

Neuroendocrine Crosstalk of Immunity

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A wide variety of diseases and disorders ranging from Alzheimer's and cardiovascular disease to cancer are associated with the cryptic nature of inflammation and the strength of immune responsiveness. Despite impressive progress in the field of immunology during the last century, the exact triggers and magnitude controllers that regulate the dynamics of immune functions and their regulatory networks are far from being completely understood. An emerging body of evidence lends strong support that immune system interacts with the nervous and endocrine systems and the three follow overlapping mechanisms of gene regulation, signaling, cell communication and supracellular organization. In fact, the central nervous system, peripheral nervous system, the endocrine system and the immune system together form an interactive cross-system network [1]. Such a cross-system interaction adds to the already complex and vast heterogeneity and plasticity of immune cells.

This brings to the fore a burning need to expose the mechanistic affinities and cross-signaling in biological systems. It is essential to unravel the underlying fundamental principles that govern the functional organization of such complex cellular systems. Recent technological progress offers a tremendous opportunity to undertake such an effort. Present day genomic and proteomic tools and the global profiling of cellular states in terms of gene and protein expression allow an unbiased reconstruction of the genetic and molecular networks and the regulatory cross-system signaling. Cells, molecules and the organs of the immune system provide a particularly useful model for applying such approaches.

One exquisite example is the thymus that simultaneously possesses nervous, endocrine and immune functions. A great deal of data indicates that hypothalamic-pituitary axis plays a critical role in the control of thymus physiology and function [2]. In addition to being the T cell development center, thymus functions as a sensor or 'rheostat', regulating immunological homeostasis in the organism [3]. Pioneering work of Selye in 1936 showed that various physiologic and pathologic stress stimuli led to adrenal enlargement and the involution of thymus [4]. Studies have also shown that progressive growth of tumor causes thymic atrophy [5-6, 3], which could be reversed with the exogenous administration of thymic hormones [7-8]. These observations suggest a role of thymic endocrine function in the control of tumor growth. Thymocyte-intrinsic genetic factors also influence the selection of a tumor-reactive TCR [9] and tumor resistance [10]. A link between hormones and cancer is well known since 1896 when George Beatson discovered that surgical removal of the ovaries slows the growth of breast tumors. Thus, it would be helpful to dissect the connectivity of thymic and other endocrine mechanisms in relation to tumor growth and rejection. Tumor cells also show chemotaxis towards neurotransmitters such as dopamine and catecholamine [11-12]. There are signs of direct interactions of tumor cells with nerve cells forming a neuro-neoplastic synapse [13]. Tumors may also initiate their own innervation by the release of neurotrophic factors including the nerve growth factor and the brain-derived growth factor. Further studies in

these directions will provide insights for novel strategies to fight the pathophysiology of cancer.

Chemokines and their receptors are molecular entities common to the immune and nervous systems. They present a prime example of a bidirectional communication system [14]. Originally, chemokines were found to be produced by the immune cells and thought to be completely devoted to assisting the development and function of the immune system. However, we now know that they are also produced by cells of the nervous system, such as microglia, astrocytes and neurons, regulating various aspects of the development of neural cortex and its function [15].

Immune cells are also capable of secreting neurotransmitters as well as expressing their receptors [16]. To fight pathogens, phagocytic macrophages – the front line defence cells – are transformed into pro-inflammatory cells that secrete catecholamines. Along with cytokines, catecholamines contribute to regulating the intensity of the immune response at the site of acute infection [17]. Recently, alternatively activated macrophages in the IL-4/IL-13-rich anti-inflammatory form have been shown to produce catecholamine and regulate the physiological task of thermogenesis [18], not previously ascribed to the immune system. Similarly, acetylcholine-synthesizing T cells have been found to relay neural signals in a vagus nerve circuit to inhibit TNF- α production in the spleen by a mechanism requiring acetylcholine signaling through the $\alpha 7$ nicotinic acetylcholine receptor expressed on cytokine-producing macrophages [19]. This reveals a new role of T cells in the production of neurotransmitter acetylcholine required to control innate immune responses.

Thus, immune cells are prone to coordination by evolutionarily ancient neural circuits that operate reflexively [20]. The nervous system is hardwired to monitor the presence of cytokines and molecular products of inflammation. Patients with rheumatoid arthritis who receive anti-TNF therapy develop significant changes in brain activity before resolution of inflammation in the affected joints [21]. Studies have shown that the fever-causing activity of the pyrogenic cytokine IL-1 requires an intact vagus nerve. Administration of IL-1 into the abdomen fails to produce fever if the vagus nerve had been cut [22]. Glomus cells, specialized to detect pH and other chemical changes in the intestinal milieu, express IL-1 receptors [23]. IL-1 binding to glomus cells may stimulate the release of dopamine, which may then trigger afferent signaling in the vagus nerve. Consequently, cytokines

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activate afferent signals in the vagus nerve, which culminate in an efferent arc to inhibit further cytokine production. The afferent arc of the neural reflex senses injury and infection by somehow “sensing” antigen and inflammatory cytokines [20, 24-25]. This activates efferent neural circuits, including the cholinergic pathway, that modulate innate inflammatory responses. This neural inflammatory reflex may provide the acute compensatory input needed to adjust the magnitude of the functional cooperativity observed among various immune cells [26,27]. Alternatively, one may be tempted to consider that the immune system may be a specialized relay system to transmit information in real time to the nervous system about the tissue response to injury and infection.

The immune and neuroendocrine systems have thus developed an intricate network of cellular specializations and communications, which allow them to sentinel the environment, sense specific changes in physical or chemical parameters and produce responses that are appropriate for and specific to the inducing signals. It would be relevant to investigate if there are any cross-system regulatory cells that have evolved and that employ common signaling mechanisms to control immuno-neuro-endocrine functional cooperativity. It is also important to understand how the complex array of ‘sensory’ information received by neurons, endocrine cells or lymphocytes converges to produce specific ‘motor’ responses, such as muscle contraction or lymphocyte activation. Methods adapted from neuroendocrinology and immunology and the powerful tools of systems biology will provide crucial leads in these integrative studies aimed at exploring neuroendocrine cross-talk of immunity.

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