CellPress

Review

Enteric Neuronal Regulation of Intestinal Inflammation

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Recent research has highlighted the importance of the two-way interaction between the nervous and immune systems. This interaction is particularly important in the bowel because of the unique properties of this organ. The lumen of the gut is lined by a very large but remarkably thin surface that separates the body from the enteric microbiome. Immune defenses against microbial invasion are thus well developed and neuroimmune interactions are important in regulating and integrating these defenses. Important concepts in the phylogeny of neuroimmunity, enteric neuronal and glial regulation of immunity, changes that occur in the enteric nervous system during inflammation, the fundamental role of serotonin (5-HT) in enteric neuroimmune mechanisms, and future perspectives are reviewed.

Inflammation and Neuroimmunity in the Bowel

Inflammatory bowel diseases (IBD) are chronic intestinal inflammatory conditions that affect approximately one million individuals in the USA [1]. The prevalence of IBD is increasing nationally and internationally. Despite significant advances in understanding the pathophysiology of IBD, its pathogenesis remains unknown and IBD continues to cause a great deal of morbidity.

The intestine is essential for life. It is the site of nutrient ingestion and also of where these nutrients, many of which are macromolecules, are digested into small molecules that the gut can absorb. Within the bowel, moreover, there is a resident microbiome, which is a net plus in value [2] but also a danger that must be restricted to the enteric lumen and prevented from invading [3]. The intestinal lumen is external to the body. The thin barrier that separates the lumen from the internal milieu of the body, which in most regions of the gut is only one cell thick, allows essential nutrients to be absorbed but prevents the absorption of toxins and invasion by commensal and pathogenic organisms. Microbial translocation across the intestinal lining triggers inflammation, which helps to control infection [3], although inflammation is also capable of inflicting a great deal of collateral damage to the intestinal wall. Managing digestion, absorption, and protection from microbial invasion is complicated and requires considerable organization, integration, and rapid direction of resources to sites where they are most needed. These resources include secretion of enzymes, ions, mucous, and water, the complex motor patterns that the intestinal smooth muscle generates, and a variety of hormones. Signaling through the nervous system evolved to accomplish organization, integration, and rapid direction of resources. In the bowel, the details of the management of these functions have been delegated to the enteric nervous system (ENS), which can, uniquely, function independently of CNS control [4]. The brain, of course, powerfully influences the ENS through sympathetic and parasympathetic nerves, but the bowel and its microbial content, possibly through the ENS, also reciprocally affect the brain. The intestinal microbiota can influence satiety, metabolism, and even mood [2,5–7]; moreover, electrical stimulation of the vagus nerves, which mimics gut–brain signaling, improves memory [8] and has been employed to treat depression [9]. One of the most important functions of the intestinal innervation, however, is to modulate intestinal inflammation [10].

Trends

Despite recent advances, the pathogenesis of inflammatory bowel disease (IBD) remains unknown.

Neuroimmune interactions contribute to the pathophysiology of intestinal inflammation, and enteric neuronal dysfunction during IBD causes considerable morbidity.

Neurotransmitters, neuromodulators, and cytokines participate in neuroimmune signaling, which is often bidirectional and may involve enteric glia.

5-HT is a paracrine, endocrine, and neurocrine signaling molecule present in the nervous system and/or mucosal epithelium of the gut of all vertebrates.

Mucosal 5-HT activates innate and adaptive immune responses, which protect against microbial invasion, but may also damage enteric neurons. Enteric neuronal 5-HT is neuroprotective, stimulates neurogenesis, and is anti-inflammatory. Pharmacological alteration of serotonergic mechanisms may be therapeutically beneficial in IBD.

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 http://dx.doi.org/10.1016/j.tins.2016.06.007

The roles of individual neurotransmitters/neuromodulators in intestinal inflammation have recently been reviewed [11] and those of tachykinins, in particular, have been extensively summarized [12]. Instead of a comprehensive examination of the pro- and anti-inflammatory activities of every transmitter in the gut, we focus on the phylogeny of neuronal regulation of intestinal inflammation, bidirectional neuroimmune interactions in the regulation and consequences of intestinal inflammation, as well as the central roles that serotonin plays as a signaling molecule in triggering, enhancing, and countering inflammation.

Phylogeny of Neuroimmune Interactions

Survival demands that every animal distinguishes between the nutrients it ingests from invaders and toxins. This ability is so fundamental that it probably arose early in evolution. Defenses against invasion include innate immune mechanisms such as the secretion of cytokines and phagocytic activity. These mechanisms appear to have preceded the evolution of adaptive immunity, which added memory, sophistication, and regulation to the layers of defense. Secreted signaling molecules function in intercellular communication, a vital component of adaptive immunity. Many of these molecules are also found in primitive organisms and thus have been retained in evolution [13]. Some molecules have been re-purposed as additional cells and systems joined the defensive community and reactions increased in specificity and speed. In the mammalian bowel, endocrine and neurocrine signaling helps to coordinate and regulate innate and adaptive immune mechanisms of defense. Macrophages and their dendritic cell relatives have now transcended their primitive phagocytic ancestors and become nexi of intercellular communication. These cells interact with the lymphocytic mediators of adaptive immune responses, and both macrophages and lymphocytes respond to hormonal and neuronal regulation [13]. Neurotransmission evolved from phylogenetically older methods of signaling. Hormones and paracrine messengers are employed for intercellular signaling in animals, such as sponges, that lack a nervous system. Environmental stimuli cause specialized cells in the epidermis and the intestinal lining of primitive multicellular organisms to secrete signaling metabolites. The hormones and metabolites that are used for signaling in animals without a nervous system diffuse throughout the organism to be recognized by target cells with appropriate receptors. Ultimately, endocrine cells and neurons separated from the epithelium but both continued to secrete signaling molecules. Endocrine cells secrete into the circulation while neurons project to individual target cells or even, at synapses, to regions of target cells [14]. Early in evolution, multicellularity led to the development of paracrine signaling, which involves the secretion of diffusible molecules that act in the neighborhood of the secreting cell. Nevertheless, even paracrine signaling enables multiple cells to cooperate for the common defense of the organism. Later, the acquisition of endocrine signaling enabled distant cells to be recruited, with specificity achieved through molecular recognition in a ligand–receptor relationship. Eventually, the exquisite anatomical specificity and speed of neuronal conduction were added to the ligand–receptor relationship to vastly enhance the adaptability and integration of responses.

The evolution of the defensive response is reflected in the mechanisms that are operative in the mammalian bowel. Paracrine, endocrine, and neurocrine signaling are all utilized; early mechanisms thus were not supplanted as newer ones evolved. The newer mechanisms have been added to, and may modulate or regulate the primitive original responses that have been retained as effectors of inflammation. Sponges, for example, contain phagocytic amoeboid cells (archeocytes) that are pluripotent stem cells [15]. These cells contribute not only to nutrient uptake but also to defense of the whole organism. Some of these primitive phagocytes secrete soluble signaling molecules, including cytokines and nitric oxide (NO), that are retained as endocrine and/or neurocrine messengers in higher animals.

The mammalian gut faces a stiff microbial challenge. It must contend with bombardment by a vast number of potential pathogenic bacteria, fungi, and viruses, while simultaneously