Don't forget to have a "second brain"

The gastrointestinal (GI) tract is innervated by intrinsic neurons belonging to the enteric nervous system and by axons of extrinsic sympathetic, parasympathetic, and visceral afferent neurons. The intrinsic innervation of the GI tract is composed of two major ganglionated plexuses: the myenteric and the submucosal plexuses (Figure 1). The myenteric plexus—the outer of the two—is formed by a network of neurons and glial cells located between the muscle layers of the GI tract. It is primarily involved in the initiation and control of smooth muscle motor patterns for peristaltic movements. The submucosal plexus is located in the submucosa between the muscle layers and the mucosa. It coordinates such reflexes as secretion and absorption as well as motor control of smooth muscles. The mucosal layer also contains delicate nerve and glial networks that collectively form the mucosal plexus that extends to the lamina propria mucosae beneath the epithelial lining. In addition to the typical afferent vagal neurons that convey information regarding the gut condition to the central nervous system, the intestine, uniquely, has other afferent neurons whose cell bodies and processes are within the enteric plexuses and do not project to the central nervous system, retaining the information in the gut and contributing to an independent control system. Moreover, the mucosal plexus is in close contact with neuroendocrine cells that are sparse within the epithelial monolayer and release their transmitters in response to various stimuli. The released transmitters act both in a paracrine manner on neighboring epithelial cells and systemically, by activating specific receptors within the enteric nervous system.

Besides controlling the absorption, secretion, and movements of the gut, the nervous system plays a role in modulating the immune function.[1] Indirect evidence for this interaction is offered by the association between stress and gut inflammation. Stress can influence several functions of the mucosal barrier, including permeability, mucin secretion, IgA secretion, and microbial composition.[2] The nervous system shares several features with the immune system and is linked to it by close interactions. The nervous system reacts very rapidly to environmental changes by releasing neurotransmitters and neuropeptides that, like immune mediators, often bind to G-protein-coupled receptors, initiating the same secondary signaling cascades. Further, released hormones and neuropeptides can modulate the function of immune cells. In the gut, the enteric nervous system, which has a nerve network reaching the lamina propria and is in close contact with epithelial and neuroendocrine cells, is ideally located to modulate the immediate nonspecific inflammatory response and to collaborate with the immune system for a joined response to pathogens. Enteric glial cells seem to regulate intestinal barrier function by releasing S-nitrosoglutathione, which upregulates the expression of tight junction proteins in epithelial cells.[3] Adult transgenic mice in which enteric glial cells are ablated develop fulminant jejunoileitis as a result of increased intestinal permeability.[3] The nervous system can thus participate in controlling intestinal immune homeostasis via the coordinated action of neuropeptides and enteric glial cells.

The mucosal immune system can be modulated at the level of the central, autonomic, peripheral, and enteric nervous systems.[1] The peripheral and enteric nervous systems modulate the response locally, either through the release of neuropeptides such as corticotropin-releasing hormone, calcitonin gene–related peptide, substance P, and anti-melanocyte-stimulating hormone, which amplify the inflammatory response, or through the release of vasoactive intestinal peptide, which has been reported to inhibit inflammation. Substance P also

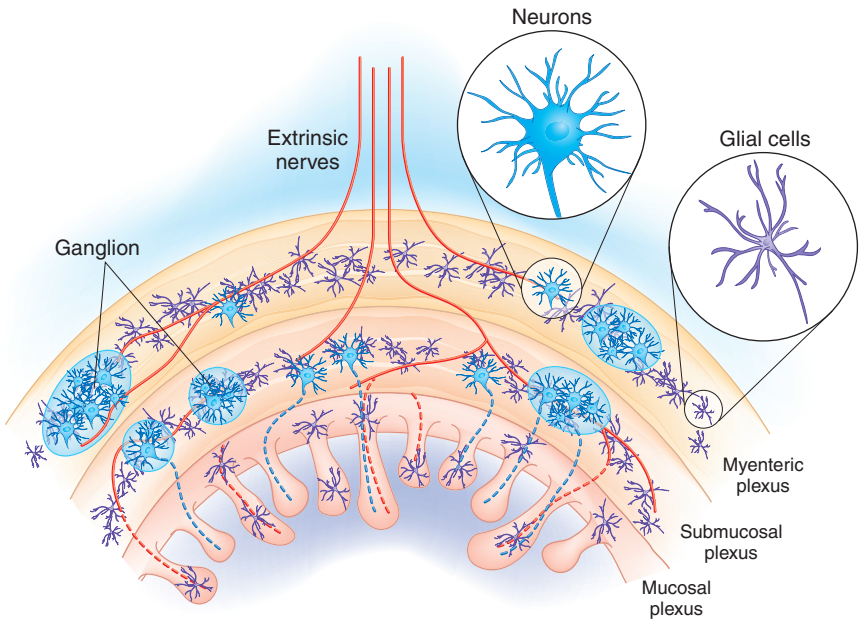

Figure 1 Schematized view of the enteric nervous system. The system is composed of two major ganglionated plexuses—the myenteric and submucosal plexuses—which form a network of neurons and glial cells. The mucosal layer also contains delicate nerve and glial networks that form the mucosal plexus, which extends to the lamina propria mucosae beneath the epithelial lining.

triggers the release of histamine and serotonin via degranulation of mast cells or neuroendocrine cells, further amplifying the inflammatory response.

The autonomic nervous system, including the sympathetic and parasympathetic nervous systems, inhibits the inflammatory response regionally via the innervation of lymphoid organs. Noradrenaline, released by the sympathetic nervous system, inhibits the production of inflammatory cytokines by dendritic cells and macrophages, as well as the chemotactic response of dendritic cells to CCR7 ligands. Sympathetic neurons release neuropeptide Y (NPY), an inhibitor of natural killer cell activation. Sympathetic neurons also release noradrenaline and NPY in response to inflammatory mediators such as interleukin-1 and tumor necrosis factor; this may produce negative feedback that switches off the immune response.

The parasympathetic nervous system releases acetylcholine, which can bind to nicotinic or muscarinic receptors. Nicotine, an agonist for the nicotinic acetylcholine receptor, has been shown to dampen macrophage cytokine production. Interestingly, although smoking has detrimental effects on the clinical course of Crohn's disease (CD), it seems to be somewhat beneficial in ulcerative colitis.[4] The central nervous system controls inflammation systemically via the release of hormones from the adrenal glands connected to the hypothalamic–pituitary–adrenal axis. Glucocorticoids released by the adrenal glands are strong inhibitors of immune cells; they can suppress the proliferation and maturation of all immune cells and drive the switch from a Th1 type of response to a Th2 type.[5]

Because the immune and nervous systems closely interact, it is likely that inflammatory diseases have a nervous as well as an immune component. An understanding of these interactions could help in the development of new therapeutic strategies. Some investigators have described alterations in the enteric nervous system in the ileum or colon of CD patients, and the presence of myenteric plexitis in the proximal margins of an ileocolonic resection is prognostic of early endoscopic recurrence of CD.[6] Mast cells in the GI tract act as mediators of the enteric nerve response. Activated mast cells release a wide range of neurotransmitters and other proinflammatory mediators. Deregulated mast-cell stimulation could lead to unwanted inflammation. Stress has been strongly correlated with mast-cell degranulation and insurgence of inflammatory bowel disease.[7]

Nearly 95% of an individual's serotonin is released in the gut. Mast cells and neuroendocrine cells release serotonin, which is fundamental for the secretory and motile activities of the gut but, depending on the receptor to which it binds, has disparate functions. Serotonin receptors are also expressed on immune cells and contribute to control of the immune response. The use of serotonin receptor inhibitors is common in the treatment of inflammatory bowel syndrome. In mice, deregulated parasympathetic function mimicking stress conditions has been associated with inflammatory bowel disease.[8]

In conclusion, the connection between the enteric nervous system and the immune system may play a fundamental role in controlling homeostasis of the gut. Deregulation at one or both levels can lead to gastrointestinal disorders related to food and/or bacteria tolerance induction, for example, obesity, anorexia, bulimia, inflammatory bowel disease, celiac disease, and inflammatory bowel syndrome. Hence, mucosal immunologists should not undervalue the contribution of the nervous system to both the basic and the more complex duties of our immune system.

Maria Rescigno, Associate Editor

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