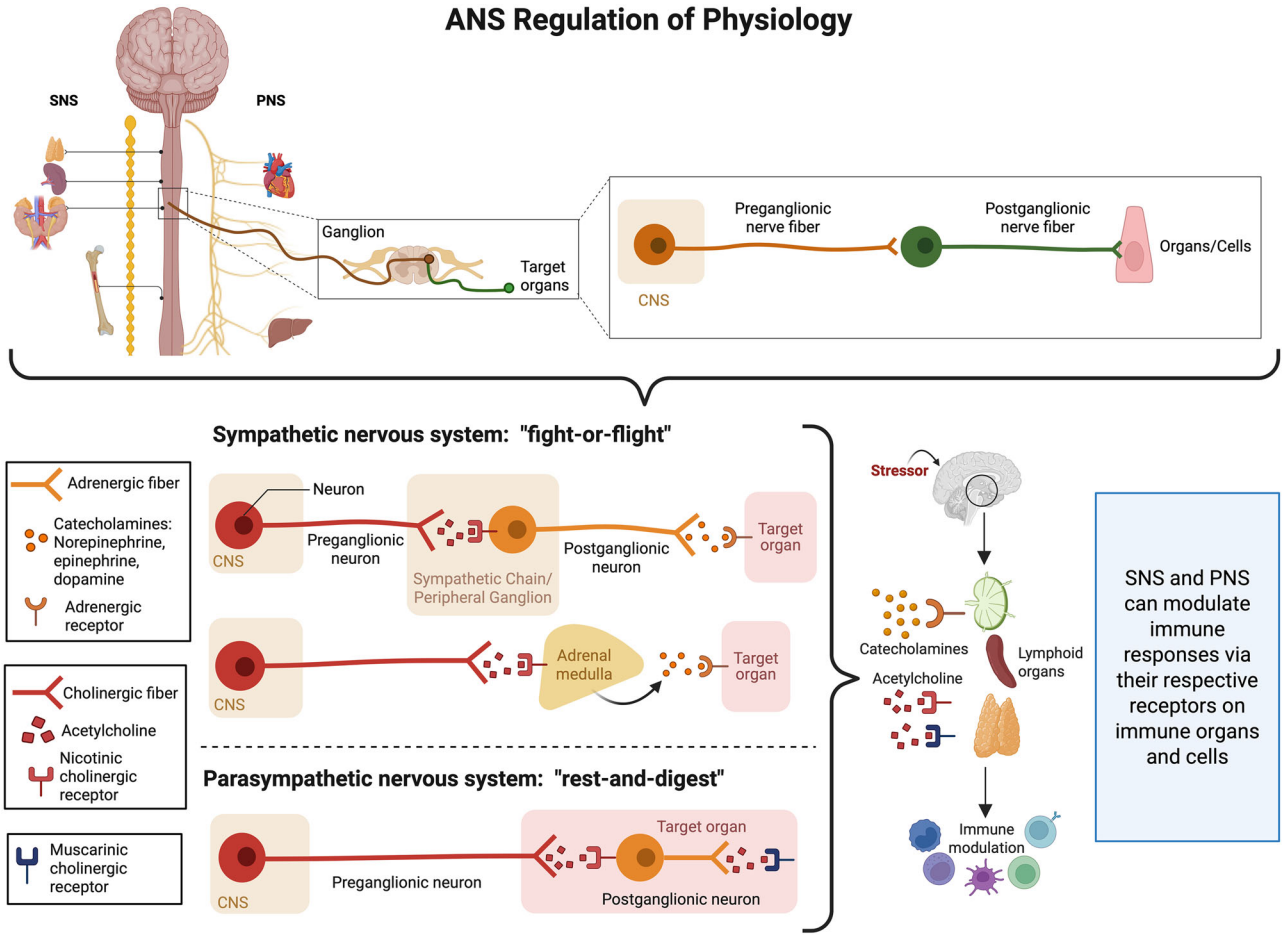

Fig. 1 | ANS regulation of physiology. Overview of the autonomic nervous system, divided into the sympathetic and parasympathetic nervous systems. Both subdivisions rely on a two-neuron circuit prior to reaching an end organ, in general. The SNS preganglionic neurons are found in the lateral horn of the spinal cord from approximately T1–L2 and are, in general, cholinergic, while post-ganglionic neurons extending to target organs release catecholamines. PNS preganglionic neurons arise from cranial nerve nuclei or the lateral gray horn of the spinal cord from T12-L1 and travel via the cranial/vagus nerves and pelvic splanchnic nerves. The PNS pre- and post-ganglionic neurons are generally cholinergic via nicotinic and muscarinic receptors, respectively. Created with Biorender.com.

of the respiratory and cardiovascular systems, along with roles in temperature regulation, thirst, satiety, digestion, micturition, and reproductive processes[3]. SNS preganglionic neuronal cell bodies are located in the lateral horn of the spinal cord from T1 to L2/4 and extend axons out to synapse with extra-spinal post-ganglionic neurons that then innervate target sites[1,2]. The SNS uses acetylcholine (ACh) with nicotinic receptors at the pre-/post-ganglionic neuron synapse[2]. The post-ganglionic neurons of the SNS then release catecholamines (predominantly norepinephrine (NE), but notably dopamine in the kidneys and epinephrine (Epi) at the adrenal medulla) and non-classical neurotransmitters such as adenosine triphosphate (ATP) and neuropeptide Y (NPY) at the target sites, with the exception of ACh in the case of sweat gland innervation[2].

The PNS, in coordination with the SNS, also maintains homeostatic function of the respiratory and cardiovascular systems in addition to its association with the "rest-and-digest" physiologic framework aimed towards the maintenance of energy stores and elimination of waste. Specifically, it has been implicated in digestion, defecation, micturition, lacrimation, salivation, reproductive activities, and visual acuity[3]. The overall anatomic organization of the PNS is described as craniosacral, reflecting the two divisions of the system. The pre-ganglionic neurons arise either from the nuclei of various cranial nerves and travel to targets through the cranial and vagus nerves or from the lateral gray horn of the spinal cord at T12-L1 and travel to the target sites via the pelvic splanchnic nerves. In contrast to the SNS, the synapses between pre-ganglionic and post-ganglionic neurons are located within the target tissue itself[1,2,4]. Additionally, the PNS utilizes the neurotransmitter ACh at both the pre-/post-ganglionic and post-ganglionic/target terminals, with nicotinic and muscarinic receptors, respectively, along with lesser releases of other neuropeptides and nitric oxide (NO)[2].

While immune organs have not classically been considered ANS "target organs," a wealth of data confirms the direct connection between the immune system and the ANS. Autonomic nerve fibers are found in both primary, immune cell-generating (thymus, bone marrow) and secondary, immune cell-supporting (spleen, lymph nodes) lymphoid organs[5–8]. As described previously, the pre-ganglionic cell bodies of these nerve fibers are located in the intermediolateral cell column of the spinal cord; they then form synapses with post-ganglionic nerve cell bodies in the sympathetic chain or other collateral ganglia[4]. In general, post-ganglionic nerve fibers then travel with vasculature to enter lymphoid organs and branch to innervate the parenchyma.

SNS impacts on immune function

Epi and NE, also referred to as adrenaline and noradrenaline, respectively, are the primary signaling molecules of the SNS (Fig. 1). Epi and NE can be released into circulation from the adrenal medulla or by sympathetic nerve terminals in target organs. Epi and NE signal through a family of G protein-coupled receptors (GPCRs) named adrenergic receptors, which are divided into two main classes, α- (ADRAs) and β-adrenergic receptors (ADRBs). These classes are divided into multiple subtypes: α1 (ADRA1), α2 (ADRA2), β1 (ADRB1), β2 (ADRB2), and β3 (ADRB3). Importantly, ADRA1 and ADRBs are $G_{q/11}$ and G_s coupled, respectively, and are therefore primarily

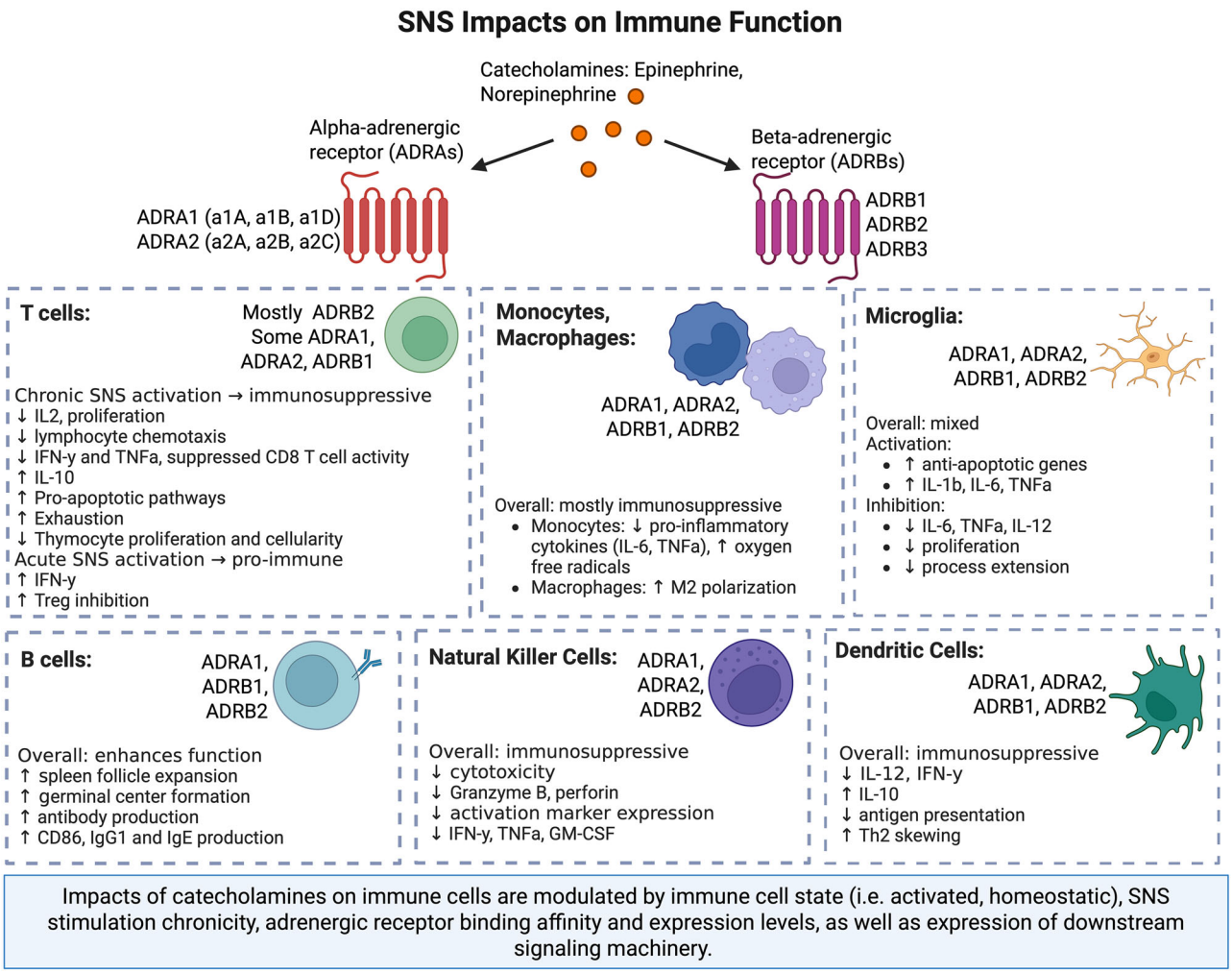

Fig. 2 | SNS impacts on immune function. Overview of adrenergic receptors found on immune cells by subset, demonstrating how catecholamines and adrenergic signals can either enhance or suppress immune responses depending on the cell type and context. Created with Biorender.com.

excitatory, while the ADRA2 receptor is $G_{i/o}$ coupled, making it primarily inhibitory[9]. The nuanced impacts of Epi and NE on target cells are modulated by the differential ligand-binding affinity of these receptors, the relative expression levels of the receptors on target cells, the G-protein coupling of each receptor, and the expression of downstream intracellular signaling machinery. An overview of SNS interactions in differing immune cell subsets and via receptor type is detailed in Fig. 2.

T cells

T cells predominantly express ADRB2, and the impact of signaling through the ADRB2 has been most thoroughly studied[10,11]. While more limited and conflicting, there is also evidence for T-cell expression of ADRA1, ADRA2, and ADRB1 in rodents and humans, but expression varies based on T-cell subset and activation state[10–13]. In resting healthy human T cells, expression of ADRAs is likely quite low, but may increase with activation, as studies report detecting ADRA expression at the mRNA and protein levels[14–18]. T cells may express ADRB3, but there have been no studies on the impact of ADRB3 signaling on T-cell function[19].

Research on the impact of adrenergic signaling, and by extension, SNS activity via catecholamines, on T-cell function, can initially seem contradictory. Some studies report pro-inflammatory effects, while others demonstrate inhibitory or anti-inflammatory impacts. Chronicity of stimulation, the relative receptor binding affinities of the specific stimuli used in each study, the activation state and T-cell subset studied, as well as the timing of adrenergic stimulus with respect to other immune stimuli are all important to consider when dissecting the impact of this axis on T-cell function. In general, acute transient activation of the SNS is likely pro-inflammatory, while chronic sustained activation appears predominantly inhibitory[20–22].

Starting with studies examining the impact of catecholamines on T-cell function, Epi and NE have been shown to impact T-cell proliferation, cytokine production, lymphocyte trafficking, and cytotoxicity. NE was found to reduce $CD4^+$ T-cell interleukin (IL)-2 production[23,24] and proliferation, effects that were recapitulated by ADRA agonism but not ADRB agonism[24]. In another study, NE inhibited lymphocyte chemotaxis, and this could be blocked with either pan-ADRB or pan-ADRA blockade[25]. Both Epi and NE have been shown to impact lymphocyte trafficking, likely through ADRB2[26]. In human peripheral blood mononuclear cells (PBMCs), NE suppresses interferon-γ (IFN-γ) production and increases IL-10 production; clonidine (an ADRA2 agonist) was sufficient to recapitulate this decrease in IFN-γ[27]. Similarly, NE decreases IFN-γ and tumor necrosis factor α (TNFα) production and suppresses cytolytic response in mouse and human $CD8^+$ T cells in vitro[28]. Catecholamines also have inhibitory effects on regulatory T cells (T_{regs}), decreasing their capacity to suppress mitogen-induced effector T-cell (T_{eff}) proliferation[11] and increasing expression of the inhibitory checkpoint receptor CTLA-4[10]. Finally, NE, through ADRBs, activates pro-apoptotic signaling pathways in mouse thymocytes and a thymoma cell line, suggesting a role for catecholamines in modulating T-cell generation[29].

Numerous studies of the specific impact of ADRA signaling on T-cell function have been conducted. Beyond the previously mentioned impacts of

ADRA1 and ADRA2 signaling on proliferation[16,24] and IFN-γ production[27], ADRA1 antagonism increases thymocyte proliferation and thymus cellularity in rats[12]. Nonspecific ADRB stimulation of human circulating T cells reduces IL-2 receptor expression[30], decreases IL-2 production[31], and impedes mitogen- and T-cell receptor (TCR)-driven proliferation[30,31]. Isolated ADRB1 signaling has recently been reported to drive T-cell exhaustion, decreasing cytokine production and proliferation[32]. However, the overwhelming majority of studies of ADRB signaling in T cells focus on ADRB2. ADRB2 agonism enhances T_{reg} suppressive capacity, leading to decreased IL-2 expression by target conventional $CD4^+$ cells, increased conversion of conventional $CD4^+$ T cells into T_{regs}, and increased CTLA-4 expression on T_{regs}[10]. T-cell expression of IL-2, IFN-γ, GM-CSF, and IL-3 has also been shown to be negatively impacted by ADRB2 agonism[19,23]. Metabolic reprogramming likely contributes to ADRB2-driven T-cell dysfunction, as ADRB2 signaling in murine $CD8^+$ T cells leads to impaired mitochondrial function and reduces glucose transporter expression following TCR activation; this effect is abrogated by propranolol or ADRB2 knockout (KO)[33].

While these findings point to a predominantly immunosuppressive effect of ADRB2 signaling, there are reports of ADRB2 stimulation enhancing T-cell function, such as increasing production of IFN-γ in murine Th1 cells[34]. Importantly, considering the timing of adrenergic signaling relative to other stimuli (TCR activation, ConA treatment, exposure to Th polarizing cytokines, etc.) is critical to understand these seemingly contradictory impacts. In studies revealing pro-inflammatory effects, closer examination typically reveals that the adrenergic stimulus was applied after Tcell activation[34]. Studies directly examining this relationship support this conclusion[35].

These findings have been extrapolated to in vivo work with a variety of disease models, including viral infection, experimental autoimmune encephalomyelitis (EAE), arthritis, and malignancies. ADRB2 agonism was found to suppress T-cell effector functions, and decrease $CD8^+$ T-cell cytokine production in response to vesicular stomatitis viral infection[28]. Complimentary findings in influenza demonstrated that ADRB2 antagonism enhances anti-viral $CD8^+$ T-cell responses[36].

ADRB2 signaling has also proven anti-inflammatory in autoimmune disease models. ADRB2 signaling was shown to reduce T-cell IL-2, IFN-γ, and GM-CSF production in EAE, thus mitigating autoimmunity and lessening disease severity[37]. In an inflammatory arthritis model, ADRB2 agonism via terbutaline reduced spleen cell proliferation, increased splenocyte IL-10 production, and decreased lymph node TNFα levels[38].

In an HPV-driven tumor model, ADRB blockade in conjunction with a Shiga toxin-coupled HPV peptide vaccine improved naïve $CD8^+$ T-cell priming at the tumor-draining lymph node and increased intra-tumoral $CD8^+$ T-cell numbers; this phenomenon was shown to be ADRB2-driven[39]. A more recent study suggested that expression of ADRB2 on $CD115^+$ monocyte-derived macrophages drove this impairment in priming, and that ADRB blockade in combination with a peptide vaccine against OVA-expressing melanoma tumors enhanced tumor-specific T-cell proliferation and function[40]. Similarly, in breast and melanoma models, blocking ADRB signaling resulted in increased $CD8^+$ effector numbers within tumors, decreased the level of PD-1 expression on those cells, and increased the IFN-γ^+CD8^+ to T_{reg} tumor infiltrating lymphocyte (TIL) ratio. These impacts translated to improved response to checkpoint blockade[41].

B cells

Studies of the impact of catecholamines or adrenergic signaling on the function of B cells are quite limited. ADRA1, ADRB1, and ADRB2 expression have all been reported at the mRNA and protein levels[42–45]. Interestingly, adrenergic signaling in B cells has been generally found to enhance B-cell function. In one study, NE was shown to impact splenic follicle expansion and germinal center formation. Meanwhile, NE depletion inhibited the primary IgM response and both the primary and secondary IgG1 responses, and ADRB2 agonism partially rescued antibody production[45]. Other groups have reported that ADRB2 stimulation increases B-cell CD86 expression, thereby leading to increased IgG1 and IgE production and increased capacity to respond to CD40L and IL-4[46,47].

Monocytes/macrophages

There is evidence for expression of ADRA1, ADRA2, ADRB1, and ADRB2 on monocytes and macrophages[48–50], although ADRB1 expression has only been reported in one study[51]. As with lymphocytes, monocytes and macrophages differentially express adrenoceptors depending on activation state[13]. While some studies have reported a lack of ADRA1 in resting human monocytes[16,18], the human monocytic THP1 cell line expresses ADRA1 mRNA at baseline[18], and there are multiple reports of monocyte activation (via LPS, TNFα, and NE) leading to ADRA1 mRNA expression[16,18]. With respect to the other adrenoceptors, macrophages in the liver have been shown to express ADRA2[52]. Monocytes and macrophages have been found to express ADRBs at higher levels than lymphocytes, with ADRB2 expression predominating[50].

The functional impacts of adrenergic signaling on monocytes and macrophages are, as with T cells, mixed. A number of studies have reported pro-inflammatory effects of Epi, NE, ADRA1 signaling, and ADRB2 signaling[52–57]. There is a larger body of work, however, linking adrenergic signaling in macrophages and monocytes to immunosuppression. NE suppresses pro-inflammatory cytokine production (IL-6, TNFα) in monocytes[58]. Epi has been shown to inhibit the expression of pro-inflammatory cytokines via ADRB2 signaling, including TNFα and MIP1a[59]. Clonidine, an ADRA2 agonist, similarly suppresses TNFα production in healthy human circulating monocytes[58]. Numerous studies have confirmed the negative impact of ADRB signaling on cytokine production (IL-6, IL-8, IL-12, IL-18, TNFα, and IFN-γ)[20,50,60], the production of oxygen free radicals[61,62], phagocytosis[63], and trafficking via inhibition of IL-18-dependent adhesion molecule expression[60]. Adrenergic signaling has also been implicated in macrophage M1/M2 polarization in multiple contexts, with numerous studies showing it promotes M2 polarization[64]. Again, the chronicity of stimulation is likely also important, as chronic ADRB2 agonism with salbutamol was shown to reduce peritoneal macrophage IL-12 and TNFα production in a collagen-induced arthritis model[20].

Microglia

A number of studies have provided direct evidence of microglial ADRA1, ADRA2, ADRB1, and ADRB2 expression at the mRNA level[49,65–67]. These studies all report a lack of ADRB3 expression in these cells, and examination at the protein level via immunohistochemistry has confirmed this expression pattern of ADRBs[68]. As with other immune cells, activation state is likely tightly linked to adrenoceptor expression[69].

Functionally, adrenergic signaling has been implicated in both activating and inhibiting microglial responses. On the activating side, ADRA2 agonism increases expression of the anti-apoptosis gene *Bcl-xL*[66]. Exposure of microglia to ADRB2 agonists in vitro in the absence of pro-inflammatory stimuli has been repeatedly shown to induce IL-1β expression[49,70], as well as TNFα and IL-6[71,72]. NE and ADRB1 agonism have also been shown to increase IL-1β expression at the mRNA level[49]. Experiments using adrenergic antagonists have confirmed these effects, as ADRB, but not ADRA, antagonism has been found to prevent microglial activation in response to stress[68].

Simultaneously, adrenergic signaling mediates inhibitory effects on other microglial responses, highlighting the precise and nuanced regulatory capacity of this signaling axis. NE, ADRA1 agonism, ADRB1 agonism, and ADRB2 agonism have all been shown to reduce IL-6 and TNFα expression as well as NO and TNFα release in vitro when simultaneously administered with LPS[66]. ADRB agonism also reduces microglial IL-12 production[73]. NE, via both ADRB2 and ADRA2 signaling, decreases microglial process extension[69], and NE and ADRB2 agonism have been found to suppress microglial proliferation[74]. Accordingly, adrenergic inhibition of microglial activation has been postulated to play a role in dampening inflammation to prevent neurotoxicity[75].

Dendritic cells

Direct evidence of dendritic cell (DC) expression of adrenergic receptors is limited, although numerous studies have illustrated the impact of adrenergic signaling on DC function. ADRA1, ADRB1, and ADRB2 mRNA transcripts have been reported in murine purified Langerhans cells and Langerhans-like cell lines[76]. Additionally, in bone marrow-derived DCs (BMDCs), ADRA2, ADRB1, and ADRB2 mRNA has been detected[77].

The vast majority of studies of adrenergic modulation of DC function have revealed anti-inflammatory effects. One study using BMDCs showed that brief NE exposure inhibits IL-12 and increases IL-10 production, skewing Th differentiation toward a Th2 phenotype[78]. Another similar study found that catecholamines inhibited BMDC IL-12 production via ADRB2 and ADRA2, while ADRB2 signaling alone mediates an increase in IL-10 production. ADRB2 antagonism in vivo increased draining lymph node IFN-γ and IL-2 levels in a contact hypersensitivity model, while ADRB2 agonism was found to impede DC migration[77]. Another group found that catecholamines suppress antigen presentation in vitro[76]. In a murine collagen-induced arthritis model, chronic ADRB2 agonism with salbutamol reduced antigen-driven lymph node cell IFN-γ production and proliferation[20]. Others showed that pan-ADRB blockade via propranolol, but not ADRB2 selective antagonism, results in increased plasmacytoid DC numbers, increased Th1 T-cell differentiation, and enhanced secretion of IFN-γ, IL-12, and IL-23 in mouse skin[79].

Similar anti-inflammatory effects of catecholamines and ADRB2 signaling have been reported in human DCs. NE inhibits LPS-induced production of IL-12, IL-23, TNFα, and IL-6 in human cord blood-derived plasmacytoid and conventional DCs, effects that would lead to impeded Th1 differentiation[80]. Exposure of human DCs to ADRB2 agonists leads to decreased IL-12 production in response to LPS stimulation, resulting in decreased generation of IFN-γ^+CD4$^+$ Th1 cells and increased generation of IL-4 producing CD4$^+$ Th2 cells[81]. NE and ADRB2 agonism in BMDCs has also been shown to result in Th17 cell differentiation when paired with Toll-like receptor 2 agonism[82]. In vivo, ADRB2 agonism impairs phagosomal antigen degradation in DCs, thereby decreasing their capacity for antigen cross-presentation to CD8$^+$ T cells[83].

Natural killer cells

Natural killer cells (NKs) have been shown to express ADRA1, ADRA2, and ADRB2 at the protein level via immunofluorescence and ligand-binding studies[17,42]. Notably, NKs have been found to express the highest density of ADRBs of all the subsets of peripheral blood lymphocytes in humans[84]. In mice, catecholamines, via ADRB signaling, have been shown to reduce NK cytotoxicity[85], reduce NK adhesion to endothelial cells[86], and impact NK migration[26]. The immunosuppressive impact of ADRB signaling on NK functions extends in vivo, where ADRB2 agonism increases susceptibility to viral infection, potentially by reducing NK IFN-γ production[87], and reduces NK numbers and activity, resulting in impaired tumor control[88]. These findings have been recapitulated in human NKs, in which exposure to NE results in decreased FcγRIII expression, reduced activation marker expression, decreased cytokine (TNFα, IFN-γ, GM-CSF) and effector molecule (granzyme B, perforin) production, and impeded direct and antibody-directed cellular cytotoxicity[89].

Innate lymphoid cells

Innate lymphoid cells (ILCs) are tissue-resident cells that play important functions in tissue homeostasis, pathogen immunity, and tissue repair. The impact of adrenergic signaling on ILC function is only beginning to be explored. One study of the ILC2 (CD45$^+$Lin$^-$ST2$^+$CD127$^+$CD90$^+$) response in parasitic infection demonstrated ADRB2 expression in both human (lung and PBMC) and murine ILC2s[90]. Using both ADRB2 KO mice and pharmacologic agonists, the authors demonstrated that signaling through the β2 adrenergic receptor inhibits ILC2 proliferation and cytokine (IL-5, IL-13) production both in culture and in vivo, impairing parasite clearance[90]. In both ILC1s and ILC3s, ADRB2 signaling appears to negatively regulate IL-22 production and impair tissue regeneration in the liver[91] and intestine[92], respectively.

PNS impacts on immune function

While confirmation of direct parasympathetic innervation of immune organs is mixed, functional evidence for immune cell responses to cholinergic signaling is abundant (Fig. 1). Immune organs and cells themselves may represent a striking deviation from the typical ANS two-neuron circuit, as findings point to immune cells as sources of PNS signaling molecules, therefore potentially operating as the "post-ganglionic neurons" in immune organs. Lymphocytes express all the necessary components to both respond to cholinergic signaling and produce cholinergic signaling themselves, including acetylcholine (ACh), choline acetyltransferase (ChAT), acetylcholinesterase (AChE), and both muscarinic and nicotinic acetylcholine receptors (mAChRs and nAChRs, respectively)[93–101]. Innate immune cells, including macrophages, DCs, and NKs demonstrate variable capacities to produce ACh and express various cholinergic receptors depending on tissue location, species, and subtype[102–104]. These findings highlight the ability of both innate and adaptive immune cells to participate in parasympathetic function indirectly.

T cells

Overall, the impact of PNS signaling in T cells is considered to be anti-inflammatory. The cholinergic receptor expression profile and agonist/antagonist specificity for certain receptor subtypes are likely crucial in dictating overall response. Indeed, the cholinergic receptor expression profiles in CD4$^+$ subsets has been shown to differ based on Th subset and activation state[105]. TCR activation itself has been found to lead to upregulation of cholinergic pathway genes; conversely, cholinergic stimulation of lymphocytes yields variable results[93,95,106,107].

Nicotine has been shown to enhance T_{reg} differentiation and CTLA-4 expression, augmenting their immunosuppressive capacity[108,109]. In CD4$^+$ T cells in vitro, nAChR signaling promotes Th1 differentiation[110,111]; while mAChR signaling promotes Th2 and Th17 differentiation[111]. Nicotinic signaling has been found to be anti-inflammatory via skewing of CD4$^+$ differentiation away from Th1/Th17 in disease models, including inflammatory arthritis, intestinal injury, and inflammatory bowel disease, with α7nAChR KO mice developing worse outcomes[112–115]. In EAE, nicotine similarly reduces antigen-driven T-cell proliferation and skews CD4$^+$ differentiation toward the Th2 phenotype to ameliorate disease[116,117]. Notably, adrenergic inputs from the splenic nerve "synapse" onto white pulp CD4$^+$ChAT$^+$ T cells, resulting in ACh release and suppression of inflammation[118]. Lastly, a few studies have addressed the effects of acute vs chronic cholinergic stimulation. Chronic cholinergic agonism in CEM cells downregulates nAChRs and decreases free Ca^{2+}[119], and chronic nicotine exposure in thymocytes has been found to lead to thymocyte developmental block[120]. While limited, these initial findings suggest that the chronicity of the stimulus likely contributes to the overall response.

B cells

B cells express various nAChRs, and in vitro activation has been shown to lead to upregulation of certain nAChR subtypes[121–123]. Signaling through the α7nAChR increases bone marrow B-cell proliferation and differentiation[124]. Similarly, signaling through the α4β2nAChR has been found to increase B-cell proliferation in response to IgM signals[121]. Functionally, signaling through nAChRs reduces IgG1 production[125], negatively impacts the proliferative response to anti-CD40 stimulation in mature B cells[121], and decreases IgM production[126]. Additionally, anti-α7nAChR antibody treatment has been shown to decrease splenic B-cell apoptosis in vivo[127]. Mucosal-associated ChAT$^+$ B cells are capable of producing ACh to modulate local intestinal immunity[103].

Monocytes/macrophages

As with lymphocytes, cholinergic signaling in macrophages and monocytes has predominantly anti-inflammatory effects. While in vitro LPS

stimulation of murine RAW264.7 cells initially decreases ACh production and induces the release of large amounts of TNFα, chronic LPS exposure leads to increased ACh production and inhibition of TNFα secretion[128]. Additional in vitro studies in macrophages have demonstrated similar inhibitory impacts of ACh or nicotine on the production of IL-1β, IL-6, and IL-18, but no impact on production of anti-inflammatory IL-10[129–134]. nAChR agonism has been shown to impact macrophage surface protein expression and increase M2 macrophage numbers in an acute lung injury model[134–136]. Similarly, signaling through the α7nAChR has been shown to decrease expression of the M1 markers CXCL9, CXCL10, and iNOS and increase expression of the M2 markers IL-10 and CD206[136]. Interestingly, signaling through the α4β2nAChR seems to enhance macrophage phagocytosis; however, the overall effects of nAChR activation, even in the face of resultant increased phagocytosis, are reduced inflammation via decreased NF-κB activation[137,138]. In addition to the anti-inflammatory impacts on cytokine production and M1/M2 differentiation, cholinergic signaling reduces the expression of chemokine receptors and adhesion factors in monocytes and macrophages, both in vitro and in arthritis models[139,140]. These effects in turn result in decreased monocyte/macrophage migration and infiltration[139,140]. In the bone marrow, nicotine has been found to result in a decreased production of pro-inflammatory monocytes by inhibiting their proliferation; simultaneously, it decreased the production of pro-inflammatory cytokines and increased IL-10 production[141]. In vivo studies using EAE models have similarly found that nicotine exposure decreases the expression of pro-inflammatory macrophage functional markers, including MHC-II, CD80, and CD86, and reduces myeloid cell CNS infiltration[108,142,143].

Dendritic cells

Studies of the impact of cholinergic signaling on DC function have revealed mixed findings. One group found that nicotine results in decreased endocytic and phagocytic activity in monocyte-derived DCs[144]. Furthermore, they showed that in the presence of nicotine, immature DCs still undergo maturation, but release decreased levels of pro-inflammatory cytokines, such as TNFα and IL-12, and induce less rigorous APC-dependent T-cell responses[144]. Follow-up studies involving nicotine exposure during cell generation demonstrated that both mouse and human nicotine-exposed DCs were capable of producing effector Th2, but not Th1, T cells, had an increased CD86:CD80 ratio, and produced less IL-12[145]. The capacity of DCs exposed to cholinergic stimuli to suppress Th1/Th17 differentiation and promote a Th2 response has been observed across other cholinergic agonists as well[117,146–148]. In another study using carbachol, researchers found that cholinergic signaling during DC differentiation resulted in increased expression of the surface markers HLA-DR and CD86, increased TNFα and IL-8 production, and enhanced T-cell priming. However, when DCs were differentiated in the presence of both carbachol and LPS, carbachol had a negative impact on these functions. These findings were recapitulated when carbachol was substituted with ACh[149]. In contrast, studies from other groups using monocyte-derived and bone marrow-derived DCs have found that nicotine enhances endocytosis, increases IL-12 production, and improves T-cell responses[150,151]. Additionally, one group found that human peripheral blood mononuclear cell (PBMC)-derived DCs generated in the presence of low-dose nicotine produced more IL-12 and generated a more robust PBMC response than those cultured without nicotine[152]. These seemingly conflicting results may be explained by the impact of cholinergic signaling in the presence/absence of additional stimuli, i.e., LPS, the dose and specific cholinergic stimulus used, the specificity of various cholinergic agonists for nAChRs vs. mAChRs, and variation in the generation of in vitro DC cell lines.

Natural killer cells

Nicotine, via signaling through the beta2 subunit of the nAChR, inhibits a number of NK cell functions. nAChR stimulation reduces NK cell cytotoxicity by decreasing production of the effector proteins granzyme B and perforin[153]. Additionally, nicotine inhibits NK cell secretion of a number of cytokines, including IFN-γ and TNFα[153]. Nicotine exposure also reduces NK cell proliferation and expression of NKG2D, a surface receptor upstream of activation pathways[153]. Similarly, nAChR signaling via the α7 subunit has also been shown to reduce IFN-γ production and NKG2D-dependent cytotoxicity[154].

The impact of ANS (SNS and PNS) signaling in malignancy

The majority of work examining the impact of ANS activation in cancer has focused on the direct impact of adrenergic signaling on tumors themselves (Fig. 3). ANS signaling has been shown to promote tumor growth and progression across a wide range of malignancies. Catecholamines, predominantly NE, have been shown to increase cancer cell migration in ovarian[155], prostate[156], colon[157], and breast cancer cell lines[158]. This effect was mediated by ADRBs specifically, as ADRB antagonism mitigated the impact of catecholamines both in vitro[156,157] and in vivo[159]. In prostate cancer, chemical and surgical sympathectomy slows tumor progression[160], and stress accelerates cancer development in vivo via ADRB2 signaling by inhibiting cancer cell apoptosis[161]. In human melanoma, NE-driven ADRB signaling induces the expression of VEGF, IL-6, and IL-8, increasing tumor aggressiveness[162]. A number of in vivo studies using chronic stress models have demonstrated that both chronic stress and ADRB agonism promote tumor growth, invasion, and vascularity in melanoma[163], ovarian[164], pancreatic[165], and colorectal cancers[166]. Retrospective human studies have revealed suggestive links between β adrenergic blockade and decreased cancer incidence, progression, metastasis, and mortality in prostate[167], melanoma[168], and breast cancer[169], respectively, though evidence ultimately remains mixed[170].

In addition to the direct impact of ANS signaling on tumor cells themselves, ANS activation has profound implications for the antitumor immune response (Fig. 4). In an ovarian carcinoma mouse model, chronic ANS activation via daily restraint stress led to increased macrophage infiltration and tumor progression[171]. In a squamous carcinoma model, chronic restraint stress increased tumor formation, decreased Th1 cytokine expression, and increased T_{reg} numbers at the site of the tumor[172]. Similarly, chronic acoustic and restraint stress increased pancreatic cancer growth, negatively impacted T-cell responses, and increased tumoral T_{regs}, effects that could be mitigated with ADRB blockade[173]. Another study demonstrated that CNS neural circuit chemo- or optogenetic modulation could reduce SNS activity in a 4T1 breast tumor model[174]. This reduction in SNS activation led to favorable antitumor immune changes, including increased numbers of $CD45^+$ immune cells, decreased T_{regs}, increased IFN-γ^+ $CD4^+$ and $CD8^+$ T cells, and an increased M1 to M2 macrophage ratio in the tumor[174]. This parallels separate findings that ADRB2 agonism and Epi increase the number of M2 macrophages in the same breast cancer model[64].

SNS activation via chronic restraint stress, as well as ADRB agonism, increases the rate of metastasis approximately 30-fold in a spontaneously metastasizing mammary adenocarcinoma model; this was also accompanied by an increase in intra-tumoral M2 macrophages[175]. Similar findings of ADRB antagonism shifting the intra-tumoral immune milieu away from immunosuppressive myeloid cells and toward pro-inflammatory immune cells have been reported in a number of other models, including melanoma, pancreatic cancer, and fibrosarcoma[176–178]. Lastly, ADRB agonism in a B cell lymphoma model was found to decrease $CD8^+$ antigen-specific T-cell cytotoxicity, IFN-γ production, and proliferation, and blunt the response to immunotherapy[179]. Paralleling these findings in breast and melanoma models, another group demonstrated that ADRB blockade increased the frequency of $CD8^+$ effector T cells, reduced expression of PD-1 on those cells, and increased the IFN-γ^+ $CD8^+$ T cell to T_{reg} ratio in chronically stressed mice, leading to increased efficacy of anti-PD-1 therapy[41].

Cholinergic signaling through the PNS appears to have a complex regulatory role in cancer immunity that has only recently been examined. PD-L1, ChAT, and the mAChR3 expression increase with increasing colorectal cancer stage[180]. In lung adenocarcinoma, alpha5nAChR enhanced downstream PD-L1 expression to promote immune escape, and inhibition of the α5nAChR in lymphocytes reduces T_{reg} function and promotes $CD8^+$

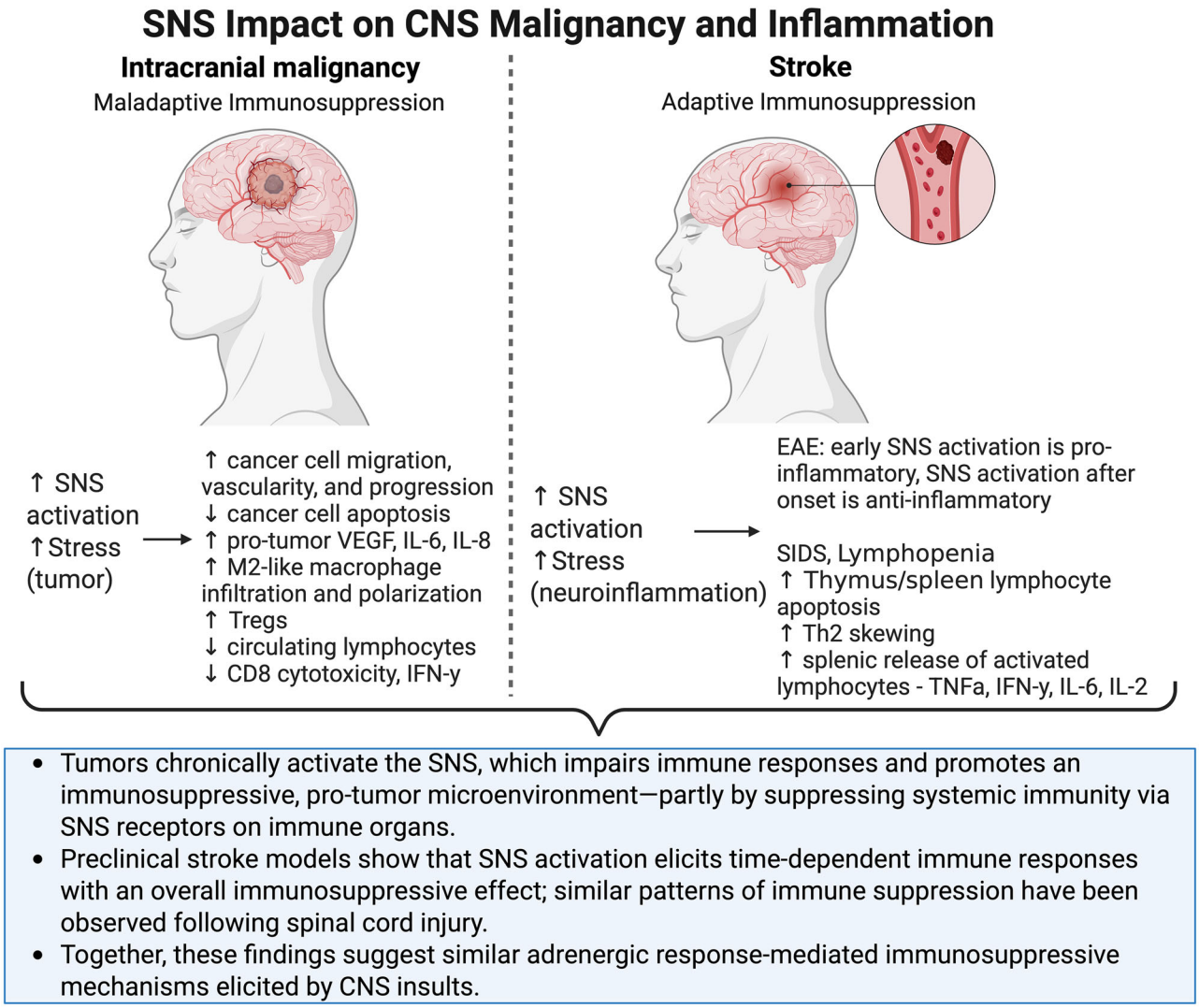

Fig. 3 | SNS signaling impact on malignancy and CNS inflammation. Overview of SNS impact on inflammation in brain tumor and stroke. In general, adrenergic signaling may directly impact the tumor by promoting cancer cell migration and progression, but also promulgates a permissive immune cell state to allow immune evasion and escape. It is likely that malignancy harnesses similar mechanisms to those seen in stroke and other CNS insults, where self-tolerance and prevention of runaway inflammation is adaptive. Created with Biorender.com.

T-cell cytotoxicity[181]. During the development of hepatocellular carcinoma, tumor antigen drives expansion of a $ChAT^{+}$ $CD4^{+}$ T cell population that appears involved in reducing effector T cell exhaustion and T_{reg} function[182].

Beyond the tumor microenvironment (TME), neuronal circuits have been shown to modulate antigen flow through the lymphatic system, impacting priming[183]. Additionally, chronic SNS activity and ADRB2 signaling have been shown to decrease circulating lymphocyte numbers and alter trafficking of T cells, NKs, and monocytes into blood[184,185]. In the bone marrow, chronic stress has been shown to activate hematopoietic stem cells and skew hematopoiesis toward myelopoiesis by decreasing signaling through the ADRB3, further reducing the available number of functional lymphocytes[186,187]. As discussed below, T cells are differentially sequestered in the bone marrow in malignancy and other stressful states, suggesting that this tissue may be a key node for targeted interventions[188–190]. Importantly, ADRB blockade can ameliorate skewed hematopoiesis and remodel the TME, further highlighting the widespread potential impacts of adrenergic modulation on the antitumor immune response[187,191]. Further studies should be aimed at identifying which modalities—pharmacologic or neuromodulatory— are most likely to have a durable impact on both the tumor itself as well as stimulate an antitumor immune response in synergy with existing therapies.

ANS impact on CNS inflammation

Insights from studies of other intracranial pathologies provide a window into likely impacts of ANS signaling in the setting of intracranial malignancy. In EAE, studies have shown an anti-inflammatory effect of ANS activation, with nicotine (via nAChR) and NE (via ADRB2) both mitigating T-cell-driven autoimmunity[37,108]. Overall, when considering findings across studies, it appears that SNS activation in the peri-induction or early phase of EAE is pro-inflammatory, whereas SNS activation after onset is anti-inflammatory and can ameliorate disease[192].

The immune impacts of ANS overactivation have been most widely studied in stroke (Fig. 3), where it has been associated with stroke-induced immunodepression syndrome (SIDS). SIDS has primarily been appreciated as a driver of post-stroke pneumonia and other post-stroke infections, a leading cause of death for stroke patients[193]. ANS activation has been observed in both mouse models of stroke and in stroke patients[194]. SNS activation, specifically, has been shown to alter lymphocyte responses and trafficking post-stroke, resulting in lymphopenia and shifting the splenic Th cytokine profile toward a Th2 response. Additionally, post-stroke SNS activation has been shown to drive lymphocyte apoptosis in the thymus and spleen. Blocking SNS, but not HPA axis, signaling, via either

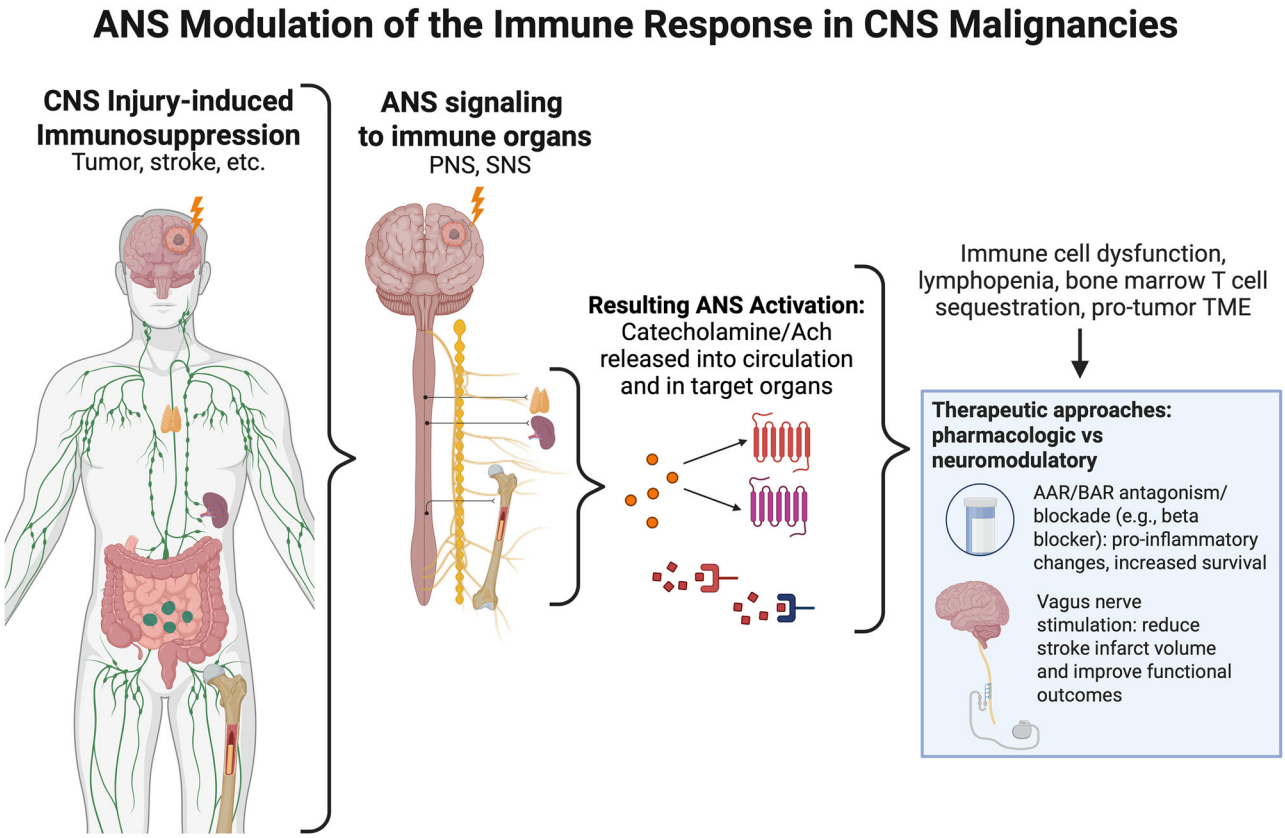

Fig. 4 | ANS overview on CNS injury effects on immune function. Working model of tumor-related or post-CNS injury ANS activation, immune effects, and therapeutic potential. Intracranial insults lead to downstream modulation of SNS or PNS signaling, which results in direct cellular effects, as well as modulation of immunity in the brain/brain tumor microenvironment to promote tumor growth and/or an adaptive immune response. Beyond the CNS, lymph nodes and organs such as the spleen and thymus demonstrate alterations in structure and function. Pharmacologic and interventional approaches for neuromodulation of the ANS may counteract adverse immune outcomes. Created with Biorender.com.

chemical sympathectomy or ADRB antagonist treatment, mitigated these immune effects and reduced mortality[195].

Following a stroke, the spleen releases activated lymphocytes that secrete increased levels of TNFα, IFN-γ, IL-6, and IL-2. These cells subsequently migrate to the infarct, increasing inflammation and infarct volume[196]. Interestingly, vagus nerve stimulation has been shown to reduce infarct volume and improve functional outcomes, potentially by limiting this inflammatory response, although it is important to note that the majority of vagal nerve fibers are sensory rather than parasympathetic (Fig. 4)[197]. Another study found that both ADRA antagonism via prazosin and combined ADRA1 and pan-ADRB blockade via carvedilol inhibited pro-inflammatory changes in the spleen, with carvedilol resulting in a significant reduction in infarct volume[198]. Similar findings of post-injury immunosuppression have been reported in spinal cord injury, further supporting the role played by the ANS in regulating immune responses to a range of CNS pathologies[199].

Implications for cancer neuro-immunology

To date, there has been minimal study of the impact of the ANS on the antitumor immune response in CNS malignancies, primary or metastatic. Therefore, we are limited in our ability to draw conclusions with regard to this specific question and must extrapolate findings from other CNS pathologies to consider the possible implications of ANS signaling in CNS tumors. When doing so, it is important to consider that the duration of ANS activation and the specific inflammatory stimulus in these pathologies present limitations for the extrapolation to CNS malignancies. However, if CNS malignancies do, in fact, lead to activation of the ANS and subsequent signaling in immune organs, one would anticipate similar immune alterations as observed in other pathologies (Fig. 4). Indeed, immune dysfunction in glioma patients has been appreciated for decades. These patients demonstrate lymphopenia, impaired cellular immunity, and reduced T-cell function[200–203]. Recent work has revealed that T cells are sequestered in the bone marrow of mice with intracranial malignancy[188]; activation of ventrolateral medullary catecholaminergic neurons projecting to the hypothalamic paraventricular nucleus was shown to be sufficient to induce T cell sequestration and ameliorate EAE, psoriasis, and delayed-type hypersensitivity[189]. Moreover, patients and mice with primary and metastatic brain tumors have elevated systemic catecholamines that impair T-cell function; this function can be restored by pan-ADRB blockade[191]. These immune derangements have been reported in a variety of other CNS pathologies, including stroke, traumatic brain injury, multiple sclerosis, spinal cord injury, and infection[204].

Importantly, other CNS pathologies that have been studied in this context all comprise transient, resolving insults, while intracranial tumors are chronic and progressive. As described above, there is a wealth of evidence supporting the differential impact of ANS activation mediating pro-inflammatory and anti-inflammatory effects depending on the duration of activation and signaling. While the exact duration of signaling necessary to transition from pro- to anti-inflammatory depends on cell type, context of signaling, and other immunomodulatory signals, in general, days or even hours of ANS signaling seem capable of achieving anti-inflammatory effects. Thus, it stands to reason that CNS tumors, evolving over weeks to months, might result in durable ANS signaling that could, in turn, drive the establishment of an immunosuppressive, anti-inflammatory immune landscape. In the context of resolving CNS pathologies, such as stroke, a rapid anti-inflammatory brain-immune reflex likely serves as a critical check on neuroinflammation. Indeed, the evidence outlined previously strongly

supports the role of sustained (i.e., on the order of hours to days, which would apply to even transient intracranial pathologies) ANS activation in dampening both innate and adaptive immune responses and shifting the immune landscape away from a pro-inflammatory profile. While adaptive in stroke perhaps, in the setting of intracranial malignancy, this reflex would cripple the immune system and impede effective antitumor immune responses. The overwhelmingly immunosuppressive TME observed in both primary and metastatic brain tumors, when compared to the TME of similar cancers situated outside the CNS, fits within this framework[205].

Conclusions and future research

Studies directly assessing ANS signaling and its impact on immune function, specifically in the setting of intracranial malignancies, are needed. Leveraging insights from the field of cancer neuroscience to dissect associated immune derangements may further our understanding of the mechanisms underlying CNS inflammation-driven ANS activation and the differential impact of progressive chronic ANS signaling (as opposed to the transient sustained signaling seen in non-malignant CNS pathologies) on the immune landscape and function. Understanding the effect of interrupting these axes on antitumor immunity will be critical to the field of cancer neuro-immunology. Based on these insights, translational strategies to inhibit or modulate ANS activation in order to achieve a more favorable immune landscape should be explored. Such approaches might lead to the licensing of immunotherapies in the brain TME, allowing for the improved application of existing therapies that have been employed successfully in extracranial solid tumors as well as the development of novel, CNS malignancy-specific therapies. Ultimately, cancer neuro-immunology represents an emerging, promising field that could revolutionize the immune-based treatment of intracranial tumors.

Data availability

No datasets were generated or analysed during the current study.

Received: 8 October 2024; Accepted: 21 May 2025;
Published online: 07 June 2025

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Acknowledgements

This work was supported by the National Institutes of Health under award number F30CA271495 (L.P.W.) and by the Eugene A. Stead Jr. Student Research Scholarship from the Duke University Department of Medicine (A.P.H.).

Author contributions

L.P.W., E.S.S., and P.E.F. conceptualized and wrote the manuscript. L.P.W., A.P.H., T.S., and P.E.F. reviewed the manuscript and provided detailed revisions. L.P.W. and B.J.P. created the manuscript figures.

Competing interests

The authors declare no competing interests.

Additional information

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