

Review Article

Neuroendocrine-Immune Interaction in Lung Diseases

Jing Lin¹, Lei Du¹, and Jerry Yu²

ABSTRACT

From the ¹Department of Anesthesiology and Translational Neuroscience Center, West China Hospital, Sichuan University, Chengdu, China; ²Department of Pulmonary Medicine, University of Louisville, and Robley Rex VA Medical Center, Louisville, USA.

Correspondence to Dr. Jerry Yu at j0yu0001@louisville.edu.

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Aim of review: This overview describes neuroendocrine immune regulation of inflammation in the lung.

Method: The articles published in past 2 decades in this area were reviewed.

Recent findings: Pulmonary diseases are often associated with inflammation, which is an essential body response to infection and injury. During inflammation, various cells are activated to release inflammatory molecules, modulating disease progression. Inflammation is regulated by the immune system, which interacts with the neuroendocrine system via the autonomic nerves and the hypothalamic-pituitary-adrenal axis. During lung diseases airway sensors are activated to produce host defense responses against inflammation, infection and trauma.

Summary: These neural-mediated responses are immediate and non-specific. They may amplify inflammation via local or axonal reflexes to enhance immune protection or suppress inflammation via the central nervous system to avoid tissue destruction.

Inflammation is a key component of immune responses, which can be innate or adaptive. Innate immunity evokes rapid, non-specific responses to insults. Adaptive immunity detects antigen and mobilizes cells to a specific target. The innate and adaptive immunities share components and act together against pathogens. The immune system also interacts with the nervous system to form a circuitry to control inflammation and maintain homeostasis by sharing ligands and receptors at several levels. The central nerve system (CNS) regulates the immune system through sympathetic and parasympathetic nerves, and the hypothalamic pituitary axis (HPA) (1). Local interaction generally intensifies inflammation, whereas central regulation suppresses inflammation. Over-activation of the immune system leads to

tissue destruction, whereas under-activation increases susceptibility to infection. This overview describes neuroendocrine immune regulation of inflammation in the lung.

Immune Response

Pathogens possess conserved molecular patterns, which are recognized by Toll-like receptors (TLRs). TLRs are a set of germ line-encoded pattern-recognition receptors (PRRs) (2). TLR (1-10) play an important role in both acute and chronic lung diseases. For example, TLR4 recognizes lipopolysaccharide (LPS, endotoxin) and the fusion protein for respiratory syncytial virus, and also reacts with endogenous tissue components degraded during the inflammatory response (2). Pathogens are encountered

by inflammatory cells. Dendritic cells recognize pathogens and stimulate naive T cell proliferation. Macrophages are the main source of cytokines, chemokines, and other inflammatory mediators that regulate immune responses (3). Neutrophils are the first cells to be recruited to sites of infection or injury, and target microorganisms and tumor cells (4). Lymphocytes include T cells (CD4 + and CD8 + ; cellular immunity) and B cells (humoral immunity). CD4 + T cells (helper T cells) consist of Th1 and Th2. Th1 cells produce interferon gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α) to drive cellular immunity to eliminate intracellular parasites, viruses and cancer cells. Th2 cells produce cytokines (IL-4, -5, -9, and -13) to stimulate humoral immunity to fight extracellular organisms (5). Mast cells are activated in various acute and chronic airway inflammatory processes (6). In addition to inflammatory cells, endothelial, epithelial, and mesenchymal cells also involved in inflammation (Figure 1) (7). Inflammatory cells secrete cytokines, which act as autocrine, paracrine or endocrine to regulate immunity and inflammation. Cytokines may also act as chemokines to attract inflammatory cells (8). Pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6, IL-8, and IFN- γ) activate the immune system in the acute inflammatory response. They stimulate antigen presentation, adhesion molecule expression on endothelial cells, inflammatory cell activity and matrix degrading enzyme expressions. In the lung, alveolar macrophages secrete the anti-inflammatory cytokines (IL-10, transforming growth factor- β (TGF- β), and IL-1ra) to suppress the inflammatory response (9). Many lung diseases are associated with dysregulation of cytokines. For example, chronic obstructive pulmonary disease is associated with production of TNF- α , IFN- γ , IL-1 β , IL-6 and GM-CSF (10). In acute respiratory distress syndrome, TNF- α and IL-1 β are increased significantly (11) yet IL-10 is relatively lower (12).

Sensory Nerve in Inflammatory Amplification

Airway sensory neurons or sensors convert mechanical or chemical information in the lung into electrical signals transmitted to the CNS through vagal and sympathetic afferents (Figure

2) (13). During lung inflammation, a variety of neural, epithelial, endothelial, and phagocytic cells produce inflammatory mediators that activate airway sensors. These include: IL-1 β , TNF- α , tachykinins [such as substance P (SP)], calcitonin gene related peptide (CGRP), prostaglandins, bradykinin, adenosine, 5-hydroxytryptamine (5-HT), histamine, and reactive oxygen species (14,15). They cause airway smooth muscle contraction, mucous secretion, vasodilation, protein extravasation into the mucosa by increased vascular permeability, inflammatory cell activation, and airway sensor stimulation. Interestingly, intravenous injection of LPS or local injection of LPS into the sensory fields activates the sensors within a few seconds (16), suggesting that LPS may directly activate vagal afferents and trigger innate immune responses. Indeed, TLR4 mRNA and protein are expressed in sensory neurons and the nodose ganglion in rats (17). Since activation of airway sensors causes neurogenic inflammation, these sensors are part of the innate immune system for host defense, providing a fast immune response. Both pro- and anti-inflammatory cytokines are mobilized to provide a dual and bidirectional regulation.

Neurogenic inflammation is a non-specific mechanism and serves as an amplifier for inflammatory processes. Electrical stimulation of vagal efferents produces neurogenic inflammation by releasing neuropeptides from sensory endings (18), causing airway epithelial cells, mast cells, and macrophages to release inflammatory cytokines (19). These cytokines may induce airway hyper-responsiveness by enhancing neuropeptide expression in airway nerves (20). The neuropeptide further stimulates inflammatory cytokine release, forming a positive feedback loop to promote innate host defense.

Mediators from epithelium, endothelium, smooth muscle, and immune cells activate airway sensors by various pathways. Any particular pathway can be activated by many structurally different agents. An agent may activate a sensor by different cellular action via multiple mechanisms. In summary, a constellation of mediators is released during inflammation. Each alters inflammation and airway sensors either directly or indirectly. Redundancy produces additive or synergistic effects and ensures sensor activation. Sensory activation

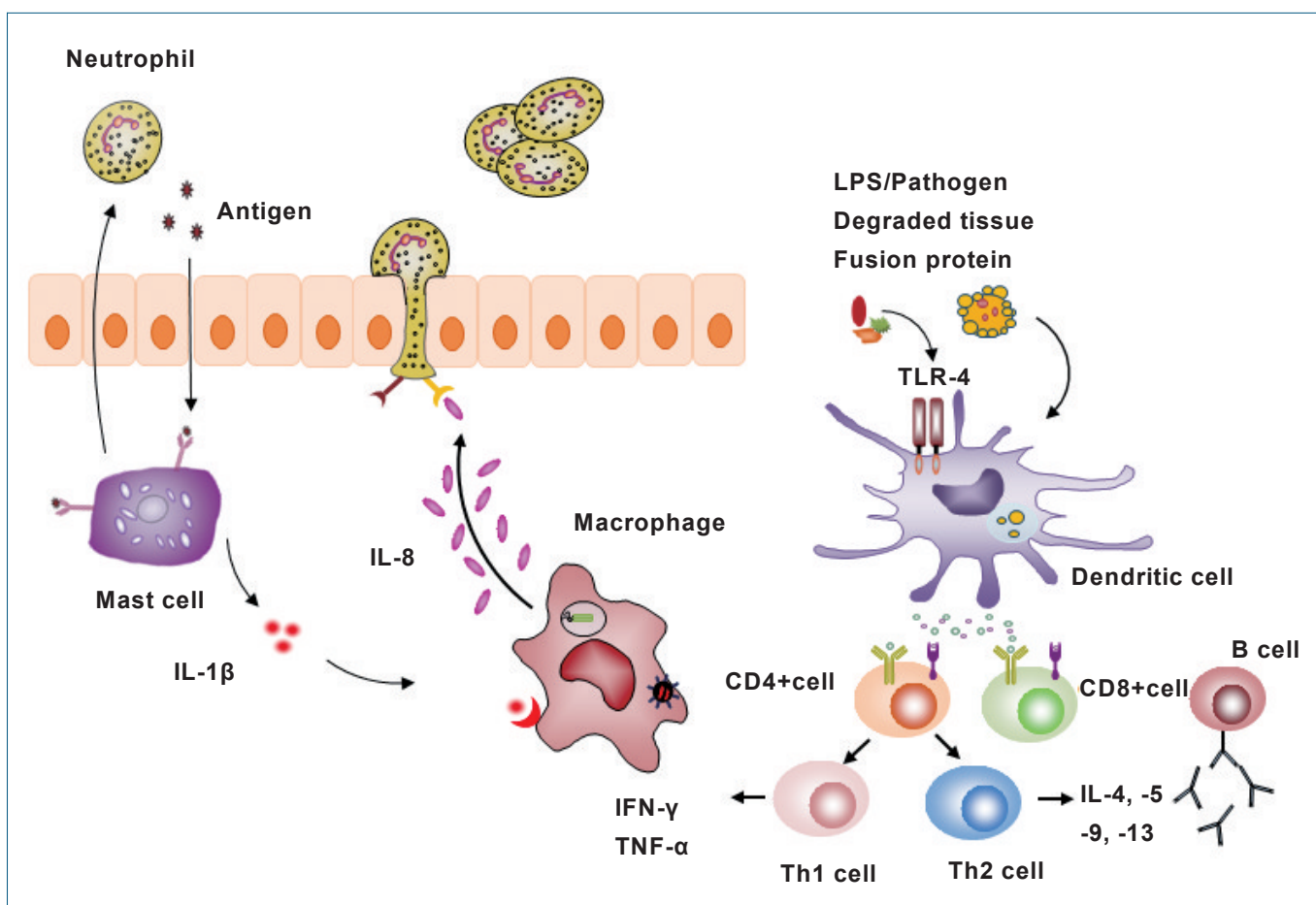


Figure 1. Summary of Immune Response.

TLR4 recognizes LPS, the fusion protein for respiratory syncytial virus, and endogenous tissue components degraded during the inflammatory response. Dendritic cells recognize pathogens and stimulate naive T cell proliferation, then release inflammatory mediators that regulate immune responses. Neutrophils are the first cells to be recruited to sites of infection or injury, and target at microorganisms and tumor cells. Lymphocytes include T cells (CD4+ and CD8+) and B cells. CD4+ T cells consist of Th1 and Th2. Th1 cells produce IFN- γ and TNF- α to drive cellular immunity to eliminate intracellular parasites, viruses and cancer cells. Th2 cells produce cytokines to stimulate humoral immunity to fight extracellular organisms.

may cause local and axon reflexes to initiate a positive feedback to amplify inflammation. In addition, each of the agents may stimulate release of other inflammatory mediators by paracrine effects, which cause secondary effects on cell populations. Secondary effects can trigger tertiary effects and so forth. Neurogenic inflammation and cell-cell interaction in the network are essential for inflammatory amplification. However, positive feedback system has to be counteracted by negative feedback to prevent self-destruction.

Regulation of Lung Inflammation

Inflammatory responses are highly regulated.

For example, activation of TLRs may provide negative feedback to suppress Th1- and Th2-mediated inflammation to prevent excessive lung inflammation (21). Cytokines, such as IL-10 (22) and TGF- β (23), produced by inflammatory cells may actually suppress inflammatory cytokine production and the inflammatory response. In addition, Type II epithelial cells in the lung can inhibit alveolar macrophages via TGF- β to limit potential immune-induced inflammation (24). Inflammation can also be regulated via neural immune interaction (25). Sensory neurons in the lung are activated during acute lung injury (26) by inflammatory cytokines and mediators, and TLR ligands (15). This activation may suppress

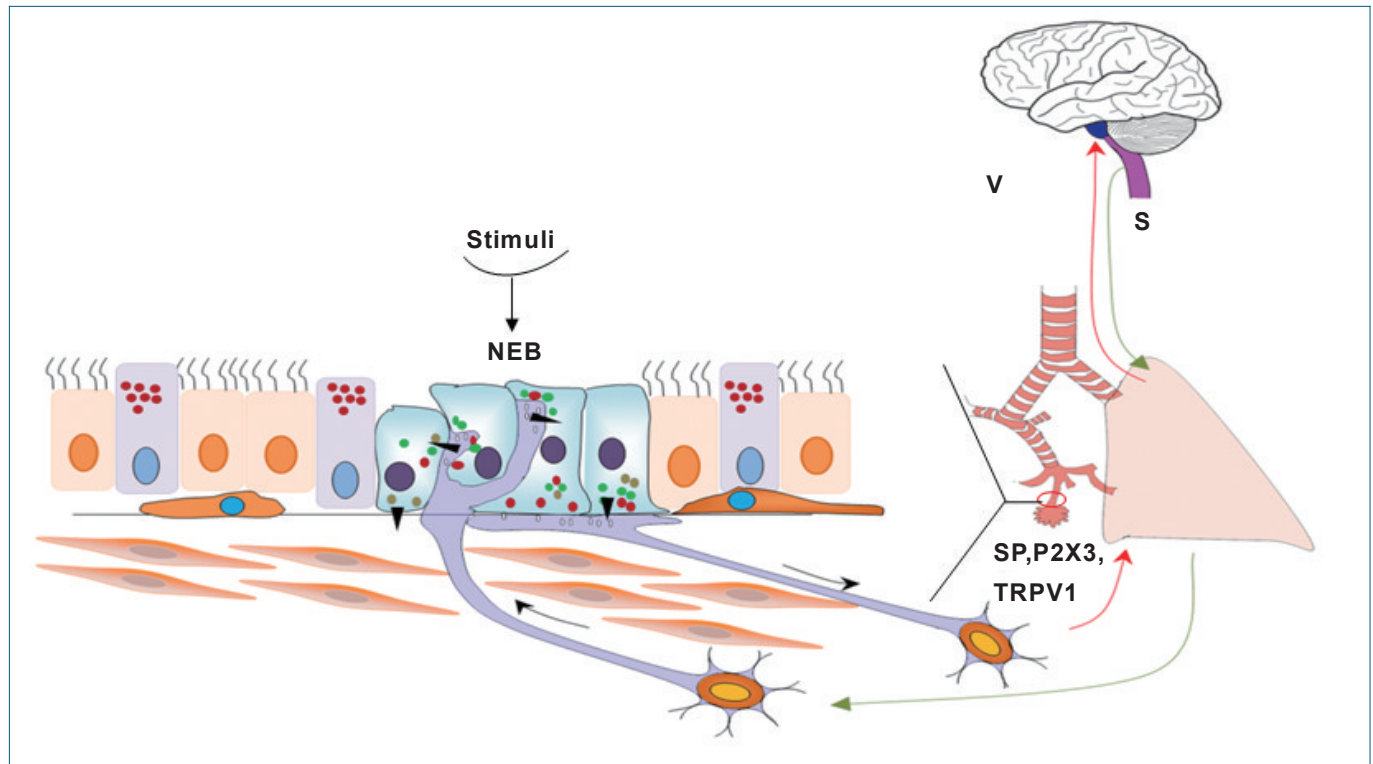


Figure 2. Schematic Presentation of Neuroepithelial Body (NEB) and its Innervation.

Afferent and efferent nerve fibers contact NEBs. These nerve fibers are immunoreactive with antibodies against SP, TRPV1, and purinergic receptors (P2X3). Vesicles are released from NEBs in response to stimuli and activate receptors in the afferent terminals. Efferent fibers may produce postsynaptic responses in NEBs (arrow). The NEB communicated with the CNS through vagal and sympathetic nerves. Many bioactive substances with growth factor and mitogenic properties contained in NEBs may play an important role in lung morphogenesis and remodeling.

production of pro-inflammatory cytokines (19) to contain inflammation via reflexes or induce neurogenic inflammation to intensify inflammation via release neuropeptides.

Potential Role of Neuroepithelial Bodies

Pulmonary neuroendocrine cells (PNECs) are extensively distributed in the airway mucosa. They can be solitary cells or aggregate to form neuroepithelial bodies (NEBs), which are connected to afferent and efferent nerves from varied sources (vagal, spinal, and parabronchial) (27). These nerve fibers are immunoreactive with antibodies against SP, Transient receptor potential vanilloid (TRPV1), and purinergic receptors (P2X3) (27). SP is associated with sensory afferents and may cause neurogenic airway inflammation (28). TRPV1 and P2X3 are known nociceptors for capsaicin and adenosine (14). Thus, NEBs may be connected with C-fiber re-

ceptor (CFRs), high threshold A-delta receptors (HTARs), or sympathetic sensory endings (28). The NEB has a strategic location and cellular machinery capable of both neural and humoral control of the local environment and communication with the CNS. PNECs and NEBs contain many bioactive substances with growth factor and mitogenic properties, such as bombesin/gastrin-releasing peptide (GRP), CGRP, and 5-HT (29). These substances play an important role in lung morphogenesis. NEBs are prominent in fetal and neonatal lungs and may promote lung development, a process much like tissue repair. NEBs have been proposed to function as oxygen sensors. Because they are capable of massive release of mediators, NEBs are excellent candidates to trigger allergic asthma attacks. NEBs may be involved in pulmonary hypertension, because they proliferate in pulmonary hypertensive patients and produce large quantities of 5-HT, a powerful pulmonary vasoconstrictor. In addi-

tion, NEBs may be closely related to pulmonary neuroendocrine tumors (30).

NEB secretory products, such as bombesin/GRP, may exert airway remodeling effects, including proliferation of fibroblasts, epithelial and smooth muscle cells (31). Tissue remodeling is an important step in chronic disorders, such as COPD, asthma, and pulmonary fibrosis. Bombesin induces alveolar myofibroblast proliferation and increases alveolar wall thickness (32). Significant hyperplasia of bombesin/GRP immunoreactive PNECs/NEBs has been reported in bronchopulmonary dysplasia, in which the airways epithelium is repeatedly injured. Intraperitoneal injection of bombesin into mice causes proliferation of interstitial myofibroblasts and increases thickness of alveolar septa. 5-HT stimulates collagen synthesis by fibroblasts (33). In addition, NEBs are thought to act as a type of stem cell and have been proposed to serve as niches for stem cells.

Following naphthalene-induced injury, airway epithelial cells regenerate from cells that reside in the NEB. Obviously, NEBs involve neuroendocrine interaction in response to lung injury.

Neuroendocrine Control of Immune System

The hypothalamus is an integrating center for the autonomic nervous system. Airway afferents terminate at the nucleus tractus solitarius (NTS) (34), and then project to neurons in the paraventricular nucleus (PVN), where corticotropin-releasing hormone (CRH) is synthesized and released. Intravenous injection of IL-1 β increases Fos expression in the hypothalamus, which can be blocked by interruption of ascending fibers from the NTS to PVN neurons. Electrical stimulation of the vagal afferents increases CRH mRNA in the hypothalamus and adrenocorticotropin (ACTH) and corticosterone in plasma (35). The hypothalamic-pituitary-target organ axis forms a circuit with the peripheral nervous system for immunoregulation. Neuropeptides in the HPA are powerful immunoregulators that exert their effects on lymphoid cells and CNS neurons, in addition to stimulating glucocorticoid production. The immune system signals inflammation in the neuroendocrine system through cytokines, such as IL-1 and TNF- α . Upon stimula-

tion, the PVN secretes CRH to the hypophysis. CRH then stimulates the anterior pituitary gland to release ACTH, which causes release of glucocorticoids from the adrenal glands. Glucocorticoids regulate gene expression and function in immune cells, suppressing expressions of cytokines, adhesion molecules, chemoattractants, and inflammatory mediators. They also influence immune cell trafficking, migration, maturation, and differentiation (36). Glucocorticoids shift the immune response from cellular immunity (Th1) to humoral immunity (Th2), and from a pro-inflammatory profile to an anti-inflammatory profile.

Sympathetic nerves innervate immune organs such as the thymus, spleen, and lymph nodes (1). Activation of the HPA axis causes glucocorticoid production, sympathetic stimulation and catecholamine release. Catecholamines inhibit pro-inflammatory cytokines (TNF- α and interferon- γ) but stimulate anti-inflammatory cytokines (IL-10 and TGF- β) (37). Stimulation of the vagus nerve exerts anti-inflammatory effects through acetylcholine (ACh) released from vagal efferents (19). ACh can act on nicotinic receptors to suppress TNF- α production in macrophages or on muscarinic receptors on alveolar macrophages to increase chemotactic activity in neutrophils, monocytes and eosinophils. IL-1 β and TNF- α stimulate airway sensors (15), forming a negative feedback. Electrical stimulation of vagal efferents during endotoxemia inhibits TNF- α synthesis in the liver and prevents endotoxemic shock (38) and use of nicotine to activate cholinergic anti-inflammatory pathways reduces mortality associated with endotoxemia. In humans, nicotine exposure attenuates the febrile response to intravenous injection of LPS and promotes an anti-inflammatory profile (increased blood IL-10 and cortisol levels) (39).

Conclusion

The lungs are essential for gas exchange, but are constantly exposed to pathogenic challenges. Through neuroimmune interaction, a forceful immune response (such as inflammation) is evoked to eliminate pathogens without extensive inflammation that alters lung function. Airway sensors may detect release of immune mediators to ampli-

fy immune responses via local mechanisms and initiate a systemic anti-inflammatory response through the CNS to contain inflammation. An intensified focal inflammation within an anti-inflammatory response is essential for lung homeostasis.

Declaration of Interests

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