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Review

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 has focused on neural-immune modulation in secondary lymphoid organs, has 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 intestinal peptide (VIP), and their affect on 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 the 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

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throughout life. Regulation of hemato- and lymphopoiesis via 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 to 3 ng per g in bone marrow tissue [11,12], 1–2 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 the 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]. ^{3}H-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 (a β-AR agonist) [17,18], intracellular adenosine 3′,5′-monophosphate (cAMP) content (second messenger for NA 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 non-selective β-AR antagonist, propranolol blocked the rise in intracellular cAMP content, suggesting a specific β-AR-mediated effect.

Embryonic and fetal development of the hematopoietic system occurs in multiple organs, including the 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 affecting 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 antagonists provide more effective protection after radiation exposure. In irradiated mice treated with the β-AR agonist, isoproterenol, proliferation of bone marrow cells 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 three-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 non-selective β-AR (propranolol) or a selective β_2-AR (butoxamine) antagonist to cultured human bone marrow cells reduces cellular proliferation by decreasing 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 predominates 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,