Neuro-immunomodulation during intestinal development and in vivo homeostasis

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Abstract
Organ function and homeostasis require interaction between the nervous system and the immune system. Evidence suggests that intestinal neurons and intestinal immune cells share a common regulatory mechanism and that they can coordinate their response to development challenges and environmental invasion. These findings reveal a systemic interaction between the physiology and the openness of the new viewpoint of therapeutic design, with under estimation of the neuro-immunological commonality. Here we highlight the results of studies addressing the importance of neuroimmune cell units (NICUs) in intestinal development, homeostasis and disease.

Keywords: Homeostasis, Neuro-immunomodulation, intestine, development

1. Introduction
The intestine is necessary for maintaining homeostasis in organisms: it is a site for food digestion and nutrient uptake, contributing to water and electrolyte balance and serving as sensory and endocrine organs. When the bowel performs these functions, the intestinal wall closely contacts the lumen of the inflatable and beneficial microbial community, ensuring effective digestion, xenobiotic degradation and protection against pathogens. Establish effective for anatomical and functional disorders of symbiotic microbes and pathogens, the intestinal wall includes an unparalleled complexity of the cellular network, including nerves and immune systems that continually monitor and respond to challenges from potentially harmful intestinal ecosystems. It is becoming clear that the normal gastrointestinal (GI) function depends on the highly coordinated response of the resident neurons and the immune cell population [1]. In addition, the emerging evidence suggests multiple the neural regulatory axis functions in immune cells, while the enteric nervous system (ENS) senses microbial prompts and coordinates immune responses. As a beneficial consequence of this progress, the conceptual and experimental barriers between traditionally different fields of study are coming down, which promise to unravel the complex neuro-immune interactions at the core of GI physiology and disease at a faster rate [1,2]. Emerging technological revolutions that have redefined this interaction in the peripheral nervous system and the central nervous system (CNS) have been reviewed elsewhere, [3-7]. Here we highlight the specific paradigm of neuroimmuno conjugation in the intestine and propose the concept of neuro-immune cellular units (NICUs) at the heart of the intestinal balance and defense. We also review neuro-immunology, in this case, Gut development, and in vivo homeostasis, and to explore the possibility that the coexistence of ENS and the gut immune system may be beneficial for their productive interactions as they progress.

1.1 Neurons and lymphoid organs occur in the world of labor
The intestinal wall consists of two branches of the autonomic nervous system (sympathetic and parasympathetic), while information from the gastrointestinal tract is transmitted to the CNS through afferent fibers originating from the sensory neurons in the nodules and dorsal root ganglia. This extrinsic innervation of the intestine is critical for the integration of gastrointestinal and systemic physiological responses. In addition to containing exogenous nerves, the intestinal wall contains large numbers of internal neurons (human 1 x 10^8) and 3 to 5 times the glial cells that make up the ENS.
These cell lines are organized into interconnected ganglion networks distributed in the outer myometrium and the inner submucosal plexus. Glial cells are closely related to neurons (located in the intestinal ganglion), but they are also found in the extra ganglion space including the mucosal lamina propria, where they form a diffusion network that spreads from the bottom of the crypt to villi [9-15]. Most of the enteric neurons and glial cells originate from neural crest-derived progenitor cells [16-20] that invade the foregut during embryogenesis, migrate the rostro-tail to colonize the entire length of the GI tract, and undergo extended neurogenesis and glial generation programs, which were only weaned in [13-24] (Fig. 1). The development of functional ENS depends on the synergistic effects of extracellular cues, including signaling through growth factors and retinoic acid (RA), as well as discrete genetic traits established at the time of occurrence of ENS tissue [21-25]. Notably, early ENS progenitors express the transcription factors SOX10, ASCL1 and PHOX2B, which act synergistically to drive the expression of the neurotrophic receptor and the neuromotor RET, the glial cell line-derived neurotrophic factor (GDNF) and Other members of the GDNF family ligand (GFL), and controls the ENS organization to occur in multiple steps [21] (Fig. 1).

RET is also a key regulator of intestinal lymph node (PP) development [26-27]. Intestinal secondary lymphoid organs, including the development of mesenteric lymph nodes and PP, occur during pregnancy, while tertiary lymphoid structures, such as crypts and isolated lymphoid follicles, respond to environmental signals after birth [28-29]. The lumen side of the PP is covered by a follicular-related epithelium, which has a high density of M cells, which serves as frontline-30 for antigen sampling and uptake. In addition, PP is conducive to B-cell antibody into a secretary type. The only immunoglobulin A isoform-31 that contributes to mucosal immunity, PP development depends on the lymphoid tissue promoter (LTin) [26-27] and lymphoid tissue induced (LTi) cells [29-32], the latter belongs to the larger congenital lymphocyte (ILC) family [33]. Both cell types are derived from fetal liver progenitor cells and colonized through the embryonic day 12.5 of the intestine [27]. The initial formation of intestinal lymphoid tissue depends on adhesion-mediated LTin cell blockade, which initiates immobilization of mesenchymal [26-28]. At this stage, LTin cells express RET, a molecule other than as a host.

The regulator of ENS development is also critical for PP formation in [26-27] (Fig. 1). Completely complemented LTi cells are required for subsequent stages and completion of PP development, depending on lymphotoxin beta and chemokines [29-34] (Fig. 1). Fetal LTi cell development depends on complex genetic pathways [35-39], but LTi cells are also affected by maternal dietary retinoic acid, which controls the transcription factor RORγt and predisposes progeny to immune health. Interestingly, RA can be provided by neurons enriched by LTi cells adjacent to lymphoid primordia to enhance proliferation of ENS precursor cells and promote neuronal differentiation. Therefore, in addition to their establishment, the cell and tissue - specific developmental processes, ENS and PPs, depend on the common principal axis of the signal for their tissue to occur.

**Fig 1:** Common regulatory mechanisms of Neuronal and Lymphoid organogenesis in gut. a: Neural crest-derived progenitor cells invade the foregut during embryogenesis and migrates rostro-caudally to colonize the full length of the intestine, producing intestinal neurons and glial cells. b: PPs development following a multi-step process of interaction of immune cells and stromal cells. RET was expressed in LTin cells near the stromal cells (step 1). [17]

**1.2 Phylogenic circumstances**

There is ample evidence that neuroregulatory molecules are expressed by intestinal immune cells and immunological pathways Acts in intestinal neurons. But why does the two systems establish such a close functional relationship? The answer to this question may be given by evolutionary considerations [9-23]. Throughout the evolutionary process, multicellular organisms produce physical barriers and innate defense mechanisms that constitute the first line of defense against environmental insults. However, the advent of sophisticated neural and immune cell networks allows animals to integrate multiple new stimuli while recalling early encounters to ensure that memory responses (at cellular and behavioral levels) are more effective in addressing environmental challenges. Discovery of Functional NICU in CNS and Peripheral Nervous System Support the idea of the interconnected evolutionary pathway of nerves Systems, and the immune system [1-23], but the cellular and molecular basis of the neuro-immune interaction has only just begun to emerge. In progress in this area, recognition of the CNS
lymphatics will drain the brain parenchyma into deep cervical lymph nodes [44] providing anatomic links between behavioral features and the immune system. In addition, some molecular mediators of CNS-immune system communication are being identified. For example, single-cell transcriptome analysis and injury models suggest that interferon-gamma signaling may control the in vivo homeostasis of neural stem cells in the adult brain. In addition, interferon-gamma has been suggested as a mediator of the effect of meningial immunity on brain function, further supporting the evolutionary link between the anti-pathogen immune response and social behavior.

Evolutionary neuro-immunological molecular traits can be exerted on common ancestor precursor cells or independent ancestors by using different characteristics of the common genetic strategy. The neurotrophic receptor RET is an example that is important not only for enteric neurogenesis but also for the development of critical subsets of immune cells. [1-51]. Although the RET signal in the enteric neurons is cis-specific after binding of GFL to the co-receptor GFRe1-GFRe4 [52-53], immune cells transact to multiple GFL responses [26-54] (Fig. 1). Thus, the tissue-specific wiring of RET signaling and the availability of RET ligands may determine different spatial and temporal responses of neuronal and immune cells to entero-RET activation. Interestingly, cis-activation of RET is also described as intestinal neuron [56] in zebrafish, suggesting that this signal axis may have evolved earlier in vertebrate evolution. However, it remains unclear whether the intrinsic RET signals of the immune cells also operate in the bony fish or whether they are restricted to the mammal.

Common neuronal and immunoregulatory mechanisms have also been described in the earliest neuronal and hematopoietic progenitor cells. Resting hematopoietic stem cells (HSCs) produce immune cells of all lineages, while the neural crests of the neuroectodermal progenitor cells produce all the intestinal neurons and glia. Significantly, the two progenitor cell types rely on the survival signal provided by activation of RET51, [56-57] induced by neurotrophins. RET ablation resulted in impaired survival and lack of response and potential for reconstitution of HSCs51, whereas Ret-deficient neuroectodermal progenitor cells developed apoptosis at an early, critical stage of ENS death [48-58]. Interestingly, RET signaling induces expression of genes that encode ant apoptotic Bcl-2 family members in immune progenitor and neuronal progenitor cells, whereas in Ret, Bcl2I1 (which codes for Bcl-xL family members of Bcl-xL) of the hematopoietic or neuroectodermal progenitor cells effectively restore their function [51-57]. Further evidence of the role of neuroactive substances in the regulation of HSC is provided by a study of the niche of HSC in bone marrow. For example, catecholamine’s derived from the autonomic nervous system mobilize HSC [59- 60] by upregulating the expression of the chemokine CXCL12 in mesenchymal stem cells, and this axis is further controlled by brain-based circadian rhythms [61-62]. In general, new evidence for functional neuro-immunological commonality suggests that the nervous and immune systems have evolved to work in a coordinated manner to promote tissue homeostasis and defense.

1.3 Neurons and immune modules of postnatal maturation

Although the presence of secondary lymphoid organs in the intestine occurs before birth, their size and the formation of germinal centers of B cells depend on the colonization of lymphocytes and neonatal intestinal tracts produced by microbes. Colonization of the intestinal tract of immune cells by some groups follows the genetic programming and developmental conditioning steps, while other development and maturation requires additional environmental signals from the postnatal tissue environment. For example, [gamma] [delta] T cells develop and colonize mucosal sites in a stepwise fashion that begins during fetal life and extends through postnatal [63]. Similarly, CD8 [alpha] [alpha] + natural intraepithelial lymphocytes, certain types of ILC and helper cells. The T-cell subsets are initialized to migrate to the gut after birth [13-65]. Finally, recruitment of induced intraepithelial lymphocytes and regulatory T cells is closely related to bacterial colonization Intestinal [64-68].
Alternatively, the microbial product indirectly modulates glial cell development and function by modulating immune cell activity. In support of this view, muscle macrophages located near the myenteric plexus are activated by microorganisms to produce cytokine BMP-2 which in turn regulates intestinal neuronal activity [96]. In addition, the activation of the sympathetic ganglion after intestinal bacterial infection modulates the protective function of adjacent macrophages to the tissue [97], whereas the activation of glial cells of microbial products drives ILC3s to produce interleukin-22 (IL-22). The key regulators of intestinal gyrus [54]. In conclusion, although intestinal lymphoid organogenesis and ENS tissue development occur predominantly in the womb, an important window of opportunity for postnatal intrinsic factors and extrinsic factors shaping intestinal function and organism homeostasis. Microbial colonization and dietary factors are most certainly a key regulator of maturation and interaction between the nervous system and the intestinal immune system.

1.4 Intestinal Health and Neuroimmunosensing in Diseases
ENS myenteric plexus contains a large number of macrophages and mast cells [98] and these immune subpopulations by nerve control. The effective signal from the vagus nerve has an anti-inflammatory effect by inhibiting macrophage activity [99-101]. In addition, the data indicate that the intestinal neuron-macrophage axis is critical for intestinal physiology and defense [96-99]. Figure 2. Thus, muscle neuron activity and bowel motility are controlled by macrophage-derived BMP-2 responsive microbial signal [96]. Interestingly, macrophages were also shown to be cues regulated by neuronal origin in the myenteric plexus [96-99]. Thus, intestinal microbial colonization induces the expression of neurons of growth factor CSF-1, which activates CSF-1 receptors in nearby macrophages [96]. The interaction of neuronal-macrophage interactions occurs in the activation of sympathetic ganglia. In the context of bacterial infection, macrophages in myenteric plexus were regulated by the signal pathway of norepinephrine-beta2-adrenoceptor [97] (Fig. 2).

The activation of norepinephrine to macrophages induces tissue protective markers [97], which may be relevant in the context of intestinal lesions such as chronic inflammation, infection and allergies. Furthermore, neuronal-mast cell interactions in the submucosal and myenteric plexuses have also been described [102,104]. Mast cells regulate neuronal and immune cell activity through tryptase expression and the release of histamine, serotonin, or tumor necrosis factor [102]. In turn, mast cells may respond to neuronal-derived factors such as substance P and corticotropin releasing factor (CRH) and immune signals (e.g., immunoglobulin E) [102], indicating that the cell population constitutes the regulatory center of the enteric nervous system - Immune System Communications.

Intestinal glial cells form a dense network around the crypts and are present throughout the mucosa [105,106]. Surprisingly, although the intestinal lamina propria contains a large number of lymphocyte subsets [107] and glial cells, as well as many neurite processes, little is known about trigeminal neuronal glial cell immune cell interactions. However, studies have demonstrated that maturation of glial cell networks, which express characteristic glial markers such as SOX10, GFAP and S100 [beta1], depend on intact complement 13 (Fig. 3) of the microbial population. The effect of microbial products on intestinal glial cells may be direct, through activation of TLRs [96], [92-95], leading to an increase in S100β and inducible nitric oxide synthase (iNOS) expression, depending on the transcription factor NF-kB108. Consistent with this idea, patients with ulcerative colitis and/or celiac disease are characterized by altered iNOS activity induced by S100 [beta1] [109-110], and abnormal regulation of iNOS activity may alter the suitability of the intestinal barrier. Intestinal glial cells from patients with Crohn’s disease have also been described [105,106].

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1.5 Future Challenges and considerations

The forces of change in new technologies have made significant progress in understanding organism physiology. In particular, effective gene targeting strategies, single-cell assays, high-throughput sequencing, and full-body imaging have catalyzed a large number of progression to explain the immune interactions of the intestinal tract. However, as in the case of scientific endeavors, current success is almost immediately a stepping stone to future problems. One such challenge is to understand the unknown anatomical units of the nervous system-immune system interactions in the intestine and the role they play in GI physiology. The lamina propria is colonized by a group of adaptive and congenital lymphocytes and is rich in glial networks. While this immediately provides a framework for efficient communication between the two systems, high resolution anatomical mapping, cell details and the molecular mediators of such interactions are still elusive. The generation and use of tissue-specific fluorescent reporter lines, in combination with whole organ or tissue clearance methods and advanced imaging techniques, have the potential to identify unknown neuronal immune units in the mucosal plexus and to show how they integrate into a broader range of tissues. From RTI & gastrointestinal tract physiology and its effects on the pathogenesis of GI disease is almost certainly the next challenge. Here, it is desirable to use tools that enhance or reduce neuronal activity, such as designer receptors, which are exclusively activated by designer drug [115] and optical genetics [120], which will reveal the complex physiology and disease of the nervous system-immune system interactions in the gut. The consequences of science ENS senses and responds to symbiotic microorganisms, but how to achieve this during development, in vivo balance, inflammation and infection is still poorly understood. For example, the network of mucosal glial cells develops in response to microbial colonization of intestinal tract [13], but it is unclear whether this is a result of innate sensing of microbiologically related factors or colonized microorganisms that are mediated and directed by the immune system & apos; s autonomic response. Intestinal glial cells directly integrate symbiotic cues to regulate innate homeostasis and inflammation of the innate lymphocyte response [34], but further studies will be needed to investigate immune cells, especially macrophages, ILC3s, and mast cells, which may indicate neuronal tissue injury to the gut Mechanisms. ENS and GI immune systems share molecular pathways and occupy overlapping niches. For example, intestinal neurons and ILC3 are similar but different targets of RET-activated neuromodulators, but the role of these molecules in shaping the neuronal or ILC3 developmental fate and the function of differentiation in adulthood remains unclear.

It is now clear that, in addition to its multiple contributions to food digestion and energy balance, the gut is also the largest sensory organ that constantly informs the CNS of the state of the lumen and its dynamic ecosystem. The method of intestinal information reaching the brain and spinal cord involves direct neuronal afferent pathways and systemic mediators. By way of example, it has been shown that intestinal microbiota regulates biosynthesis [129] of serotonin in the host by colonic chromaffin cells. Regardless of the specific mechanism involved, synergistic activity of the intestinal epithelial barrier, mucosal immune system, and nearby glial network constitutes an effective relay station for multiple feedback pathways between the spinal cord and the intestine. A detailed understanding of the components and relationships that make up these relay stations will ultimately provide the means to modulate brain activity and behavior in both normal and pathological conditions. In conclusion, the coordination of the enteric nervous system and the immune system may have ensured an effective response to environmental pollution during evolution. Over the past decade has provided strong evidence of functional NICU. This information on how to shape the treatment strategy is the next challenge. Description the commonality of functional NICU may provide novel, improved interventions for complex inflammatory bowel disease and colorectal cancer.

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