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Sympathetic Modulation of Immunity: Relevance to Disease

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Abstract

Optimal host defense against pathogens requires cross-talk between the nervous and immune systems. This paper reviews sympathetic-immune interaction, one major communication pathway, and its importance for health and disease. Sympathetic innervation of primary and secondary immune organs is described, as well as evidence for neurotransmission with cells of the immune system as targets. Most research thus far as focused on neural-immune modulation in secondary lymphoid organs, and have revealed complex sympathetic modulation resulting in both potentiation and inhibition of immune functions. SNS-immune interaction may enhance immune readiness during disease- or injury-induced 'fight' responses. Research also indicate that dysregulation of the SNS can significantly affect the progression of immune-mediated diseases. However, a better understanding of neural-immune interactions is needed to develop strategies for treatment of immune-mediated diseases that are designed to return homeostasis and restore normal functioning neural-immune networks.

Keywords

Noradrenergic; autonomic; sympathetic innervation; lymphoid organs; immune modulation

1. Introduction

Autonomic (mainly sympathetic) efferent nerves innervate primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid organs, providing a conduit for the brain to alter immune reactivity. The origin, pattern of distribution and targets of sympathetic nerves in primary and secondary lymphoid organs across life span are reviewed here. Sympathetic nerves release norepinephrine (NE), as their primary neurotransmitter, into the lymphoid microenvironment to affect the functioning of cells of the immune system. Thus, noradrenergic (NA) influences on immunity, while still not entirely understood, have been the most extensively investigated. Neural regulation of immune function by peptide neurotransmitters that co-localize with NE, such as neuropeptide Y (NPY), adenosine triphosphate (ATP), opioid peptides, corticotropin-releasing hormone (CRH) and vasoactive

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intestinal peptide (VIP), and their affect NA-immune modulation is much less understood. Studies reporting the expression and location of the neurotransmitter-specific receptors on immune cells and ligand-receptor mediated intracellular signaling to alter immune responses are also described here. Finally, we discuss functional and clinical significance of aging-induced changes in sympathetic-immune interactions and the consequences of sympathetic dysregulation in the development and progression of immune-mediated diseases such as rheumatoid arthritis, infections, cancer, and after major injury.

2. Sympathetic Neurotransmission in Bone Marrow

Lymphohematopoietic stem cells in the bone marrow replenish the immune cells in the adult immune system throughout life. Regulation of hemato- and lympho-poiesis via the brain-immune signaling occurs through nerves that innervate bone marrow cells, as well as neuroendocrine hormones that circulate in the blood. Efferent sympathetic nerves enter the nutrient foramina of long bones, course along blood vessels in the Haversian and Volkmann's canals to distribute to bone marrow [1–7]. NA sympathetic nerves provide the densest innervation of rat bone marrow and contain NE, NPY, and VIP. Sympathetic nerves immunoreactive for tyrosine hydroxylase (TH), the rate-limiting enzyme for NE synthesis, are more abundant than those containing NPY and VIP, however, the peptide-containing nerve fibers display a similar pattern of distribution [2].

NA nerves closely associate with hematopoietic and stromal cells in the bone marrow [2,4–9]. Sympathetic nerve terminals directly appose periarterial adventitial cells, a particular type of stromal cell, that is an important source of growth factors and adhesion molecules [8]. Periarterial adventitial cells interconnect via gap junctions with sinus adventitial reticular cells and intersinusoid reticular cells, which are also apposed by these efferent nerves. Collectively, these findings provide anatomical evidence for sympathetic regulation of hematopoiesis and lymphopoiesis in bone. The findings that temporal development of rat bone marrow innervation correlates with the onset of hemopoietic activity [10] provides additional support for sympathetic nervous system (SNS) regulation of bone marrow function. The SNS also innervates the vasculature to regulate vasomotor activities and the release of mature blood cells from the bone marrow.

In mice, NE concentration ranges from 1–3 ng per g in bone marrow tissue [11,12], 1 to 2 orders of magnitude lower than generally found in rat secondary lymphoid organs [13,14]. NE concentration and its levels and metabolites exhibit diurnal variations in murine bone marrow, with levels peaking at night [11]. Further, NE content, but not epinephrine (EPI), positively correlates with the proportion of cells in the G2/M and S phases of cell cycle [11]. Sympathetic nerves in the bone marrow respond to generalized systemic stressors that increase NE turnover. Exposing mice to cold temperatures increases NE turnover rate by 36%. More impressive is that a primary immune challenge, peritoneal *Pseudomonas aeruginosa* infection, increases NE turnover rate in the bone marrow by 131% [15].

Functional assays and radioligand binding studies indicate that marrow cells express functional α -adrenergic receptor (AR) [16]. ^3H -labeled prazosin, an α_1 -AR antagonist, binds to both bone marrow cell membranes and intact bone marrow cells with high and low affinity. Lymphoid/stem cell fractions express the high-affinity binding site, but the cell subset that expresses the lower affinity site is not clear. β -AR expression has not been demonstrated on bone marrow cells using radioligand binding, northern blot or reverse transcription-polymerase chain reaction (RT-PCR) techniques. However, both *in vivo* and *in vitro* functional studies demonstrating β -AR signal transduction support their expression on bone marrow cells. In mice exposed to NE, EPI, or isoproterenol (β -AR agonist) [17,18], intracellular adenosine 3', 5'-monophosphate (cAMP) content (second messenger for

noradrenergic signaling via β -AR) biphasically increases in bone marrow cells 1 and 15 min later. Similarly, intracellular cAMP concentration rises in bone marrow cells in mice sublethally irradiated [19]. In both cases, the nonselective β -AR antagonist, propranolol blocked the rise in intracellular cAMP content, suggesting a specific β -AR-mediated effect.

Embryonic and fetal development of hematopoietic system occurs in multiple organs including, yolk sac, liver, thymus, spleen, lymph nodes and red bone marrow. After birth, hematopoiesis is largely confined to red bone marrow, with clonal expansion occurring in lymphoid tissue. Stem cells of T lymphocytes migrate from the bone marrow to the thymus to become immunocompetent. After maturation in the bone marrow or thymus, immune cells circulate using the blood vascular and lymphatic systems as conduits to patrol tissues. Specific growth factors, cytokines and cell-to-cell contact regulate hemato- and lymphopoiesis. Sympathetic nerves that supply bone marrow may directly or indirectly affect stem cell development and differentiation by affect the release of signaling molecules that guide these processes. This role for sympathetic nerves is supported by anatomical and pharmacological studies.

Both α -AR and β -AR antagonists provide protection against radiation-induced bone marrow cell death [20, 21]. The protective effects of these antagonists are time dependent with respect to radiation treatment. β -AR antagonists are protective when administered prior to irradiation, while the α -AR antagonist provide more effective protection after radiation exposure. In irradiated mice treated with the β -AR agonist, isoproterenol, proliferation of bone marrow cell increases 16 h later [18]. These early studies suggest that catecholamines stimulate proliferation of bone marrow cells rendering them more vulnerable to the toxic effects of irradiation. Findings using a 3-dimensional culture system support these early studies. Adding isoproterenol to murine bone marrow cultures increases cellular proliferation and granulopoiesis dose-dependently [3], while the addition of either a nonselective β -AR (propranolol) or a selective β_2 -AR (butoxamine) antagonist to cultured human bone marrow cells reduces cellular proliferation by the number of cells entering the S phase, and slows granulocyte-macrophage colony (GM-CFU) formation [22]. These data also support a temporal expression of α - and β -AR subpopulations on bone marrow cells, whereby β -AR expression predominate during early bone marrow cell activation, and α -AR expression increases during later stages.

β -AR activation affects both proliferation and differentiation of bone marrow cells. Albuterol, a selective β_2 -AR agonist, added to bone marrow cells cultured from Friend leukemia virus-infected mice inhibited the formation of erythroid colony forming units (CFU-E) [19], an effect that was reversed by addition of the selective β_2 -AR antagonist, butoxamine. Restraint stress induced an increase in both the proportion and number of specific subpopulations of bone marrow cells, an effect partially reversed by pretreatment with RU-486, a steroid receptor antagonist, and profoundly augmented by chemical sympathectomy with 6-hydroxydopamine (6-OHDA) or *in vivo* exposure to propranolol [23]. These data taken together suggest that restraint stress induces tissue-specific changes in the immune-cell distribution, that both stress pathways are important for this effect on bone marrow, and that corticosteroids (enhancing) and catecholamines (suppressive) may act in opposition in regulating immune cell accumulation in bone marrow.

Studies support the modulation of hematopoiesis by functional α_1 -AR on bone marrow cells [reviewed in 24]. Reconstituting NE-depleted mice with syngeneic bone marrow cells increases GM-CFU formation and accelerates myelopoiesis. Similar effects occur in reconstituted, sympathetically-intact mice exposed to prazosin, an α_1 -AR antagonist, but not to propranolol (β -AR antagonist) [25]. Prazosin treatment in these mice reduces the differentiation of transferred precursor cells into thymocytes and splenic T and B cells [26].

Bone marrow cells treated with NE or methoxamine (α_1 -AR agonist) reduces the number of GM-CFU, an effect blocked by prazosin [16,26]. Treatment with an α_2 -AR agonist has a similar, but smaller effect [16]. Collectively, these data suggest that treatment of bone marrow cells with α -AR agonists suppress myelopoiesis and augment lymphopoiesis. Whether NE released from NA nerves exerts these effects directly on stem cells or indirectly by influencing bone marrow stromal cells, or both is not known.

The SNS also regulates the migration of immune cells from the bone marrow into the periphery. Within 24 h after transecting the femoral nerve, or after chemical sympathectomy with 6-OHDA, bone marrow cellularity decreases [9]. This effect is due to the egress of mature and progenitor hematopoietic cells into the peripheral blood [9]. In another study, NE mobilized fat from the bone marrow [27]. In contrast, Benestad et al. [28] report no effects of neonatal chemical sympathectomy, surgical denervation of the hind limb, or electrical stimulation of the hind limb on blood flow, bone marrow cellularity, or efflux of tibial marrow cells into the circulation. While these data are controversial they provide evidence that the SNS influences the mobility of bone marrow precursor cells into the peripheral circulation.

3. Sympathetic Neurotransmission in the Thymus

The thymus is the primary site for differentiation and maturation of T lymphocytes, whereby they can selectively recognize and respond appropriately to foreign antigen – a process called T cell “education”. Developing and differentiating thymocytes do not respond to foreign substances, because foreign antigens cannot cross the blood-thymic barrier to enter the thymic microenvironment. Intrathymic T cell precursors undergo a complex series of programmed developmental changes resulting in the production of mature, self-major histocompatibility complex (MHC) restricted, single-positive (SP) T lymphocytes (express either CD4 or CD8 on their cell surface). The earliest thymocytes lack detectable CD4 and CD8 (double negative or DN cells). The majority of DN thymocytes rearrange the T cell receptor (TCR) genes, then transiently express both CD4 and CD8 (double positive or DP thymocytes) before differentiating into mature SP thymocytes. During the selection process most of the immature thymocytes undergo apoptosis, but thymocytes that successfully mature, enter the blood and home to secondary lymphatic tissues. Intrathymic T cell development is controlled by numerous factors, including cytokines, neuroendocrine hormones and locally released neurotransmitters.

The thymus of young adult animals is richly innervated by the SNS [29–38]. Thymic NA nerves originate primarily from the superior cervical and stellate ganglia [30,39,40]. Dense plexuses of NA nerves enter the thymus with large blood vessels, coursing into the capsule and interlobular septa. From these vascular nerve plexuses, smaller vascular plexuses diverge into the cortex. NA nerves exit these plexuses to enter parenchymal regions of both the outer and deep cortex where they reside adjacent to stromal cells and thymocytes. NA nerves predominate in the cortex, with a much lower density present in the medulla. A slightly higher density of NA nerves reside near the corticomedullary junction where the more mature thymocytes localize. This is consistent with autoradiographic data demonstrating increased β -AR density in the inner thymic cortex [41]. There is also a greater density of yellow autofluorescent cells, a macrophage-like cell population, in the inner cortex that closely associates with NA nerves. In the deep cortex and medulla, NA nerves are adjacent to the thymic epithelial cells (TEC) [42]. NA nerves coursing in the interlobular septum continue along the venous sinuses, a prominent feature of the thymic medulla [4,5,31,35,38,43,44,45], with the occasional nerve fiber extending from the septa and sinuses into the medullary parenchyma. In the capsule and interlobular septa, NA nerves course adjacent to mast cells [5–7,46], CRH-immunoreactive cells [7,47], and ED3⁺

macrophages [7]. NA nerves also course in close proximity to ED1⁺ corticomedullary macrophages [46].

The tonic release of NE from NA nerves in the thymus and spleen is tightly regulated by numerous receptors types including prejunctional α -AR, muscarinic and nicotinic cholinergic receptors, P1-purinergic and prostaglandin E₂ (PGE₂) receptors [36,48,49]. NE release from NA nerves feeds back to inhibit its own release via interaction with prejunctional α -AR. Treatment with the α_1 -AR antagonist prazosin or an α_2 C-subtype selective AR antagonist [50] augments stimulation-evoked release of NE *in vitro* [36,48,49]. Stimulation of prejunctional muscarinic receptor also inhibits the release of NE; but activation of prejunctional nicotinic receptors increases the stimulation-evoked release of NE from sympathetic terminals [51,52].

β_2 -AR are expressed on thymic cell membranes as demonstrated using radioligand binding studies and Northern blot analysis [41]. Compared to mature T cells, unfractionated thymocytes express very low levels of high-affinity β -AR [53]. Mature corticosterone-resistant thymocytes express β -AR at levels equivalent to those seen in peripheral T cell populations [54,55]. These data suggest that β -AR expression is limited on immature thymocytes, but increases as thymocytes mature and differentiate. Autoradiographical data which primarily localizes β_2 -AR expression to the medullary region of the rat thymus is consistent with a maturation-dependent regulation of β -AR expression in thymocytes [41]. However, the limited numbers of β_2 -AR expressed on the unfractionated thymocytes may be offset by the efficiency of receptor-coupling to adenylate cyclase, which is greater in the unfractionated thymocytes compared with spleen or lymph nodes [53]. This suggests that thymocytes that do express β -AR are exquisitely sensitive to β -AR agonist signaling.

Changes in biological functions can induce changes in the number of AR expressed on cells in the thymus. For example, β_2 -AR receptor surface expression on thymocytes changes over the course of an immune response [56]. Thymocytes express fewer β_2 -AR 3 days, but higher β_2 -AR number 7 and 15 days after immunization with the protein antigen, bovine serum albumin, compared with naïve controls. The mechanism for immunization induced changes in β_2 -AR gene expression in the thymus is not known. Changes in hormone levels can also alter the number of β_2 -AR expressed on rat thymocytes. In the estrous phase of female reproductive cycle, and during pregnancy, β_2 -AR expression increases, while castration decreases receptor density [41,56] suggesting that steroid sex hormones modulate β_2 -AR expression on thymocytes. Additionally, *in vitro* exposure of rat TEC to isoproterenol, a nonselective β -AR agonist, reduces basal and serum-stimulated proliferation, without affecting interleukin (IL)-1 production [34], suggesting the expression of β_2 -AR on this thymic cell population as well.

Based on Northern blot analysis and RT-PCR for mRNA, radioligand binding, and cAMP induction, TEC, which are essential for positive and negative selection in the thymus, also express α_1 - and α_2 -AR [34]. The addition of an α -AR agonist to unstimulated or lipopolysaccharide (LPS)-stimulated cultures of rat TEC dose-dependently increases IL-6 production, but has no effect on IL-1 production. This effect is blocked by an α -AR antagonist [57].

The regulation of thymic function by the autonomic nervous system has been explored by numerous laboratories. Early studies in the 1970s and 1980s allude to β -AR-induced enhancement of thymocyte differentiation and suppression of thymocyte proliferation in the presence of intact NA innervation [58–63]. Isoproterenol exposure *in vivo* reduces thymic weight and thymocyte number in mice [64]. Similarly, catecholamines or isoproterenol decrease concanavalin A (Con A)- or LPS-induced proliferation of murine thymocytes, an

effect not observed with α -AR agonist treatment [65]. Although there are no reports directly relating β -AR stimulation and the induction of apoptosis, studies have demonstrated that elevating thymocyte intracellular cAMP induces apoptosis [66–68]. Thymocyte proliferation increases with treatment with high concentrations of either EPI or isoproterenol [69] or low concentrations of NE. It has been proposed that signaling differences exist between the signaling pathways induced by β - or α -AR, assuming that NE stimulates the α -AR in this study. Thus, second messenger signaling data support that stimulation of β_2 -AR on cells within the thymus elevates the level of intracellular cAMP, with the possibility that α -AR stimulation by NE induces a rise in intracellular Ca^{2+} .

Thymic weight and cellularity decrease, apoptosis increases, and the number of T cells proliferating in the periphery are reduced following chemical sympathectomy [35], suggesting that catecholamines exert a positive effect on cell viability and function in the thymus. Chemical sympathectomy in mice also increases thymocyte apoptosis and reduces spontaneous proliferation *in vitro* [70,71]. NA nerve ablation is necessary to induce this response as pretreatment with desipramine blocks the 6-OHDA-induced increase in apoptosis [71]. However, this effect could be a direct effect of 6-OHDA on thymocytes as incubation of thymocytes *in vitro* with 6-OHDA (10^{-5} M) also induces apoptosis, an effect prevented by addition of desipramine to the cultures. These findings suggest that thymocytes may possess catecholamine uptake mechanisms. Therefore, chemical sympathectomy-induced changes in the thymus must be interpreted with caution, because the thymus is not depleted of NE as completely as other tissues, such as the spleen [72]. Furthermore, the possibility that 6-OHDA-induced elevation in corticosterone drives the sympathectomy effects in the thymus has not been adequately addressed. The latter, however, seems unlikely as Delrue-Perollet et al. [70] has shown that corticosterone levels are not altered in sympathectomized animals at the time of sacrifice (3 days after the first injection of 6-OHDA). Together, these data suggest that NA innervation in the thymus can influence thymocyte development.

Sympathetic modulation of thymocyte development and maturation has been evaluated recently using a variety of pharmacological approaches. β -AR blockade with propranolol for 4 or 16 days increases thymocyte proliferation and apoptosis, and causes disturbances in kinetics of thymocyte differentiation, expanding the most mature SP (CD4^+ , CD8^+) thymocyte pool, and increasing the relative number of $\text{CD8}^+\text{CD25}^+$ cells [73,74] in adult male Dark Agouti rats. In contrast, β -AR blockade has no effect on the relative proportion of CD4^+ and CD8^+ peripheral blood lymphocytes (PBL). Prolonged exposure to the β -AR antagonist augments these responses. Treatment with anabolic doses of clenbuterol, the β_2 -AR agonist, reduces thymocyte average nuclear area and increases the apoptotic index [75], supporting an immunosuppressive role for β_2 -AR agonists. Collectively, these studies support the feasibility of using pharmacological agents that target AR as a means of modulating T cell development (and hence T-dependent immune responses). They also provide specific insight into the role of β -AR in T cell maturation.

NE differentially modulates thymocyte maturation in young and aged mice [76], an effect that may be related to increased sympathetic innervation of the aged, involuted thymus of both in rats and mice [31,77]. To study age-associated changes in β -AR modulation of thymocyte differentiation, Madden and Felten [76] have implanted 2- and 18-month-old BALB/c mice with pellets subcutaneously containing the non-selective β -AR antagonist, nadolol. β -AR blockade alters thymocyte $\text{CD4}/\text{CD8}$ co-expression in old, but not in young mice. The frequency of the immature DN $\text{CD4}^-\text{CD8}^-$ population increases, and the intermediate DP $\text{CD4}^+\text{CD8}^+$ population decreases in nadolol-treated old mice. There is a corresponding increase in the frequency of mature SP $\text{CD4}^-\text{CD8}^+$, but not SP $\text{CD4}^+\text{CD8}^-$ cells. This increase in SP $\text{CD4}^-\text{CD8}^+$ cells is most likely not mediated by increased positive selection

as CD3^{high} expression in the DP CD4⁺8⁺ population is not altered by nadolol. In all probability the increase is due to an increase in the numbers of SP CD4⁺8⁺ cells exported from the thymus to the periphery as the percentage of CD8⁺44^{low} naive cells in peripheral blood increases in nadolol-treated mice. These results indicate age-associated differences in sympathetic modulation of thymocyte maturation. Pharmacological manipulation of NA innervation may provide a novel means of increasing naive T cell populations and improving T cell diversity, thereby, enhancing T cell responses to novel antigens with age.

Chronic treatment (0.20 mg/kg body weight/day for 15 consecutive days, s.c.) with urapidil, an α_1 -AR antagonist, reduces body weight gain and thymic weight in immature peripubertal rats. Reduced thymic weight in treated rats results from decreased thymocyte numbers and thymic cortical volume compared to age-matched saline-injected controls [78]. The percentage of SP CD4⁺8⁺ thymocytes is lower, while that of SP CD4⁺8⁺ is higher suggesting dysregulation in the final steps of the positive selection. In contrast, thymic weight, cortical size and cellularity increase after treatment with an α_1 -AR blocker in adult rats. There is also a decelerated transition from the DN to DP stage of thymocyte development as the percentage of immature DN CD4⁺8⁺ cells increases, whereas with percentage of immature CD4⁺8⁺ DP thymocytes decreases. The treatment also evokes changes in the relative numbers of SP cells in adult rats, but contrary to immature animals, the maturation of SP CD4⁺8⁺ is favored over SP CD4⁺8⁺ thymocytes. These findings demonstrate an age-dependent effect of chronic α_1 -AR blockade on thymic structure and thymocyte differentiation. Further, targeting α_1 -AR pharmacologically modulates intrathymic T cell maturation under conditions where immunocompetence is impaired, such as in HIV infection and aging.

Xylazine, an α_2 -AR agonist, both inhibits and promotes thymocyte proliferation depending on its concentration. Treatment with xylazine, an α_2 -AR agonist, *in vivo* or applied to unfractionated thymocytes in culture stimulates proliferation triggered by Con A [79]. In contrast, higher concentrations of xylazine, both *in vivo* and *in vitro*, are inhibitory [80]. There is also a decrease in IL-2 production (*in vivo* and *in vitro*) and down-regulation of IL-2 receptor alpha (IL-2R α) expression (*in vitro*). Exogenous IL-2 completely restores the inhibitory effect of xylazine *in vivo*. However, exogenous IL-12 has a minimal influence on the high-dose xylazine-inhibited thymocyte proliferation *in vitro*. This stimulatory effect of xylazine on proliferation of thymocytes is mediated through α_2 -AR, since it is blocked by yohimbine, an α_2 -AR antagonist. It seems that the pathways involved in inhibition of thymocyte proliferation by high-dose xylazine are more complex because the xylazine-suppressed thymocyte proliferation is potentiated by yohimbine. Furthermore they indicated that these effects are not mediated via α_2 -AR. Suppressed thymocyte proliferation induced by high-dose xylazine may be mediated by increased cell death, since concentrations of xylazine between 100 and 500 μ M induce apoptosis of rat thymocytes *in vitro*. Xylazine, at concentrations higher than 50 μ M, also induce apoptosis of a thymocyte hybridoma (BWRT8), and increase TCR cross-linking-induced apoptosis. Xylazine-induced apoptosis of the BWRT8 hybridoma is not prevented by yohimbine (a selective α -adrenergic antagonist) or by antibodies to Fas and Fas-L. However, cell death is completely blocked by a caspase inhibitor, z-Val-Ala-Asp (OMe)-CH2F. Cyclosporine, a calcineurin blocker, partly inhibits the xylazine-induced apoptosis of activated BWRT8 cells. These data taken together suggest that the β -AR and α -AR are expressed on cells in the thymus and that β -AR stimulation of these cells may exert a suppressive effect, while α -AR stimulation may have a positive effect on thymocyte differentiation.

Findings that NA nerves run in close contact with TEC and TEC express β -AR [42,34,36] suggest that the SNS could also have indirect effects on thymocyte maturation. EPI from the adrenal gland or NE released from perivascular nerves may target the outer thymic cortex

through the TEC that form the blood-thymus barrier. TEC create a microenvironment that influences the maturation and differentiation of thymocytes. The demonstration of their capacity to respond to catecholamines suggests that adrenergic stimulation may interfere with the regulation of immune functions. In particular, catecholamines influence the synthesis of IL-6, which is known to affect T cell proliferation and differentiation [81]. Co-stimulation of cultured rat TEC with EPI, NE, or isoprenaline has an additive (tumor necrosis factor (TNF)- α) or synergistic (LPS) effect on IL-6 release mediated by β -AR that is linked to the elevation of intracellular cAMP levels [57]. A close association between mast cells and NA nerves exists in the thymus, which suggests a possible role for NE regulating mast cell function to affect thymocyte development in the thymus. These nervous system-mast cell contacts are seen in all lymphoid organs, with the exception of the spleen [82], and NE, via stimulation of α - and β_2 -AR, is known to stimulate and inhibit, respectively, the release of histamine from mast cells [83,84]. Regulation of mast cell histamine release is another possible mechanism through which NE released from postganglionic nerve terminals may exert an immunomodulatory role on immune function.

4. Sympathetic Innervation of Secondary Lymphoid Organs

4.1. The spleen

The spleen receives a rich supply of sympathetic nerves primarily from the superior mesenteric and celiac ganglionic plexuses [85–87] and to a lesser extent, the sympathetic trunk [86,88]. In fact approximately 98% of the nerve fibers in the splenic nerve are sympathetic [89]. In the rat spleen, NA innervation primarily develops postnatally [90–91]. The splenic nerve enters the spleen as perivascular plexuses coursing along the splenic artery, in the splenic capsule and trabeculae in the mature animal [7,29,43,92–94]. NA nerves in vascular and trabecular plexuses continue into the white pulp primarily associated with the central arterioles and their branches. NA varicosities labeled using immunocytochemistry for TH radiate from these plexuses into the periaarterial lymphatic sheaths (PALS) [43] ending among OX19⁺ (pan-T cell marker) T lymphocytes and interdigitating cells [4,5,43,90,95–100]. NA nerves that enter the marginal and the parafollicular zones distribute among IgM⁺ B cells and ED3⁺ macrophages [4,5,43,90,95–100]. Few NA nerves course in the parenchyma of the red pulp; most NA nerves present in the red pulp course as plexuses along the trabeculae and venous sinuses [97,100]. NE-containing nerves that distribute to the spleen also express acetylcholinesterase [101], since surgical or chemical ablation, but not bilateral sub-diaphragmatic vagotomy, prevent histochemical staining of acetylcholinesterase⁺ nerve profiles [85,86,101]. NPY and enkephalin also colocalize with NE in splenic NA nerves [7,102,103].

An ultrastructural study of spleen sections immunocytochemically stained for TH has revealed TH⁺ nerve terminals in direct contact with lymphocytes in the PALS and marginal zone [99,104,105]. These NA terminals have long, smooth zones of contact with lymphocyte and macrophage plasma membranes, separated by as little as 6 nm. These terminals are not present in spleens from chemical sympathectomized or surgical removal of the superior mesenteric-celiac ganglionic complex with 6-OHDA or after ganglionectomy.

The spleen is hyperinnervated, particularly the marginal zone of the white pulp in transgenic mice that overexpress nerve growth factor (NGF) in the skin and other epithelial structures compared to wild type mice [106]. This finding is consistent with the neurotrophic role of NGF in sympathetic neurons. Spleen cells from NGF transgenic mice display lower splenic mitogen-induced proliferative responses, suggesting that increased NGF expression and/or NGF-induced increase in sympathetic innervation have consequences for immune responses. In contrast, with advancing age splenic NA nerves are lost in Fischer 344 (F344), Lewis and Brown-Norway rats concomitantly with a decline in splenic NGF concentrations [107].

Additionally, changes in NGF concentrations in the red and white pulp of the spleen are associated with the redistribution of NA nerves in experimental arthritis [108].

4.2. The lymph nodes

The distribution of sympathetic nerves has been described in the lymph nodes from rats [7,100,109–113], several strains of mice [5,110,111,113,114], cats, pigs and humans [110]; however, the origin of the NA nerves in lymph nodes is still unclear. It is presumed that their innervation is regionally supplied as lymph nodes are regional structures draining the areas with which they are associated. For example, in the rat when the superior cervical ganglia are removed, sympathetic nerves are lost in the cervical nodes [109]. NA nerves supplying the cervical, mesenteric and popliteal lymph nodes course along the vasculature that provides their blood supply [5,7,100,109–114]. Sympathetic nerves enter lymph nodes along with blood vessels at the hilus, and continue into the subcapsular plexus or perivascular plexuses in the medullary cords. NA nerves entering the medulla also course adjacent to blood and lymphatic vasculature, where they enter into paracortical and cortical regions. There are also a large number of NA nerves that distribute to medullary and paracortical areas independently of the blood vessels. They supply the T cell-rich regions, such as the paracortical and cortical zones, but not the B cell-containing areas such as lymph nodules and germinal centers. Electron microscopic studies reveal NA nerves establishing contacts with the vascular smooth muscle, reticular cells, plasma cells and lymphocytes in the lymph nodes [115,116]. These nerve fibers contain at least 3 types of synaptic vesicles, each presumed to contain a different neurotransmitter. Similar to the spleen of NGF transgenic mice, peripheral lymph nodes that drain the skin where NGF is overexpressed are more densely innervated compared with control mice and with mesenteric lymph nodes, lymph nodes that do not drain the skin) [106]. The NGF concentration in peripheral lymph nodes from NGF transgenic mice is 13-fold higher than control mice. These findings demonstrate the potential for plasticity of this nerve population under the influence of neurotrophic support by NGF.

4.3. Mucosal-associated lymphoid tissues

The wet epithelial surfaces of the respiratory, urogenital, and gastrointestinal tracts are associated with the majority of lymphoid tissue as these sites are continuously exposed to an external environment of antigens from pathogens, food, and particles in the air. The lamina propria of the intestines receives an extensive plexus of nerves arising from the enteric nervous system, the sympathetic and parasympathetic systems, and the dorsal root ganglia. The relationship between nerves and immune compartments in mucosal-associated lymphoid tissues is not well studied compared with other lymphoid organs, despite the importance of these sites in host defense. Depending on the specific neurotransmitter they contain nerves have a precise location in the lamina propria. Nerves that contain NE extend throughout the lamina propria and form a dense plexus around the epithelial crypts, and ramify throughout the villi in the ileum [7]. TH⁺ nerves extend beneath the basement membrane of the epithelium and somatostatin-positive nerves course in pericryptal networks, but are infrequently found in the villi. In this region, capillaries supplying the villus coalesce to form postcapillary venules, suggesting a role for these nerves in trafficking of activated effector blast cells, and unactivated effector cells from the blood stream into the mucosa [117–119].

Double-label immunocytochemistry demonstrates the spatial relationships between NA nerves and subsets of immunocytes in the rat ileum [7]. These NA nerves (TH⁺) reside in close proximity to OX19⁺ T cells and with CD8⁺ T cells scattered throughout the lamina propria. TH⁺ nerves course adjacent to the basement membrane of the epithelium in close proximity to CD8⁺ intraepithelial lymphocytes and closely appose ED3⁺ macrophages in the

lamina propria. Similarly, enteric nerves contact plasma cells and B immunoblasts in the mucosa and submucosa [120].

Aggregated lymphoid tissues located in the gut also receive a rich nerve supply, including the tonsils, Peyer's patches, and appendix. NA nerves distribute among immunocytes in the palatine tonsils and paratonsillar glands in man [121,122], and the appendix [123], sacculus rotundus, and Peyer's patches in the rabbit [124]. Similar to the spleen and lymph nodes, these nerves course along the vasculature, ramify into T cell compartments, are scarce in lymph nodules (B cell compartments), and closely appose lymphocytes, enterochromaffin cells, plasma cells and other accessory cells in these compartments.

In bronchus-associated lymphoid tissue, NA nerves also closely appose cells of the immune system [125]. These nerves are associated with smooth muscle layers, and travel along the vasculature, under the epithelium and among immune cells in the bronchus-associated lymphoid tissue (BALT) parenchyma. TH⁺ nerves preferentially supply blood vessels, enter the central zone of the BALT, and ramify within the parenchyma. Peptidergic and NA nerves form contacts with mast cells, ED1⁺ macrophages, and other lymphoid cells with varying frequency.

5. AR expression on Cells of the Immune System

5.1. T Lymphocytes

Human and murine T lymphocytes express β_2 -AR [54,55,126–140]. T helper (Th)1 and Th2 cell clones generated from naïve cells differentially express β_2 -AR [141]. In contrast, normal T cells do not possess functional high-affinity β_1 -AR or β_3 -AR. Collectively, these reports indicate a range of 500–2500 binding sites on CD8⁺ T lymphocytes, and 200–750 binding sites on CD4⁺ T lymphocytes. Resting Th1 effector cell clones express approximately 250 binding sites per cell with a K_d of 100 pM; however, Th2 clone do not appear to express β_2 -AR [140,142].

Studies using activated splenic or lymph node T cells have reported either increased [55,134,143] or decreased [55,144] β_2 -AR expression 24 h after activation with either Con A or phorbol 12-myristate-13-acetate (PMA)/calcium ionophore. Contact sensitization increases expression of β -AR in murine draining lymph node cells [145]; however, immunization with a Th cell-dependent antigen significantly decreases β -AR expression in unfractionated spleen cells [54]. Variability in the absolute numbers of β -AR per cell reported may result from different experimental conditions, such as the T cell isolation techniques, source of T cells, types of radiolabel used to tag pharmacological ligands, using ligands with different affinities, or specific activity of the radioligand. β_2 -AR number increases over time with Th1 effector cell activation via stimulation of the CD3 complex associated with the TCR, while β_2 -AR remain undetectable in activated Th2 effector cells [139]. Collectively, these studies indicate the expression of β_2 -AR on CD4⁺ Th1 cells and CD8⁺ T cells and differential expression of β_2 -AR on murine Th1 and Th2 cells.

Treatment of CD4⁺ T cells with NE, EPI, isoproterenol (non-selective β -AR agonist) or terbutaline (selective β_2 -AR agonist) increases intracellular cAMP concentrations [127,128,131,135–137,146–148] and adenylate cyclase activity via β -AR mechanisms [146,149]. Elevating cAMP inhibits either mitogen- or anti-CD3 antibody-induced T cell proliferation [150–156], providing an explanation of β -AR agonist-induced inhibition of T cell proliferation described above. Further, Th1 clones, but not Th2 clones, increase cAMP concentrations after treatment with terbutaline [140]. These data suggest that stimulating β_2 -AR on T cells increase the activity of protein kinase A (PKA), which activates adenylate cyclase to increase cAMP intracellularly.

5.2. B Lymphocytes

Based on radioligand binding and RT-PCR studies, B cells express a higher density of β -AR than CD4⁺ Th cells [54,126,129,131,133,157–159]. These receptors are of the β_2 -AR subtype [54,129,131,160] and their stimulation also elevates intracellular concentrations of cAMP [127,131,135–137,148,160]. B7-2 expression is enhanced following β_2 -AR stimulation, an effect inhibited by a PKA inhibitor, suggesting the increased cAMP is PKA-dependent [161]. The enhancement or inhibition of B cell proliferation through the β_2 -AR is dependent on the type of mitogen used. Receptor stimulation and/or elevation of cAMP inhibit LPS-induced B cell proliferation [151,155] and production of anti-immunoglobulin (Ig) antibodies [162–165] through mechanisms that inhibit phosphatidyl inositol hydrolysis and phosphorylation of the phospholipase C- γ 1 [162,164,166]. However, activation of β_2 -AR and increases in cAMP enhances ionomycin-induced B cell proliferation [163,165,167].

5.3. Natural Killer (NK) Cells

Radioligand binding [133,168,169] and functional studies [169,170–174] indicated that β_2 -AR and α_1 - and α_2 -AR are expressed on NK cells. Stimulation of the β_2 -AR on NK cells is also linked to increased intracellular cAMP.

5.4. Macrophages

Radioligand binding studies indicate α_2 - and β_2 -AR are expressed on normal macrophages [175–181]. The density of β_2 -AR range from approximately 1,000 or 23,000 binding sites per cell with a Kd of 50 or 800 pM in rat peritoneal [176] or guinea pig alveolar macrophages [180–181], respectively. β_2 -AR stimulation elevates cAMP in a concentration-dependent manner in macrophages from a variety of locations and different species [176,177,181–187]. Macrophage β -AR stimulation also inhibits activation of Ca²⁺-dependent K⁺ channels [177], while stimulation of α_1 -AR on macrophages activates Ca²⁺-dependent K⁺ channels by mobilizing intracellular Ca²⁺ stores, presumably via the activation of phospholipase C and a G-protein-dependent mechanism [188]. Activation of Ca²⁺-dependent K⁺ channels is important for modulating macrophage phagocytic activity and may explain the α -AR-mediated enhancement of macrophage phagocytic activity [189]. The functional effects of stimulation of AR on macrophages are dependent on the subtype of receptor. β_2 -AR stimulation suppresses macrophage activity, whereas α_2 -AR stimulation enhances it [reviewed in 190].

6. Functional Significance of Sympathetic Innervation of Secondary Lymphoid Organs

Immunocompetent cells in secondary lymphoid organs provide for host defense against pathogens. Foreign substances in the blood are filtered through the spleen. Blood flows through the white pulp and continues into the red pulp where macrophages remove foreign substances, and signal other cells of the immune system to help with removal. Like the spleen, lymph nodes filter regionally draining lymph, with the purpose of detecting and removing bacteria and foreign materials. Diffuse lymphatic tissue under wet epithelial surfaces contains dispersed and aggregated lymphocytes, macrophages and other immune cells. In these locations they survey and detect foreign materials and pathogens that enter from the external environment. Thus, microorganisms or other foreign substances, upon detection, can initiate an immune response in the respiratory, urogenital or gastrointestinal tracts, or in the blood or lymph. Activation of the innate immune responses mobilizes cellular and immune mediators to sites of injury or infection. After activation of an acquired immune response, clonally expanded pools of lymphocytes enter the blood stream from the spleen and/or lymph nodes. Subsequently, they leave the blood and enter sites of infection or

injury. Sympathetic signaling within lymphoid compartments modulate immune responses to antigens by affecting clonal expansion, cytokine production and/or responsiveness of target cells by altering receptor expression, shifting the balance between cellular and humoral responses, enhancing or inhibiting the inflammatory response and mobilizing immunocytes.

In vitro, adrenergic agonists can modulate all aspects of immune responses (initiative, proliferative and effector phases). Stimulation of either β - or β_2 -AR inhibits mitogen- or anti-CD3 antibody-induced T cell proliferation [146,149,191–196], and particularly inhibits naïve T cells differentiation into Th1 cells [139–141,197,198] by affecting early events involved in the initiation of proliferation [199]. β -AR-mediated inhibition of T cell proliferation may be explained, at least in part, by its ability to inhibit IL-2R expression and/or IL-2 production by activated T cells [139,140,146,191,200–206].

β -AR stimulation also affects the production of interferon- γ (IFN- γ), which may contribute to this effect under certain conditions. Pretreating with terbutaline and other pharmacological agents that increase cAMP before antigen challenge, but not at the time of or after activation [139], decreases IFN- γ production from Th1 clones [140,197,198]. In contrast, under Th1-promoting culture conditions, β -AR stimulation drives Th1 effector cell development from naïve T cells. These effector Th1 cells produce greater IFN- γ after restimulation [141]. Under Th2-promoting culture conditions, naïve T cells exposed to NE or terbutaline develop into Th2 cells, but adrenergic agents have no effect on IL-4, IL-5 or IL-10 production [139–141]. Other studies support a dichotomy in β_2 -AR effects on Th1 and Th2 cells, such that their activation modulates Th1 cell differentiation and cytokine production, but does not alter Th2 effector cells [131,197,203,198,207–209]. Interestingly, increasing intracellular cAMP levels in Th2 cells can modulate IL-4 production [210–213]. Therefore, cAMP-mediated modulation of cytokine production by Th2 effector cells may depend on the manner in which the Th2 cells are activated or the level of cAMP attained intracellularly [190].

In vivo studies indicate that β -AR stimulation modulates Th1 effector cell-driven responses, including delayed-type hypersensitivity. Chemical sympathectomy before sensitization with 2,4,6-trinitrochlorobenzene (TNCB), reduces ear swelling in mice with second challenge compared with controls [145]. Splenic T cell from NE-depleted mice proliferate less and produce less IL-2 and IFN- γ in response to Con A *in vitro*, but lymph node cells proliferate less, despite greater IL-2 and IFN- γ production [214]. Giving the *in vitro* data, these findings suggest that NE stimulation of β_2 -AR may play a role in generating Th1 cell-driven cell-mediated immunity.

CD8⁺ T cells also express β -AR, and depletion of NE prior to TNCB sensitization reduces hapten-specific cytotoxic T lymphocytes (CTL) generation compared with controls [145]. *In vitro* studies demonstrate that β_2 -AR stimulation can enhance [215] or suppress [216–218] CTL activity. In the latter study, β_2 -AR stimulation was important for optimal CD8⁺ T cell lytic activity. CTL clonal studies indicate that rises in intracellular cAMP can inhibit the TCR-dependent release of granules [219], which may explain β_2 -AR-mediated inhibition of cytotoxic T cell activity.

β_2 -AR stimulation has been reported to enhance [220] or inhibit LPS-induced B cell proliferation [195,220] and anti-IgG antibody production [166,220]. Similarly, *in vitro* Th cell-dependent antibody production increases [220,221] or decreases [13,222–225] following β -AR stimulation. These studies suggest that stimulation of β_2 -AR expressed on B cells can either enhance or suppress humoral immunity. These confusing data may be explained in part, by differences in the signaling pathway induced in B cells by LPS or

crosslinking surface Ig compared with the signaling pathway engaged by Th cells, and that these pathways are modulated differently by cAMP [reviewed in 190].

Th cell-dependent antibody production can be modulated by the SNS *in vivo*, which indicates that NE is likely to be required for optimal antibody production, and may directly affect either B cells and/or Th cells that participate in the response. *In vivo* studies employing chemical sympathectomy in adult rodents prior to antigen challenge with a T-cell dependent antigen reduces [54,91,145,226–228] or enhances [13,229,230] antibody production. Chemical sympathectomy in C57Bl/6 mice, a strain with a predominant Th1 antibody profile, enhances Th1-associated serum IgG_{2a} and Th2-associated IgG₁ production after immunization with keyhole limpet hemocyanin (KLH). However, in BALB/c mice, a strain with a preference toward a Th2 profile, chemical sympathectomy only slightly elevates serum IgG₁ levels [231]. Direct toxic effects of 6-OHDA, bolus release of NE, and elevated corticosterone levels do not mediate the effects of chemical sympathectomy [232]. Taken together, these data indicate that the effect of NA ablation on specific components of the immune response, including the effector (antibody) stage, is dependent on Th dominance. These studies were the first to use an *in vivo* model system to address the effect of NE-depletion on Th1- and Th2-dependent antibody production, and they suggest that intact NA innervation inhibits the immune response to KLH. Consistent with these findings, antibody production increases in surgically denervated submaxillary lymph nodes relative to sham-denervated lymph [233]. However, these findings conflict with other *in vivo* and *in vitro* studies examining sympathetic modulation of cell-mediated immune responses described above.

In another study [160], severe combined immunodeficient (SCID) mice were used to further assess the role of the SNS in primary antibody response. When mice are chemically sympathectomized before reconstitution with murine β_2 -AR^{neg} KLH-specific Th2 clones and β_2 -AR^{pos} splenic naïve trinitrophenyl (TNP)-specific B cells IgM and IgG₁ antibody production is suppressed during a primary antibody response. However, during a secondary response to antigen only IgG₁ production is suppressed [160]. The histology of the spleen is similar in NE-intact and NE-depleted mice before antigen exposure, but the expansion of the follicle and formation of the germinal center are suppressed in NE-depleted mice after antigen exposure. Similar results have been obtained using SCID mice reconstituted with murine clones of β_2 -AR^{pos}-KLH-specific Th1 cells and β_2 -AR^{pos} splenic naïve TNP-specific B cells [160]. Collectively, these findings suggest that β_2 -AR stimulation of B cells is necessary to maintain an optimal primary and secondary Th2 cell-dependent antibody response *in vivo*.

The number of IgM-secreting cells increases following NE treatment of murine spleen cells cultured with a Th cell-dependent antigen, an effect blocked by addition of a β -AR antagonist [234–235]. This finding suggests that the NE-induced enhancement in IgM production is mediated via β -AR stimulation. The timing of β_2 -AR stimulation is important for this effect, since addition of NE or terbutaline at the time of antigen challenge or shortly after, but not 24 h later, enhances the IgM response. The ability of β_2 -AR antagonists to block β -AR-mediated enhancement of IgM production is limited to the first 6 h after the addition of the agonist, indicating that the effects of β_2 -AR stimulation take place during early stages of the IgM response. The target cell(s) through which β -AR agonists interact(s) to produce this effect on antibody response are unknown since whole spleen cell cultures were used in these studies. Another study [236] suggests that β_2 -AR agonists affect antibody production by increasing the frequency of B cells that differentiate into IgM-secreting cells, without affecting burst size. Since in this study naïve TNP-specific B cells are stimulated with TNP-KLH in the presence of KLH-specific Th2 clone cells that lack detectable levels of β_2 -AR either at rest or when activated [139,140], B cells may be affected directly by β_2 -

AR agonists in a B cell-Th2 cell clone culture system. Again, the timing of β_2 -AR stimulation relative to antigen presentation is important for influencing the antibody response. When Th cells are exposed to terbutaline before activation by antigen-presenting B cells, the Th1 or Th2 cell-dependent antibody response is either inhibited or unchanged, respectively [140]. When B cells are exposed to antigen and terbutaline (i.e., during B cell antigen processing) before interacting with Th2 cells, IgG₁ and IgE, but not IgM or IgG₂, production are enhanced [161]. Increased B cell responsiveness to IL-4 and B7-2 expression and signaling mediate the β_2 -AR enhancing effect on IgG₁ and IgE production [161]. Further, addition of terbutaline 12 h after Th1 cell-B cell or Th2 cell-B cell interaction increases the IgG_{2a} or IgG₁ response, respectively, whereas no significant effects are found when terbutaline is added at other times [140].

Contradictory effects of sympathectomy on immune reactivity may be explained by differences in the Th cytokine responses, differences in the microenvironment of the lymphoid organs draining the site of antigen challenge and/or the nature of lymphocyte activation (i.e., the type of antigen-presenting cells that engages the T cell). Differences in the response to sympathectomy in the spleen compared with the inguinal lymph nodes of nonimmunized mice have also been demonstrated, such that mitogen-induced B cell proliferation is increased in lymph nodes but is reduced in the spleen [214]. Sympathectomy reduces Con A-stimulated spleen cell proliferation, which parallels a decrease in IL-2 and IFN- γ production; however, IL-2 production remains unchanged and IFN- γ production increases in lymph nodes. Denervation-induced changes in lymphocyte migration in inguinal lymph nodes, which is not apparent in the spleen, may explain these differences [237]. The immunological stimulus may also affect the outcome following sympathectomy; as sympathectomy reduces spleen cell Con A-stimulated T cell proliferation, but enhances antigen-specific proliferation in mice [238].

Few studies have revealed an effect of α -AR stimulation on B lymphocyte function [13,143,239–244]. α_1 - or α_2 -AR stimulation increases or decreases *in vitro* T-dependent IgM production, respectively [13,143]. Stimulation of α -AR during the effector phase of the antibody response may limit the primary antibody response. In mice treated with amphetamine to stimulate NE release *in vivo* for 9 days after antigen exposure [241], α -AR stimulation suppresses *in vitro* proliferation of hen eggwhite lysozyme-primed lymph node cells. It is not possible to rule out direct effects of α -AR agonists on macrophages in this study, since macrophages express α -AR and α -AR-mediated changes in macrophage function subsequently influence the ability of T cells to produce cytokines and proliferate.

Macrophages exposed to antigen rapidly increase consumption of oxygen and generate superoxide anions (O₂⁻) and hydrogen peroxide. Production of H₂O₂ and other reactive oxygen species by macrophages is suppressed by adding a α_1 -AR agonist to cultured pulmonary macrophages [180,245]. However, since this effect is not reversed by adding an α -AR antagonist, the agonist is most likely functioning as a nonspecific antioxidant [180]. β_2 -AR stimulation suppresses superoxide anion and H₂O₂ production in human peritoneal macrophages [246]. Similarly, both α_1 -AR and β_2 -AR activation suppresses bovine pulmonary alveolar macrophage production of reactive oxygen [247]. Alveolar macrophages exposed to isoprenaline (β -AR agonist), or the β_1 -AR agonist dobutamine (which has α -AR effects) also reduces PMA-induced production of H₂O₂, but the β_2 -AR agonist, salbutamol, has no effect. Further, neither β_1 - or β_2 -AR agonist has an effect on phagocytic activity [180]. Isoprenaline also has no effect on zymosan-induced activation or superoxide production by human alveolar macrophages [248], but does suppress the phagocytosis [249]. These data indicate that stimulation of β -AR may induce different effects on reactive oxygen species and hydrogen peroxide, depending on the population of macrophages under study and the stimulus used to activate macrophages.

Macrophage microbicidal and tumoricidal activities not only are mediated through the production of reactive oxygen species, but also by adhesion and phagocytosis and secretion of regulatory proteins like TNF [250]. Macrophage adhesion is augmented following β -AR agonist treatment [251]; however, the β_2 -AR agonist treatment suppresses phagocytic activity of murine peritoneal macrophages [176,252]. Similarly, α -AR agonist treatment inhibits phagocytosis [176,253] by enhancing Ca^{2+} -dependent K^+ channels activation in macrophages [177]. Treatment with low levels of NE enhances macrophage phagocytosis and tumoricidal activity, suggesting α -AR involvement [254]. Similarly, peritoneal macrophage phagocytic activity was enhanced following treatment with metaraminol and phenylephrine, α -AR agonists, as well as NE [255]. Macrophage α_1 -AR stimulation also induces the production of complement cascade components [256]. α - and β -AR stimulation appear to have opposing effects on TNF production. NE, EPI and isoproterenol reduce the LPS-induced TNF production in rat spleen macrophages cultures [178]. In contrast, α_2 -AR stimulation enhances LPS-stimulated TNF production in these cells [175,257]. *In vivo* studies using chemical sympathectomy in mice indicate that the SNS stimulates the production of TNF by macrophage after LPS challenge [258,259]. Collectively, these findings suggest that α_2 -AR stimulation augments TNF production and phagocytic activity, whereas β_2 -AR stimulation inhibits these functions.

Functional AR expressed on NK cells influence their lytic activity. Several studies report that under *in vitro* conditions, prolonged exposure to NE, EPI, β - or β_2 -agonists reduce NK cell lytic activity [170–172,260]. In contrast, pre-treating NK cells with EPI before adding the target cells enhances lytic activity [260]. There also are reports of a transient enhancement of lytic activity after β_2 -AR stimulation, which returns to control values within 1 h [173,174]. β_2 -AR-mediated suppression of NK cell adherence to cultured endothelial cells [261,262] may explain *in vivo* data showing that administration of NE, EPI or a β -AR agonist increases NK cell circulation [133,174,263]. A similar rise in circulating NK cell numbers occurs with natural stimuli that increase circulating catecholamines, such as acute stress or exhaustive exercise, [261,173,264,265]; an effect that is blocked by pretreatment with β_2 -AR antagonists [264], but not with β_1 -AR antagonists [173].

Rats treated with a β -AR agonist *in vivo* have reduced NK cell lytic activity *ex vivo* and compromised resistances to growth and metastasis of a NK-sensitive tumor *in vivo* [266]. Chemical sympathectomy increases the number of metastases, but has no effect on NK cell activity in mice challenged with lung tumor cells [267]. Additionally, CRH-induced sympathetic activation reduces NK cell lytic activity, an effect mediated via β_2 -AR stimulation [268,269].

Lymphocyte trafficking, which is important for recognition of foreign materials, and upon detection, the rapid mobilization of appropriate leukocytes to sites of antigen entry, is also regulated by the SNS. A rapid and transient leukocytosis is induced by physical and mental stressors, increasing NK cells, lymphocytes, and monocytes in the blood. These effects can be mimicked by EPI or isoproterenol treatment and blocked by β -AR antagonist administration [174,270]. The SNS via increased circulating catecholamines promote the homing of lymphocytes to secondary lymphoid organs [237,271,272], an important function since antigen presentation and clonal expansion occurs at these sites. For example, *In vitro* incubation with isoproterenol increases the numbers of injected murine lymphocytes that home to the spleen and lymph nodes [272]. Consistently, chemical sympathectomy alters the migration of adoptively transferred lymphocytes to Peyer's patches, mesenteric and inguinal lymph nodes. Catecholamines also regulate the egress of lymphocytes from the spleen. Infusion of catecholamines into the spleen increases leukocyte output by either β - or α -AR mediated mechanisms in the absence of changes in blood flow [273]. Besedovsky and colleagues [274] have demonstrated that sympathetic innervation of the spleen alters flow

resistance to affect leukocyte output from the spleen. Collectively these studies support a role for the SNS in regulating the cell entry, retention, and release from lymphoid organs. Understanding the mechanisms through which the SNS regulates lymphocyte trafficking may provide a means of enhancing or preventing cell mobilization during local immune and inflammatory responses.

7. Relevance of Sympathetic-Immune Interactions for Disease

7.1. SNS and infections

The adaptive response that develops after host invasion is governed by the predominant Th cell population, Th1 versus Th2, and will determine the outcome of infectious diseases [275–277]. Catecholamines suppress cellular and enhance humoral immunity by inhibiting type 1 and augmenting type 2 cytokine production. This Th1/Th2 balance is regulated in healthy rodents, through the increase in SNS activity following an immune challenge [reviewed in 278]. In individuals whose immune systems are compromised and have heightened SNS activity, the SNS may profoundly affect the susceptibility of the organism to infection and/or influence disease course. Additionally, early life experiences and/or previous stressful life events that developmentally program the SNS may alter an individual's resiliency against infectious disease. There is abundant literature linking psychosocial factors with autoimmunity, psychosomatic illnesses and infectious diseases. Tuberculosis susceptibility increases and disease prognosis is worse in individuals who experienced stressful life events [discussed in 279]. Since cellular immunity is essential for host defense against mycobacterial infections, particularly IL-12 and its ability to induce IFN- γ secretion [280], SNS inhibition of Th1 cell-dependent immune may explain, at least in part these observations [281,282]. Psychosocial stress and/or elevated inflammatory mediators induce abnormalities in sympathetic activity with *H. pylori* infection [283], the bacteria associated with chronic gastritis that leads to peptic ulcer development. These events skew the immune response towards a Th2 profile and promote the onset and/or progression of the *H. pylori* infection [discussed in 284,285,286].

In HIV infection, sympathetic innervation of lymphoid tissue is particularly relevant as the lymphoid organs are the primary site of HIV pathogenesis. HIV1 disease progression correlates with a Th2 shift, reduced IL-12 and enhanced IL-10 production [discussed in 287], which promotes the HIV infection and accelerates HIV-1 replication by up to 11-fold in acutely infected human PMBC [288]. This effect on viral replication is mediated via the β -AR-cAMP-PKA signaling cascade. A synthetic, immunosuppressive, retroviral envelope peptide uses the same mechanism, i.e. induction of intracellular cAMP, to shift the cytokine balance toward a Th2 profile [287,289,290]. Infection with the LP-BM5 mixture, a cocktail of murine retro viruses used in a mouse model for acquired immunodeficiency syndrome (MAIDS), depletes splenic NE concentration as the viruses destroy the sympathetic innervation within two weeks [291,292]. Treatment with an NE reuptake blocker, desipramine does not prevent LP-BM5-induced NE depletion, suggesting that splenic nerve loss is not caused by excess release and reuptake of NE. This phenomenon is consistent with the autonomic and peripheral neuropathies associated with acquired immunodeficiency syndrome (AIDS).

7.2. Sympathetic activation and endotoxic shock: inflammatory and anti-inflammatory effects

The suppression of Th1 cytokine production and cell-mediated defense mechanisms may increase susceptibility to infection. During established sepsis, however, a state of immune hyperactivity occurs that is characterized by the excessive production of multiple inflammatory cytokines and is associated with high mortality that can follow a hyporeactive

immune system. While the production of the proinflammatory cytokines TNF- α and IL-1 is critically important to fight gram-negative bacterial infections, when these cytokines are produced in excessive amounts, like in sepsis, they trigger a cascade of events that lead to the production of various inflammatory mediators that can cause septic shock and multiple organ dysfunction syndrome. In endotoxic shock, the excess TNF- α produced enhances nitric oxide (NO) production that promotes hypotension, peripheral vasodilatation, and vascular hyporeactivity to vasoconstrictor agents. Surprisingly, treatment with anti-TNF- α agents, IL-1 receptor antagonists, inhibitors of NO or other agents that target inflammatory mediators have been disappointing and have not improved survival [293,294].

Sustained SNS activation during sepsis [295–297], including increased gut-derived NE release [298] may have either beneficial or detrimental consequences. Ablation of the SNS prior to gram-negative bacteria challenge, such as *Listeria monocytogenes*, *Pseudomonas aeruginosa* or *Escherichia coli*, reduces bacterial dissemination [299–302]. This SNS effect is mediated via increased secretion of peritoneal TNF, phagocytic activity, and influx of monocytes into the peritoneal cavity [302]. Sympathetic activation by experimental stress elicits a similar increase in gram-negative bacterial tissue burden [303]. In contrast, sympathectomized mice given an injection of gram-positive *Staphylococcus aureus* have increased bacterial burden, an effect mediated by reduced HPA activity, lower IL-4 production by peritoneal cells, and decreased influx of lymphocytes into the peritoneal cavity [302]. To this end, the SNS may differentially affect the influx of inflammatory cells into bacterially infected sites by regulating adherence of bacteria to the gastrointestinal epithelium [304], chemokine production [305], and/or expression of cellular adhesion molecules [306]. The SNS inhibits CC-chemokine ligand 3 or CCL3 production by subsets of neutrophils, which increased the susceptibility of thermally-injured mice to sepsis [305]. This dual role of the SNS in sepsis appears to depend on the innate immune effector mechanisms necessary to eliminate the infectious agent. Thus, adrenergic agents used extensively in intensive-care units to stabilize blood pressure during sepsis, may either support or inhibit bacterial clearance. In order to optimize treatment of patients with sepsis it will be important to understand how the SNS, as well as the HPA axis, regulates bacterial clearance. Comprehending these important neural-immune-bacterial interactions should lead to better manipulation of stress hormones during sepsis.

Clearly targeting specific subpopulation of AR offers a unique opportunity for pharmacologic manipulation of cytokine production during septic shock, given the anti-inflammatory effects of α_2 -AR antagonists and β_2 -AR agonists, either alone or in combination. These classes of adrenergic drugs regulate Th1 and Th2 cytokine production, particularly inhibiting TNF- α and IL-12, and augmenting IL-10 production. Pretreatment of healthy human volunteers with EPI prior to endotoxin challenge *in vivo* inhibits circulating TNF- α levels and increases IL-10 release [307]. Furthermore, isoproterenol suppresses NO production by macrophages and prevents the LPS-induced suppression of vascular contractility to NE in the thoracic aorta *ex vivo* [308,309]. These findings confirm studies in LPS-treated mice showing: (1) β -AR blockade pretreatment increases; (2) β -AR agonist pretreatment inhibits; and (3) α_2 -AR blockade with the highly selective α_2 -antagonist, CH 38083 reduces plasma TNF- α . Pretreatment with chlorisondamine (a sympathetic ganglionic blocker) prevents the CH 38083-induced effect, suggesting that the α_2 -AR effects are mediated presynaptically [reviewed by 310]. Further, the CH 38083-induced reduction in TNF- α is blocked with addition of the nonselective β -blocker, propranolol, and the β_1 -selective antagonist, atenolol, but not the β_2 -selective antagonist, ICI 118,551, suggesting the effect of the α_2 -antagonist is mediated by β_1 -AR [310]. Together, these data suggest a dual role for SNS activation after LPS administration: (1) reduction of TNF- α through β -AR, and (2) inhibition of NE release through presynaptic α_2 -AR. Other investigators have

demonstrated *in vitro* that macrophages participate directly in the β -AR-mediated inhibition of TNF- α through the modulation of IL-10 [257,311–314].

In endotoxemic mice, IL-10 induces suppression of TNF- α production and down-regulates an inflammatory response, which reduces their mortality [315]. However, the anti-inflammatory effects of β -AR stimulation are not dependent on IL-10 [312]. In contrast, IL-10 regulation by α -AR stimulation may indeed influence the inflammatory response. Isoproterenol and EPI increases LPS-induced IL-10 production by macrophages *in vitro* and β -blockade reduces LPS-induced plasma IL-10 in mice, *in vivo* [307,316]. IL-10 is also an indicator of the Th2 or humoral immune response, as IL-10 drives the β -AR-induced shift towards a Th2 response after LPS treatment. Further, β -AR stimulation inhibits the production of the Th1 cytokines IL-12 and IFN- γ after immunization with LPS [312], or in activated monocyte and dendritic cell cultures [317]. The inhibition of IL-12 and IFN- γ in culture required much lower concentrations of agonist than is required to inhibit TNF- α production. These data suggest that in addition to the potential benefit of adrenergic therapy in sepsis, therapeutically manipulating catecholamine regulation of cytokine production in clinical diseases that exhibit Th1/Th2 predominance may prove beneficial.

In contrast to the inhibitory effects of β_2 -AR stimulation, *in vitro* studies demonstrate α_2 -AR activation stimulates TNF- α production by macrophages [175,257], however, reports of *in vivo* proinflammatory effects of α_2 -AR stimulation are limited. Fessler et al. [318] have reported increased mortality in LPS treated rats that are previously given UK 14304 (α_2 -agonist); however, plasma TNF- α levels are not measured in these animals. In contrast, pretreating with an α_1 -antagonist, rauwolscine, protects all rats from an LD100 dose of LPS [318]. Blocking α_2 -AR reduces circulating TNF- α , liver enzymes, bilirubin, prevents bowel hemorrhage and increases arterial pressure, suggesting that many tissues are targets for α_2 -AR stimulation.

Pharmacological cardiovascular support human septic shock includes the administration of α -AR agonists to maintain perfusion pressure, β -AR agonists to improve cardiac output and, thereby, oxygen delivery; and dopamine-receptor agonists to augment renal and mesenteric perfusion [for more details see 293]. Despite early claims of improved outcome, more recent studies regarding the use of dobutamine suggest poorer survival and increased end-organ injury [319]. Moreover, in humans, it is the β_2 - not β_1 -ARs that appear to control monocyte/macrophage cytokine profiles. Therefore, currently, a clear recommendation for a specific catecholamine regimen in septic shock is impossible. Systemic examination will be necessary to determine the correct combination of adrenergic agents to acquire the optimal balance between cardiovascular support and immunomodulation during septic shock.

Hensler et al. [320] have reported low preoperative macrophage IL-12 production precedes the onset of sepsis, which underscores the associative data that immunosuppression predisposes patients undergoing major surgery or trauma to sepsis. Additionally, catecholamines can dramatically increase the growth of gram-negative bacteria such as *Escherichia coli* and *Yersinia enterocolitica in vitro* [321]. Thus, an early intervention with adrenergic drugs that suppresses IL-12 production and/or possibly increases bacterial growth may be harmful.

Anti-TNF- α strategies demonstrate that patients with high systemic levels of IL-6 might benefit most from anti-cytokine therapy [294]. Therefore, the benefits of immune therapy would be optimized based on the individual inflammatory response condition. Thus, it is proposed that immune stimulatory protocols should prove beneficial for patients showing hyporeactive immune response conditions, whereas patients with a hyperactive immune system may selectively benefit from anti-inflammatory therapies [320]. In conclusion,

patient stratification, timing issues, and the type of intervention, including adrenergic agents, are important factors in successful therapeutic strategies in sepsis and its complications. The role for targeted AR interventions and the temporal relationship between endotoxin administration and catecholamine-induced alterations in cytokine production *in vivo* may lead to clinical studies that maximize the benefits and minimize unwanted side effects of stimulating AR in the treatment of sepsis.

7.3. Major injury

Suppression of Th1 cytokines and potentiation of Th2 cytokine production impair lymphocyte proliferation, reduce delayed-type hypersensitivity skin test response, lower cell surface MHC class II antigen expression, and suppress neutrophil functions (chemotaxis, phagocytosis and oxygen radical production) correlate with trauma and major surgery. Serious traumatic injury, major burns or major surgical procedures often lead to severe immunosuppression, which contributes to infectious complications, the most common cause of late death after trauma. Activation of the neuroendocrine pathways is an essential component of the adaptive process to trauma, brain injury, and major surgery. After extracerebral brain injury there is a biphasic response, with an early increase in sympathetic outflow followed by an altered stimulation of the HPA axis during the ebb phase, the first phase is followed by a decrease in both responses [322]. The intensity of these changes (particularly with catecholamines and cortisol plasma levels) correlates with the severity of both cerebral and extracerebral injury and is a predictor of an unfavorable prognosis [322–325]. Cellular immunity is suppressed in patients with traumatic major injury and in animal models of burn injury, as there is a reduction in production of IFN- γ and IL-12 and increase in IL-10, i.e., a Th2 shift [326]. Further, TNF- α production is reduced in LPS-stimulated whole blood after trauma [327], whereas the production of type 1 cytokines, such as IFN- γ , TNF- α , and IL-2, are down-regulated on postoperative day 1 following conventional but not laparoscopic surgery [328]. SNS activation may drive the increase in systemic IL-10 indicated in the immunosuppression after injury [329]. Thus, high levels of systemic IL-10 documented in patients experiencing a “sympathetic storm” due to acute accidental or iatrogenic brain trauma correlated with the high incidence of infection. β -AR blockade by propranolol dose dependently inhibited catecholamine-induced release of IL-10 and prevented the increase of circulating IL-10 in the rat model [329]. Similarly, in a mouse model of focal cerebral ischemia, blocking the SNS but not the HPA axis prevented the defective IFN- γ response and the life-threatening spontaneous systemic bacterial infections in ischemic mice [330]. These data suggest that catecholamine secretion triggered by major injury may contribute to the severe immunosuppression observed in these patients. These observations may have two important implications: 1) they provide direct evidence that the sympathoadrenal system coupled with a systemic immunosuppressive response triggers a high incidence of infections and complications; and 2) they emphasize the importance of neurotransmitter/hormone-associated modulation of immunity [331].

7.4. Sympathetic regulation of autoimmune diseases

Inflammatory autoimmune diseases have dysregulated Th1 versus Th2 immune responses and altered IL-12/TNF- α versus IL-10 balance. An excess of IL-12 and TNF- α production is seen in rheumatoid arthritis (RA), multiple sclerosis (MS), type 1 diabetes mellitus, autoimmune thyroid disease (ATD) and Crohn’s disease resulting in the cytokine balance being skewed toward Th1 cell-mediated immune response and as a result the Th2 activity and the production of IL-10 are deficient [277,332–334]. This is a critical factor determining the proliferation and differentiation of Th1-related autoreactive cellular immune responses in these disorders [335]. In contrast, systemic lupus erythematosus (SLE) is associated with excessive production of IL-10 and a deficiency in IL-12 and TNF- α production, which skews cytokine production toward a Th2 profile [336,337].

The influence of SNS in autoimmune disorders is complex [332,338–340]. Considering the Th2-driving effects of catecholamines via β_2 -AR receptors under normal conditions, a hypoactive SNS may facilitate or sustain the Th1 shift in MS or RA, whereas SNS hyperactivity may intensify the Th2 shift and induce or facilitate flares of SLE. This hypothesis is supported by several animal studies and certain clinical observations. F344 rats, which have a hyperactive stress system, are extremely resistant to experimental induction of Th1-mediated autoimmune states, including arthritis, uveitis, and experimental allergic encephalomyelitis (EAE) [332]. Similarly, remission of Th1 type-mediated autoimmune diseases, such as RA, MS, type 1 diabetes mellitus, and ATD, possibly via the increased cortisol and probably catecholamine levels may suppress proinflammatory and potentiate anti-inflammatory cytokine production in women in the third trimester of pregnancy [341,342]. In contrast, increased SNS activity seems to drive the higher Th1 vs. Th2 cytokine profiles in the Lewis rat model for RA. Treatment with a β -AR agonist or an α -AR antagonist exacerbates disease pathology. However, combined treatment with these compounds appears to balance Th1/Th2 drive and reduce disease severity [334], suggesting that the role of the SNS is more complex, involving both promotional and inhibitory mechanisms under conditions where chronic inflammation plays a major role in disease pathology. Through a reciprocal mechanism, Th2-mediated autoimmune disorders, such as SLE, during stress or pregnancy, may flare under conditions of high cortisol and catecholamines to drive IL-10 production [332,333]. There are different opinions [343–345] regarding dysregulation between the nonspecific and specific immune responses in pregnancy. However, Lewis rats, which exhibit dysregulated stress systems, are extremely prone to develop experimentally-induced Th1-mediated states, such as arthritis, uveitis, or EAE [332]. Similarly, patients with Th1 type-mediated autoimmune diseases such as RA, MS, and ATD have heightened, blunted or dysregulated stress activity. This might include the postpartum period, the period that follows cessation of chronic stress or a rebound effect upon relief from stressors [281,332,339].

Several lines of evidence suggest that in MS and in EAE, the experimental model for MS, the sympathetic-immune interface is defective. In progressive MS, sympathetic skin responses decrease and lymphocyte β -AR expression increase [346]. While the density of β -AR on monocytes, B cells, and CD41 cells remain unchanged, receptor numbers on CD8+ T cells increase 2- to 3-fold, compared with age-matched controls [338,346,347]. Increased β -AR may result from a compensatory response to reduced concentration of NE in secondary lymphoid tissues in EAE [348], and suggests an adaptive response to lower NE availability in the spleen observed in MS [338]. An “up-regulating” effect of cortisol or IL-1 on β -AR receptor expression may further contribute to this effect [349].

The “protective” role of the SNS in EAE pathogenesis is further supported by observations that chemical sympathectomy augments disease severity [229], even in the presence of elevated circulating glucocorticoids. Splenic NE content increases at peak disease an effect that is more difficult to interpret [350], but may suggest reduced NE release which would further support protection by the SNS in EAE. NE turnover studies are needed to confirm this hypothesis. Additionally, isoproterenol or terbutaline, β -AR and β_2 -AR agonists, respectively, or prazosin, an α_1 -AR blocker are reported to suppress chronic/relapsing EAE in Lewis rats [351,352]. These drug actions may result from receptor-mediated changes in production of type 1 cytokines. This is further substantiated by recent evidence that the drug rolipram, a selective inhibitor of phosphodiesterase type IV and consequently the production of type 1/proinflammatory cytokines, such as TNF- α , IFN- γ , and IL-12, ameliorates EAE.

The role of SNS in RA is less clear as the SNS appears to play both a permissive and inhibitory role in the disease pathogenesis. Clinically, there are multiple reports of autonomic dysregulation in both juvenile chronic and RA, such as increased resting heart

rates and elevated levels of urinary NE metabolites [353] and augmented SNS reflex responses to orthostatic stress [354], the valsalva maneuver [354], deep breathing [355], pupil size [355] and perspiration [356]. These reports suggest increased sympathetic tone. If the sympathetic-to-immune modulatory effects were solely mediated via β -AR stimulation, heightened SNS tone should afford protection by shifting the immune response toward humoral immunity. However, denervation studies in animal models for RA report mixed results depending on whether sympathetic denervation is local or systemic. Systemic depletion of NE using guanethidine, reserpine, or 6-OHDA treatment in rodent models of RA attenuates inflammation and joint destruction [357–362]. Additionally, administration of propranolol, a β -AR antagonist, or regional sympathetic blockade with guanethidine reduces symptoms associated with RA in clinical studies [359]. Unlike other Th1-driven autoimmune diseases, these studies suggest a promiscuous role for SNS in disease pathology.

Based on findings from our laboratory using an animal model for RA, the reasons for this difference in sympathetic-immune modulatory effects in RA are 4-fold. First, it is important to realize that the SNS regulates immune events that take place in secondary lymphoid organs as well as immune responses that occur locally in the inflamed joint. In the former site, sympathetic regulates Th1 vs. Th2 drive through clonal expansion of autoreactive immune cell, and affects immune cell migration and blood flow through secondary lymphoid organs. In the latter site, the SNS regulates the movement of antigen-presenting cells such as dendritic cells from the inflamed site into draining lymph nodes, and the localized inflammatory response including blood flow, vascular permeability, influx of inflammatory cells, and release of inflammatory mediators. Additionally, sympathetic nerves in the inflamed joint interact with substance P-containing nerves that convey pain and modulate local immune responses. Levine et al. [363] using an adjuvant-induced arthritis (AA) model in Sprague-Dawley rats has shown that chronic administration of the β -AR blocker, propranolol, attenuates the severity of joint injury. In contrast, selective denervation of the lymph nodes that drain the hind limbs (the popliteal and inguinal) prior to immunization to induce experimental arthritis exacerbates the disease [364]. This latter finding is consistent with a protective role of the SNS, likely afforded by shifting the immune response toward a humoral response based on circulating and immune organ cytokine profiles [334,365] or by preventing the autoreactive immune cell populations from homing to the joint.

A second factor important in understanding SNS regulation in RA is the multiple roles of the SNS that occur across the progression of the disease. This is underscored by studies in animal models for RA where the timing of sympathetic manipulation, either via pharmacological agents or denervation of sympathetic nerves, relative to the arthrogenic antigen challenge differs. Continuous infusion of EPI or salbutamol (β_2 -AR agonists) beginning 2 days before and continuing through day 28 after immunization with adjuvant increases the severity of AA, respectively [366]. Consistent with these findings, continuous infusion of propranolol and ICI118 551 (β -AR or β_2 -AR antagonists, respectively) over the same time frame relative to challenge ameliorates disease severity. These data indicate that heightened SNS activity prior to exposure to the arthrogenic antigen and continuing through disease progression is detrimental. Conversely, treatment with β_2 -AR agonists, like salbutamol, beginning at disease onset and continuing every other day for 10 days potentially suppresses disease processes to prevent joint damage in established collagen-induced arthritis [367]. Malfait et al. [367] attribute these differences in disease outcome to the way the drug salbutamol was administered, continuous infusion rather than individual injections and to differences between the animal models used in these studies. However, studies from our laboratories suggest that differences in outcome may be due to the timing of adrenergic drug treatment relative to the adjuvant challenge and the disease course. Treatment of AA

rats with terbutaline, a β_2 -AR agonist, started at the time of adjuvant injection to induce disease, exacerbated disease severity; however, a directionally opposite effect of terbutaline treatment occurs when treatment begins at the time of disease onset significantly reduced disease severity [365]. Collectively, these findings suggest that at different time frames across the development and progression of AA, the SNS may differentially modulates afferent phase of the immune response and chronic inflammation once the disease has been established.

Changes in AR expression with development and progression of AA are the third factor that may contribute to controversies in the reported adrenergic drug effects on severity of inflammatory arthritis. The surprisingly small effects of sympathectomy and β -AR drug treatments on disease severity that have been previously reported [362,364] may be explained by altered AR expression and/or signaling capacity with disease progression. β_2 -AR numbers and functional responses to agonists in peripheral blood mononuclear cells (PBMC) are lower in RA patients [368–370]. The density of β -AR is lower in synovial fluid lymphocytes and CD8⁺, but not CD4⁺, lymphocytes in RA patients [370] compared with cells from healthy donors. Altered β -AR expression may explain diminished catecholamines-stimulated OKT3 (T cell mitogen)-induced PBMC activation. These findings suggest impaired SNS regulation of cellular proliferation, effects that are expected to contribute to the pathogenesis of RA. Reduced PBMC expression and activity of G-protein receptor-coupled kinase, important for regulating β_2 -AR cell surface expression, may also influence disease progression in RA patients [371]. Defective β_2 -AR signaling is also seen in PBMC from children with active systemic and polyarticular juvenile RA as the disease develops, reflected by impaired β_2 -AR agonist-stimulated cAMP production [372]. Collectively, these studies indicate dysregulated sympathetic-immune signaling in immune target cells in RA.

Concomitant with altered functional β_2 -AR, α_1 -AR are induced abnormally on peripheral blood monocytes in juvenile RA patients [373]. Stimulation of these α_1 -ARs increases the production of IL-6 [373], a proinflammatory cytokine. Similarly, AA rats treated with an α -AR antagonist reduces the production of proinflammatory cytokines [374]. Increased sympathetic activation (and/or circulating cortisol) may induce monocyte α_1 -AR expression, since treatment of monocytes *in vitro* with a β_2 -AR agonist or dexamethasone can induce monocyte α_1 -AR expression [375]. Disease-induced AR subtype switching and impaired β_2 -AR signaling capacity sensitivity to catecholamines likely drives the inflammatory response with consequent disease exacerbation, since reduced β -AR and increased α -AR stimulation would be disinhibitory and excitatory, respectively [314,317,257,307,376–378]. For example, β_2 -AR stimulation inhibits TNF- α and IL-12 and increases IL-10 production, so impaired receptor function promotes TNF- α production. Similarly, α_1 - and α_2 -AR stimulation increases TNF- α production.

While the role of α -AR in autoimmunity is not entirely clear, intriguing evidence exists for this class of receptors to plays a profound role in models of RA and MS. The effects of treatment with drugs that interact with α -AR on disease pathology are dependent on time of treatment relative to disease course [365]. Treating rats with α - or α_2 -antagonists from adjuvant challenge through severe disease increases disease severity [363, 365,366]. However, if α -, α_1 - or α_2 -AR antagonist treatment begins at disease onset, disease pathology is significantly ameliorated ([365, 366] Lorton and Lubahn, unpublished observations). Based on these data, both α_1 and α_2 -AR mediate sympathetic influences on disease outcome. Mechanistically, α -AR antagonists may alter antigen processing and apoptosis within the secondary lymphoid organs during initiation of the disease via blocked interaction of NE with α -AR on sympathetic nerve terminals and/or on cells of the immune system. α_2 -AR antagonists acting through presynaptic α_2 -AR, would reduce NE release

from sympathetic nerves and lower NE available for binding to β_2 -AR expressed by immune target cells. As mentioned above during the effector phase, inhibiting α -AR signaling inhibits inflammatory cytokine production in arthritic joints. Additionally, α_1 - and α_2 -antagonists could impact disease pathology by targeting the smooth muscle and endothelial cells in the vasculature by affecting immune cell migration from secondary lymphoid organs, homing of immune cells into the arthritic joints, plasma extravasation and edema. Further studies are needed to elucidate the mechanisms of α_1 - and α_2 -AR antagonists on the inflammatory and disease processes of RA.

Interestingly, a study from our laboratory reveals a striking reorganization of NA nerves and immune cell populations in secondary lymphoid organs as AA develops [379; reviewed in 365]. NA innervation of splenic white pulp (site of antigen processing and clonal expansion of T cells) is reduced, particularly in white pulps most distal from the point of nerve entry into the spleen and suggestive a peripheral neuropathy. In contrast near regions where the nerves enter the spleen splenic white pulps are hyperinnervated by sympathetic nerves. Taken together, these findings suggest an injury-sprouting response, with a dying back of sympathetic nerves in regions distant to the nerve entry regions as the disease progresses and a subsequent attempt to replace, reorganize, and repair lost innervation with a sprouting response at nerve entry points. Additionally, we report an increase in the sympathetic innervation of the red pulp, a region that normally is sparsely supplied with NA nerves and where activated immunocytes reside in AA rats with severe disease. The red pulp also is a site of immune cell exiting from the spleen. Reduced sympathetic innervation and NE concentrations in the spleen also precedes the onset of other autoimmune diseases in other animal models, including the New Zealand mouse strains as models for hemolytic anemia and lupus-like syndrome [114,380], and EAE [348]. However, the growth of sprouting NA nerves into the red pulp with severe disease appears to be unique to the AA model.

Altered nerve distribution and density in spleens of AA rats occurs concomitantly with changes in ED3⁺ macrophages and CD4⁺ T cells, which are target cells of sympathetic nerves. The density of these immune cell populations are reduced the white pulp and increased in the red pulp. This disease-mediated effect is further exacerbated by chemical sympathectomy. The density of IgM⁺ B lymphocytes the splenic follicles [7] throughout the spleens of AA rats also decreases with disease development, but does not appear to be dependent on changes in NA innervation, since chemical sympathectomy did not have an effect of numbers of IgM⁺ cells seen with disease development. These findings underscore the disease-associated pathology of sympathetic nerves in secondary lymphoid organs. Altered sympathetic nerve density and distribution may reflect changes in the activational states and redistribution of immune target cells as the disease progresses, and may, in turn, alter antigen processing and clonal expansions of future antigenic challenges. Given that NA nerves, through β -AR mechanisms, promote Th2 cell and impede Th1 cell development, a loss of these nerve fibers in the splenic white pulp may support aggressive cell-mediated immune responses. The abnormal NA innervation of the red pulp may facilitate SNS signaling of immune system effector cells residing in this compartment prior to homing to arthritic joints. These signals received in the red pulp may promote joint inflammation once they arrive in the arthritic joints.

Antigen- and hydrogen peroxide-induced arthritic animals [381] and RA patients [reviewed in 382,383] have markedly reduced sympathetic innervation of the synovium in affected joints. Additionally, bradykinin, a potent mediator of inflammation, stimulates the release of transmitters (specifically, PGE₂) from these nerves, which promotes plasma extravasation and thus inflammation [384]. Bradykinin-induced neurotransmitter release is not dependent on increased activity of NA neurons or release of NE from these nerve terminals [385]. From these findings it appears that NA nerves can have two distinct actions: classical

transmission regulated by impulse activity to release NE and locally-induced release of non-adrenergic transmitters, both of which modulate inflammatory processes [384]. In summary, the SNS's ability to modulate immune functions is compromised in this disease. The complexities of adrenergic drug effects on severity of inflammatory arthritis appear to result from altered AR expression with disease progression, differential outcomes from sympathetic regulation of different target organs, both in lymphoid organs and affected joints, the relationship between onset of drug delivery and timing of drug treatments relative to the arthritis inducing antigen challenge, and the reorganization of sympathetic nerves and immune cell populations in SNS target organs.

7.5. SNS and Tumor growth

Based on both clinical and animal research, inhibited tumor growth and better patient prognosis is positively associated with good social support. While the mechanisms for this association are not clear, we do know that interactions between the nervous, neuroendocrine, and immune system are important [386,387], and that positive social interactions positively influences these systems to buffer against tumor growth. Psychosocial factors alter the activity or stress-reactive areas of the brain to affect tumor immunity, which in turn significantly affects the progression of certain types of cancer [reviewed in 388,389]. These anti-cancer effects are mediated through innate and acquired immune-directed killing mechanisms. NK cells of innate immunity targets tumor cells that express low levels of MHC I [390–398]. In metastatic breast cancer, *in vitro* NK cell activity is a good predictor of the rate of disease progression [399]. Anti-tumor defense is also provided by the functions of macrophages and granulocytes [400]. Specific killing of tumor cell is directed by CD4⁺ T cells or antibody-complement-mediated immune mechanisms [401,402].

Evidence for psychosocial effects on tumor immunity has been provided from clinical and animal research. Higher stress levels predict lower NK cytotoxicity, mitogen- induced T cell and IFN- γ stimulation responses [403–410]. Negative psychosocial factors and chronic stress interact to negatively affect tumor immunity, whereas psychosocial interventions for stress reduction and improved coping strategies positively impact immunity [407,411,412; reviewed in 413]. In contrast, acute psychological stress increased circulating NK cell numbers and/or NK cell activity [414–416], but this effect may be followed by reduction below baseline shortly after stress [416]. Interpersonal difficulties, depression, anxiety and chronic stress reduce the number and function of circulating NK cells [417–423]; effects associated with elevated cortisol levels [424]. Positive supportive relationships mitigate the stress-induced immunosuppression [418], such as chronic stress-induced reduction in NK cell number and functions in cancer patients [425]. Negative emotions are linked to lower lymphocytic infiltration into the tumor site, increased tumor growth, and poorer disease outcome [426]. In studies with rats inoculated with a mammary carcinoma stress-associated increases in tumor growth occur concomitantly with suppressed NK cell activity and reduced survival time [427,428].

Psychosocial factors alter SNS activity to affect tumor immunity and disease outcome. Catecholamines, the major neurotransmitter released by the SNS, modulate immune functions important for tumor immunity, including Th and B cell functions, NK cell trafficking and activity and T suppressor cell cytotoxicity [429–434]. In a model where mammary tumors are subcutaneously injected into a sympathetically denervated ear, tumor growth is attenuated approximately 50% over that observed in the contralateral, sympathetically intact ear [435]. Evidence of increased lymphocyte metabolism in draining lymph nodes supports immunological mechanisms as being responsible, at least in part, for this result. In this study, sympathectomy had no effect on tumor metastases. In another animal study, treatment with deprenyl, a monoamine oxidase B inhibitor, reduces age-related spontaneous mammary and pituitary tumor growth [438]. Lower spontaneous tumor

growth by deprenyl treatment is linked to partially restoration of the age-related decline in splenic NA innervation and improvement in immune function in old rats [436–437]. Not all studies, however, report attenuated tumor growth under conditions of reduced sympathetic activity. Brenner et al. [439] have reported an increase in the number of pulmonary metastases in mice chemically sympathectomized before injection of alveolar carcinoma cells, an effect that is independent of changes in NK cell activity. No effects of sympathectomy occur when mice are denervated after injection of cancer cells. *In vivo* priming of the immune system with irradiated carcinoma cells abrogates tumor cell metastases, but, NA denervation before priming has no effect on T cell-mediated attenuation in metastases. These findings suggest NA innervation can decrease tumor metastases through non-immunological mechanisms. They also emphasize a complex modulatory role for the SNS in cancer cell migration and proliferation. From these studies it is clear that a number of factors are important in determine effects of sympathetic activity on tumor immunity, including timing of manipulations relative to tumor inoculation, the tumor type, and the species/strains and the age of the animals used for study.

It is becoming increasingly clear that the SNS, along with the hypothalamic-pituitary adrenal axis, mediate the effects of psychological stress on breast cancer progression. Studies by Ben-Eliyahu and coworkers report that sympathetic ganglionic blockade, adrenal demedullation, or administration of a non-selective β -blocker either ameliorated or attenuated swim stress-induced increases in MADB106 tumor metastases compared with non-stressed animals [440]. Similarly, the tumor enhancing effects of social confrontation and hypothermic stress are lowered by adrenal demedullation or β -AR blockade [441]. These studies indicate that adrenal catecholamines are responsible for some of the stress-induced increases in MADB106 metastasis, via a β -AR-mediated mechanism. The effects of acute stress on MADB106 metastasis are mimicked by treatment with β -AR agonists, blocked by nadolol, and not observed in NK-depleted rats [442], suggesting that catecholamines interact with β -AR on NK cells to exert SNS effects on tumor metastases. Conversely, stress-induced effects on NK cell activity and tumor metastasis are not directly mediated via the HPA axis, since corticosterone administration (1, 3, or 9 mg/kg, sc) does not alter tumor metastasis [reviewed in 443].

The SNS mediates the effects of housing stress and social isolation on tumor development for several types of cancer in mice [444]. In syngeneic C57Bl/6 and BALB/c mice, social isolation reduces host resistance to B16 melanoma and Meth A fibrosarcoma growth, respectively. Oral administration of propranolol, a non-selective β -adrenergic antagonist, but not chronic treatment with corticosterone, completely abrogates the effect of social isolation on tumor growth. These data support the SNS as a modulator of the effects of social isolation stress on the progression of several types of cancer.

Of clinical relevance, prostate cancer patients receive selective α_1 -AR antagonists to reduce the discomfort associated with urethral blockage by relaxing smooth muscles in the prostate gland and urethra. Several studies in mice suggest that treatment with quinazoline-derived α_1 -AR antagonists, doxazosin and terazosin, which are long-lasting drugs used to provide acute relief of the obstructive symptoms, also reduce tumor growth [445]. The *in vivo* mechanism(s) is(are) not clear, however, culturing prostate cells with α_1 -AR antagonist reduces cellular proliferation and increases the rate of apoptosis [445,446] via an α_1 -AR independent mechanism [447]. Sympathetic activation may also regulate prostate cancer progression via β -AR-mediated mechanisms. In rat prostate cells, β -AR agonists stimulate adenylyl cyclase and raise cAMP levels [448,449], and in human prostate cancer cell lines elevated cAMP production drives their differentiation toward a neuroendocrine phenotype [450,451], an effect reversed by removing the cAMP-generating agents [451]. These findings are important because tumor grade, loss of androgen sensitivity, autocrine and

paracrine activity, and poor prognosis all correlate with appearance of this neuroendocrine phenotype in human prostate cancer cells. Therefore, adrenergic regulation via β -AR on prostate tumor cells by the SNS could play an important role in advanced prostate cancer.

8. Summary and Concluding Remarks

The SNS innervates all primary and secondary immune organs (bone marrow, thymus, spleen, lymph nodes and gut-associated lymphoid tissue) and release catecholamines to modulate immune functions. Further, some immune cells synthesize, store and release catecholamines that can act as autocrine and/or paracrine factors to regulate immune function. The literature summarized and discussed above overwhelmingly indicates that even small effects of catecholamines on immune responses can have significant effects on health outcomes. The mechanisms for neuroimmune modulation via the SNS are not well delineated. Further research is necessary to expand our knowledge of the role the SNS in modulating cellular- and humoral-mediated immune responses to advance the development of therapeutic interventions.

Sympathetic innervation of lymphoid tissues meets the criteria for neurotransmission with immune cells as target cells. These criteria include demonstrating the presence of NA nerve fibers in lymphoid organs, the release of NE from the NA nerve terminals in these organs, and the expression of AR on lymphoid cells, which respond functionally to stimulation. Electron microscopic studies reveal direct contacts between NA nerve terminals and lymphocytes and macrophages in the PALS and marginal zone of the spleen. Whether direct contacts function in neurotransmission is not clear. As in many peripheral sympathetic target organs, NE released from NA terminals diffuses away from the terminal site to interact with AR expressed on adjacent and distant target cells; this is called paracrine release. The release of NE is modulated presynaptically by negative feedback of NE acting on $\alpha_{2A/C}$ -AR. Thus, the SNS is a “hardwired” integrative and regulatory pathway between the CNS and the immune system. Sympathetic-immune interactions are complex. The spleen and lymph nodes are the sites of interest for the majority of studies examining sympathetic modulation of immune functions in basic research using animals. The SNS’s role in regulating immune functions in primary lymphoid organ and mucosal lymphoid tissues is a neglected area if research thus far. There is enough data to support a functional role of the SNS in regulating the functions of primary lymphoid organs (bone marrow and the thymus) and mucosal-associated lymphoid tissue.

Catecholamines released by increased sympathetic activation “fine tune” immune responses. The release of co-localized transmitters or modulators, such as NPY and ATP, also bind to selective receptors on immune target cells, and can modify NA signaling [452]. The influence of co-released neurotransmitters on immune response also is poorly understood. The effects of catecholamines allow for quick adjustments of immune responsiveness (within minutes). Peripheral catecholamines also may tonically inhibit certain immune functions (i.e., type 1 proinflammatory cytokine production). One important effect of catecholamine release from sympathetic nerves is to opposing effects on cellular and humoral immunity. Stimulation of β -AR on Th1 inhibits the production of Th1 type cytokines. The production of cytokines by Th2 cells, which do not appear to express β -AR, is potentiated by reduced production of Th1-type cytokines. Additionally, catecholamines can affect other effector cells to suppress cellular and boost humoral immunity. Sympathetically-driven humoral responses can be either beneficial or detrimental to disease progress depending on the pathological condition. For example, heightened sympathetic activation of an autoimmune disease mediated by a Th2 bias would predict a poorer outcome. Under normal conditions, the above-mentioned Th2-driving force of catecholamines, in concert with the Th2-driving effect of glucocorticoids, serves as an

important feedback mechanism to reduce excessive Th1 proinflammatory cytokine production and prevent bystander damage after the antigen has been cleared. Catecholamines also regulate the production of pro- and anti-inflammatory cytokines produced by macrophages locally at sites of inflammation, and therefore play a regulatory role in innate immune responses.

An abnormal increase or decrease in SNS activity, defects in normal sympathetic-to-immune signaling, or changes in NA innervation of immune organs and chronically inflamed tissues can contribute to the pathophysiology of immune-mediated diseases, particular under conditions where chronic inflammation and/or a selection of Th1 (type 1) versus Th2 (type 2) responses play a significant role in disease pathogenesis. Examples of such diseases include, but are not limited to, some types of infections, major injury and its complications, autoimmune/inflammatory diseases, allergic (atopic) reactions, and cancer. Specific immune responses regulated by the SNS are influenced by many factors including the nature, clearance and presence or absence of an antigen. In addition, the timing of sympathetic activation relative to the antigen challenge, the presence and expression level of AR subtypes on the immune cells (e.g., β_2 - versus α_2 -ARs), the type of G-protein coupled to the β_2 -AR (e.g., G_s versus G_i) and second messenger system activated and the stage of activation/differentiation of the immune cell. Research directed at gaining a better understanding of the dynamic changes in AR subtype expression on different immune cells, the mechanisms for altered AR coupling to G proteins with consequent effects on intracellular pathways used to mediate the actions of catecholamines, and the conditions necessary for these changes to take place is clearly needed. Better knowledge and understanding of the physiology and pathophysiology of sympathetic-immune interactions will be critical for development of novel therapeutic approaches aimed at ameliorating diseases in which abnormal immune functions contribute to, or drive, the underlying pathophysiology of the disease. Patients with infections that are difficult to clear and certain types of cancer may benefit from β_2 -AR antagonist or α_2 -AR agonist interventions, which would boost cell-mediated immune responses; while Th1-mediated autoimmune diseases, such as RA and MS, may benefit from β_2 -AR agonists and/or α_2 -AR antagonists treatment that would dampen chronic inflammation.

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