Developmental and Comparative Immunology xxx (2016) 1–6

Contents lists available at ScienceDirect

Developmental and Comparative Immunology

journal homepage: www.elsevier.com/locate/dci

Sympathetic neural-immune interactions regulate hematopoiesis, thermoregulation and inflammation in mammals

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ARTICLE INFO

Article history:
Received 7 January 2016
Received in revised form
6 April 2016
Accepted 18 April 2016
Available online xxx

Keywords:
Sympathetic nervous system
Immune system
Hematopoiesis
Thermogenesis
Inflammation
Norepinephrine

ABSTRACT

This review will highlight recently discovered mechanisms underlying sympathetic nervous system (SNS) regulation of the immune system in hematopoiesis, thermogenesis, and inflammation. This work in mammals illuminates potential mechanisms by which the nervous and immune systems may interact in invertebrate and early vertebrate species and allow diverse organisms to thrive under varying and extreme conditions and ultimately improve survival.

1. Introduction

In mammals, communication between the central nervous system (CNS) and peripheral physiological systems is critical to survival in response to an external threat, such as an encounter with a predator. Equally important to survival is the ability to sense an internal threat, such as exposure to a pathogen. The CNS is closely involved in regulating the immune response to optimize the response to an internal threat. One of the unique features of the immune system is its mobility, and circulating immune cells are responsible for constant surveillance of the organism, signaling recognition of a foreign entity, and responding appropriately to eliminate a potentially dangerous pathogen. Bi-directional communication between the nervous system and immune system regulates the tempo, magnitude, and duration of the immune and inflammatory response to pathogen, to foreign antigens, and to injury. An important CNS outflow pathways in mammals mediating these neural-immune interactions is the sympathetic nervous system (SNS). The SNS is responsible for the 'fight or flight' response to threatening situations and consists of neural hard-wiring emanating from the spinal cord to innervate target organs, including primary and secondary lymphoid organs. Diverse stimuli (stressors, cytokines, infection), trigger the SNS and catecholamine release by nerves and by the adrenal medulla, leading to functional alterations in immune function that alter susceptibility to infection and other pathologies. The literature describing SNS innervation of primary (bone marrow and thymus) and secondary lymphoid organs (spleen and lymph nodes) and its impact on immune reactivity in mammals has been extensively reviewed (Bellinger and Lorton, 2014; Bellinger et al., 2008; Padro and Sanders, 2014). This review will highlight recent reports that illuminate the significance of neural-immune interactions in mammals and the underlying molecular mechanisms in hematopoiesis and in thermoregulation (Fig. 1). These reports emphasize the role of catecholamines in fine-tuning inflammatory and immune responses, including mobilization and recruitment to inflammatory sites. This fine-tuning is critical to maintaining homeostasis, and dysregulation of the communication between the nervous system and immune systems results in autoimmune disease, sepsis, and cancer progression (Cole et al., 2015; Padro and Sanders, 2014; Sternberg, 2006). Other major components of neural-immune interactions, including the danger-sensing capabilities of afferent innervation of lymphoid organs and the immunomodulatory impact of the hypothalamic-pituitary-adrenal axis activation will not be discussed here. The interested reader is directed to excellent reviews (Bellinger and Lorton, 2014; Silverman and Sternberg, 2012; Sternberg, 2006).

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http://dx.doi.org/10.1016/j.dci.2016.04.015
0145-305X/

The neurotransmitters of the SNS are the catecholamines norepinephrine (NE) and epinephrine (EPI). NE is released locally by sympathetic nerves and is the primary SNS effector in lymphoid organs. EPI is released by the adrenal gland into the blood stream to act by a humoral mechanism on target cells throughout the host. The production of catecholamines by cells of the immune system and the integration of non-neuronal sources of catecholamines in physiological responses will be discussed in more detail below. NE and EPI are the endogenous ligands for the adrenergic receptors (AR) consisting of α1-AR, α2-AR, and 3 β-AR subtypes, β1, β2, and β3. NE and EPI bind to AR subtypes with varying sensitivity. For example, EPI has higher affinity for β2-AR compared to NE. AR expression by cells of the immune system has been well characterized (Padro and Sanders, 2014). AR expression, ligand affinity, and local ligand concentration determine the immune cell response elicited by SNS activation.

2. New insights into SNS interactions with the immune system

2.1. SNS regulation of hematopoietic stem cell mobilization from the bone marrow

Hematopoiesis is the creation of lymphoid and myeloid lineages from early multipotent stem cell progeny that have the capacity to differentiate into all blood cell lineages. A specialized bone marrow microenvironment, called the stem cell niche, is required for hematopoietic stem cell development and mobilization of newly differentiated lymphoid and myeloid cells into the circulation. Hematopoiesis is maintained under steady state conditions and is up-regulated under conditions that require greater output of stem cells, such as with chemo- or radiation cancer therapies (Katayama et al., 2006; Mendez-Ferrer et al., 2008; Yamazaki et al., 2011). Recent research has demonstrated that SNS innervation is a critical regulator of hematopoiesis (Katayama et al., 2006; Mendez-Ferrer et al., 2010b) (reviewed in Hanoun et al. (2015)). In the stem cell niche, sympathetic nerves are associated with a highly specialized nestin-positive perivascular stromal cell population to form the neuroreticular complex (Frenette et al., 2013; Kunisaki et al., 2013; Mendez-Ferrer et al., 2010b; Yamazaki and Allen, 1990). This unit lies in close proximity to bone-lining osteoblasts and blood vessels to support hematopoietic stem cell activity and is the anatomical basis for sympathetic regulation of hematopoietic activity.

Frenette and colleagues have demonstrated that sympathetic input is critical to hematopoietic stem cell release, and have elucidated the underlying mechanisms. Under steady-state conditions, mobilized hematopoietic stem cells show a circadian rhythm with elevated circulating hematopoietic stem cell counts during periods of inactivity; highest in the morning for rodents, higher in the evening for humans (Lucas et al., 2008). Loss of sympathetic input by either chemical or surgical denervation prevented the steady-state circadian rhythmicity of circulating hematopoietic stem cells (Mendez-Ferrer et al., 2008) and attenuated G-CSF-induced hematopoietic stem cell mobilization (Katayama et al., 2006). Circadian rhythmicity was lacking in mice unable to express molecular clock genes, and β2-AR activation of the stromal cell population induced clock gene expression (Mendez-Ferrer et al., 2008, 2010a), suggesting that sympathetic input maintains circadian rhythms under baseline conditions. Granulocyte-colony stimulating factor (G-CSF) facilitates hematopoietic stem cell release into the circulation by acting through CXCL12 and its receptor CXCR4 expressed by nestin+ perivascular stromal cells. In the absence of intact SNS signaling, a β2-AR agonist elevated G-CSF-induced mobilization of hematopoietic stem cells and restored the deficiency in stem cell mobilization. It should be noted, however, that stimulation of SNS signaling in the absence of G-CSF did not elicit hematopoietic stem cell mobilization, suggesting that another unidentified G-CSF-induced mechanism is active in modulating and maintaining hematopoietic homeostasis. Interestingly, G-CSF decreased bone marrow NE levels, suggesting G-CSF regulates local NE release within the bone marrow (Katayama et al., 2006). This body of work demonstrates how non-immune cells (in this case, a mesencyhmal stromal cell population) may be incorporated as intermediaries in the interactions between the nervous and immune systems.

This new understanding of the critical role of bone marrow SNS innervation in steady-state and induced hematopoietic stem cell release has led to the proposal of new therapies for neoplasms associated with the bone marrow (Lucas et al., 2013). For example, β-AR agonists that stimulate G-CSF-induced hematopoietic stem cells may be used to increase hematopoietic stem cell yields after chemotherapy and for stem cell transplantation. Understanding the interactions between the SNS and immature immune and non-immune of the bone marrow will be beneficial for developing therapeutics that target local neural input in cancer and other diseases associated with hematopoiesis.

2.2. SNS regulation of circulating leukocytes

Cells of the immune system constantly re-circulate to replace old and dying cells and to survey the environment for life-threatening pathogens or foreign antigen. Under homeostatic conditions, the entire pool of naïve T cells in a lymph node is replaced 2–3 times a day in the mouse, increasing the chance for antigen-specific naïve T cells to encounter its cognate antigen (Evans et al., 2015). Stimuli such as psychological stressors and exercise that activate the SNS regulate leukocyte migratory behavior (Dhabhar, 2002; Engler et al., 2004; Kruger et al., 2008; Viswanathan and Dhabhar, 2005). The SNS also appears to incorporate circadian rhythmicity into immune surveillance to provide optimal immune responsiveness when the animal is most active and has a greater likelihood of injury (Curtis et al., 2014; Mendez-Ferrer et al., 2008; Nguyen et al., 2013; Scheiermann et al., 2012, 2013). Recent work has revealed a novel ß-AR-mediated mechanism that retains lymphocytes within lymph nodes.

Pharmacological and other stimuli that activate β2-AR elicit a rapid reduction in B and T lymphocytes in the blood (lymphopenia) (Kruger et al., 2008; Nakai et al., 2014). Nakia and colleagues extended this finding by demonstrating that pharmacological β2-AR activation also reduced lymphocytes within the lymph, suggesting that the emigration of lymphocytes from lymph nodes into lymph and blood was inhibited by β2-AR activation (Nakai et al., 2014). Adoptive transfer studies demonstrated that β-AR stimulation of hematopoietic cells, most likely the T cells themselves, initiated this response. β2-AR activation of T cells induced a physical interaction between β2-AR and chemokine receptors (CCR7 and CXCR4) that increased retention-promoting signals initiated through CCR7 and CXCR4. The clinical potential for this mechanism was demonstrated by the finding that β2-AR-induced retention of autoreactive T cells within lymph nodes prevented the development of inflammation at distant sites (Nakai et al., 2014). Thus, direct AR stimulation of T cells regulate their retention and release from primary and secondary lymphoid organs via chemokine signaling mechanisms. These interactions between chemokines, chemokine receptors, and β2-AR demonstrated in mammals raises the question whether such mechanisms may be present across the phyla. Chemokine families have been identified in birds, amphibians, fish, and lamprey (Bird and Tafalla, 2015; Chadzinska et al., 2014; Laing and Secombes, 2004). Less is known about chemokine influences in neural-immune interactions, but is actively being

Please cite this article in press as: Madden, K.S., Sympathetic neural-immune interactions regulate hematopoiesis, thermoregulation and inflammation in mammals, Developmental and Comparative Immunology (2016), http://dx.doi.org/10.1016/j.dci.2016.04.015