Journal of Entomology and Zoology Studies

Available online at www.entomoljournal.com

Journal of Entomology and Zoology Studies

E-ISSN: 2320-7078
P-ISSN: 2349-6800
JEZS 2018; 6(1): 1196-1203

Received: 15-11-2017
Accepted: 16-12-2017

Javed Ahmed Ujan
Departemnt of Zoology,
Shah Abdul Latif University,
Khairpur, Sindh, Pakistan

Om Parkash
Institute of Microbiology,
Shah Abdul Latif University,
Khairpur, Sindh, Pakistan

Waheed Ali Panhwar
Departemnt of Zoology,
Shah Abdul Latif University,
Khairpur, Sindh, Pakistan

Shahnawaz Ujjan
Departemnt of Zoology,
Shah Abdul Latif University,
Khairpur, Sindh, Pakistan

Correspondence
Javed Ahmed Ujan
Departemnt of Zoology,
Shah Abdul Latif University,
Khairpur, Sindh, Pakistan

Neuro-immunomodulation during intestinal development and *in vivo* homeostasis

Javed Ahmed Ujan, Om Parkash, Waheed Ali Panhwar and Shahnawaz Ujjan

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 neurotrophin 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 secretory 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.

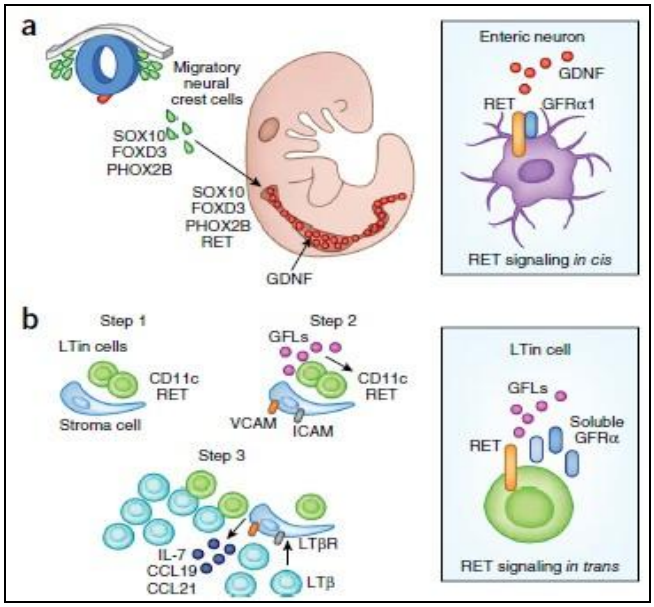

Fig 1: Common regulatory mechanisms of Neuronal and Lymphoid organogenesis in gut. **a:** Neural crest-derived progenitor cells invade the foregut during embryogenesis and migrates rostro-caudally to colonize the full length of the intestine, producing intestinal neurons and glial cells. **b:** PPs development 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).[117]

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 [7-43]. 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 [1-43], 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 meningeal 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 GFRα1-GFRα4 [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 [55] 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 antiapoptotic Bcl-2 family members in immune progenitor and neuronal progenitor cells, whereas in Ret, Bcl2l1 (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 [33-65]. Finally, recruitment of induced intraepithelial lymphocytes and regulatory T cells is closely related to bacterial colonization Intestinal [64-68].

There is clear evidence that the intestinal immune cell subsets are regulated by dietary cues in addition to the involvement of these endogenous and exogenous intestinal homing signals. For example, RA regulates the development of Group 3 ILC (ILC3) by directly modulating ROR [gamma] t40, and the lack of RA signaling has been shown to affect ILC3 development while promoting ILC2 responses [70-71]. [RA signal transduction has also been shown to modulate the expression of gut homing receptors in conventional T cells, ILC1s and ILC3s [72-73], to promote the development of regulatory T cells, to control effector T cell responses [74-75], and to enhance immunity by gut- Globulin A Produces B cells. Consistent with this finding, different intestinal immune cell subsets are a direct target of dietary phytochemicals. For example, the activation of aryl receptors by ligands derived from cruciferous plants controls the maintenance of intradermal lymphocytes and entero-resident memory cells and the proliferation of ILC3s [77-80].

As mentioned for the secondary lymphoid organs of the intestine, a cell basis for vertebrate ENS is established during embryogenesis. However, new enteric neurons continued to be added to the mouse ENS a few weeks after birth [23-81]. In addition, intestinal colloid formation extends beyond neurogenesis and is thought to be maintained at low levels throughout life [13-82], whereas colonization of glioblast-derived lamina propria begins in the immediate postnatal stage and Complete complement formation of mucosal glial cells occurs only after weaning. Besides, these reports, *in vitro* and *in vivo* physiologic studies have demonstrated functional maturation of the enteric nerve circuits after birth. Thus, by using the spatiotemporal mapping of colon motility, the myogenic pattern of bowel movements has been shown to switch from a rather confused pattern (ripple) early in life to a highly co-ordinated neurogenic pattern after day 10 postnatal [83]. Together, these studies demonstrate that cell and functional maturation of the enteric nervous circuit is accomplished in a highly dynamic microenvironment of the postnatal gut, presumably under the influence of intestinal tissues such as the intestinal immune system, as well as external factors such as diet, dietary allergens and emerging Microbial communities [23-85]. Consistent with this concept, the homeostasis of mucosal glial cells depends on the intact supplementation of the microflora, which is required to continuously replicate glial cells within the lamina propria from presumptive precursor cells in the enteric ganglion.

Interestingly, the sterile mice had fewer intestinal neurons and altered neuronal subtypes in proportion and showed abnormal peristalsis, suggesting that microbial clues affect intestinal neuron development and homeostasis in [86-88]. Although the mechanism by which microservice products regulate ENS remains elusive, intestinal neuron and glial expression may directly infect Toll-like receptors (TLR) 84 of microbial products. Notably, intestinal neurons express TLR2 and TLR4 [89-91], whereas intestinal glial cells express TLR2, TLR3,

TLR4 and TLR7 [90-95]. 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 [96-97] (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).

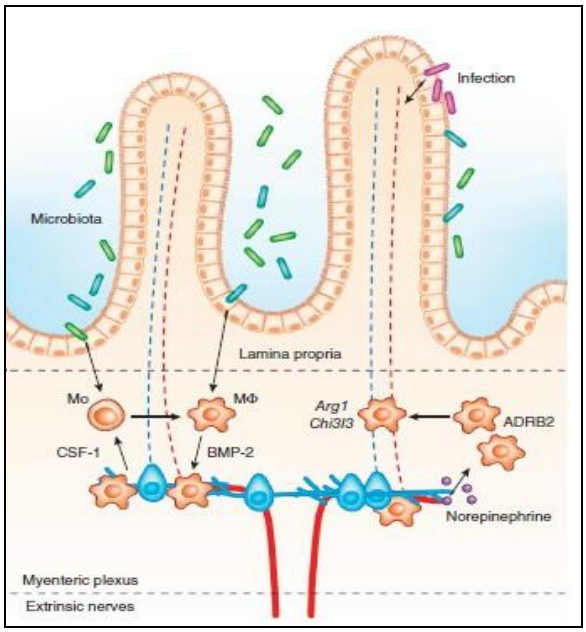

Fig 2: In the myenterium of the neuron-macrophage axis. In the mesenteric plexus (left), the intestinal microflora promotes the interaction between macrophages (MΦ) and neurons by supporting the development and survival of macrophages by CSF-1 derived from neuronal derivatives.

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 SOXlO, GFAP and S100 [beta] l 1, 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 [90], [92-95], leading to an increase in S100β and inducible nitric oxide synthase (iNOS) expression, depending on the transcription factor NF-κB108. Consistent with this idea, patients with ulcerative colitis and / or celiac disease are characterized by altered iNOS activity induced by S100 [beta] [109-119], and abnormal regulation of iNOS activity may alter the suitability of the intestinal barrier. Intestinal glial cells from patients with Crohn & apos; s disease also altered the expression of major histocompatibility complexes II [113, 114]. Amazingly, pharmacogenetics studies have shown that intestinal glial cell ablation rapidly induces acute ileitis and intestinal barrier integrity loss [115, 116].

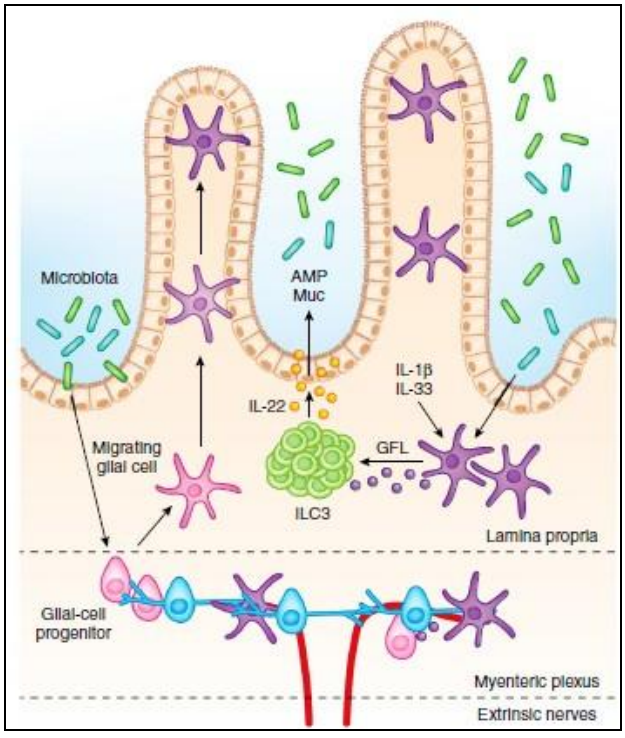

Fig 3: The environment is sensed by glial cells and glial cells by ILC3 units. Neuronal progenitor cells in the myenteric plexus (left) sense the microbial product continuously replenishing the glial cells in lamina propria.

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 Lt; / RTI & gt; Understanding the broader role of this NICUs in intestinal 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 microbially 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 [54], 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 [120] 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.

2. Acknowledgement

I'm very much thankful to Prof. Dr. M. Kamran Azim and Dr. Ishtiaq Ahmed Khan International Centre for Chemical and biological Sciences, University of Karachi, Karachi

3. References

1. Veiga-Fernandes H, Mucida D. Neuroimmune interactions at barrier surfaces. Cell. 2016; 165:801-811.
2. Tracey KJ. Reflex control of immunity. Nat. Rev. Immunol. 2009; 9:418-428.
3. Ordovas-Montanes J. The regulation of immunological processes by peripheral neurons in homeostasis and disease. Trends Immunol. 2015; 36:578-604.
4. Talbot S, Foster SL, Woolf CJ. Neuroimmunity: physiology and pathology. Annu. Rev. Immunol. 2016; 34:421-447.
5. Margolis KG, Gershon MD, Bogunovic M. Cellular organization of neuroimmune interactions in the gastrointestinal tract. Trends Immunol. 2016; 37:487-501.
6. Hanoun M, Maryanovich M, Arnal-Estapé A, Frenette PS. Neural regulation of hematopoiesis, inflammation, and cancer. Neuron. 2015; 86:360-373.
7. Kipnis J. Multifaceted interactions between adaptive immunity and the central nervous system. Science. 2016; 353:766-771.
8. Uesaka T, Young HM, Pachnis V, Enomoto H. Development of the intrinsic and extrinsic innervation of the gut. Dev. Biol. 2016; 417:158-167.
9. Furness JB, Rivera LR, Cho HJ, Bravo DM, Callaghan B. The gut as a sensory organ. Nat. Rev. Gastroenterol. Hepatol. 2013; 10:729-740.
10. Phillips RJ, Powley TL. Innervation of the gastrointestinal tract: patterns of aging. Auton. Neurosci. 2007; 136:1-19.
11. Boesmans W, Lasrado R, Vanden Berghe P, Pachnis V. Heterogeneity and phenotypic plasticity of glial cells in the mammalian enteric nervous system. Glia. 2015; 63:229-241.
12. Gulbransen BD, Sharkey KA. Novel functional roles for enteric glia in the gastrointestinal tract. Nat. Rev. Gastroenterol. Hepatol. 2012; 9:625-632.
13. Kabouridis PS. Microbiota controls the homeostasis of glial cells in the gut lamina propria. Neuron. 2015; 85:289-295.
14. Nijhuis LE, Olivier BJ, de Jonge WJ. Neurogenic regulation of dendritic cells in the intestine. Biochem. Pharmacol. 2010; 80:2002-2008.
15. Van Landeghem L. Enteric glia promote intestinal mucosal healing via activation of focal adhesion kinase and release of proEGF. Am. J Physiol. Gastrointest. Liver

Physiol. 2011; 300:976-987.
16. Le Douarin NM, Teillet MA. The migration of neural crest cells to the wall of the digestive tract in avian embryo. J Embryol. Exp. Morphol. 1973; 30:31-48.
17. Yntema CL, Hammond WS. The origin of intrinsic ganglia of trunk viscera from vagal neural crest in the chick embryo. J Comp. Neurol. 1954; 101:515-541.
18. Druckenbrod NR, Epstein ML. The pattern of neural crest advance in the cecum and colon. Dev. Biol. 2005; 287:125-133.
19. Young HM. Dynamics of neural crest-derived cell migration in the embryonic mouse gut. Dev. Biol. 2004; 270:455-473.
20. Young HM. Colonizing while migrating: how do individual enteric neural crest cells behave? BMC Biol. 2014; 12:23.
21. Avetisyan M, Schill EM, Heuckeroth RO. Building a second brain in the bowel. J Clin. Invest. 2015; 125:899-907.
22. Hao MM, Young HM. Development of enteric neuron diversity. J Cell. Mol. Med. 2009; 13:1193-1210.
23. Laranjeira C. Glial cells in the mouse enteric nervous system can undergo neurogenesis in response to injury. J. Clin. Invest. 2011; 121:3412-3424.
24. Young HM, Bergner AJ, Müller T. Acquisition of neuronal and glial markers by neural crest-derived cells in the mouse intestine. J. Comp. Neurol. 2003; 456:1-11.
25. Niederreither K. The regional pattern of retinoic acid synthesis by RALDH2 is essential for the development of posterior pharyngeal arches and the enteric nervous system. Development. 2003; 130:2525-2534.
26. Patel A. Differential RET signaling pathways drive development of the enteric lymphoid and nervous systems. Sci. Signal. 2012; 5:55
27. Veiga-Fernandes H. Tyrosine kinase receptor RET is a key regulator of Peyer's patch organogenesis. Nature. 2007; 446:547-551.
28. Ferreira M, Domingues RG, Veiga-Fernandes H. Stroma cell priming in enteric lymphoid organ morphogenesis. Front. Immunol. 2012; 3:219.
29. Van de Pavert SA, Mebius RE. New insights into the development of lymphoid tissues. Nat. Rev. Immunol. 2010; 10:664-674.
30. Ohno H, Intestinal M cells. J Biochem. 2016; 159:151-160.
31. Reboldi A, Cyster JG. Peyer's patches: organizing B-cell responses at the intestinal frontier. Immunol. Rev. 2016; 271:230-245.
32. Mebius RE, Rennert P, Weissman IL. Developing lymph nodes collect CD4+CD3– LTβ+ cells that can differentiate to APC, NK cells, and follicular cells but not T or B cells. Immunity. 1997; 7:493-504.
33. Artis D, Spits H. The biology of innate lymphoid cells. Nature. 2015; 517:293-301.
34. Honda K. Molecular basis for hematopoietic/mesenchymal interaction during initiation of Peyer's patch organogenesis. J Exp. Med. 2001; 193:621-630.
35. Yokota Y. Development of peripheral lymphoid organs and natural killer cells depends on the helix-loop-helix inhibitor Id2. Nature. 1999; 397:702-706.
36. Xu W. NFIL3 orchestrates the emergence of common helper innate lymphoid cell precursors. Cell Rep. 2015; 10:2043-2054.
37. Kurebayashi S. Retinoid-related orphan receptor γ (RORγ) is essential for lymphoid organogenesis and controls apoptosis during thymopoiesis. Proc. Natl. Acad. Sci. USA. 2000; 97:10132-10137.
38. Eberl G. An essential function for the nuclear receptor RORγ(t) in the generation of fetal lymphoid tissue inducer cells. Nat. Immunol. 2004; 5:64-73.
39. Sun Z. Requirement for RORγ in thymocyte survival and lymphoid organ development. Science. 2000; 288:2369-2373.
40. Van de Pavert SA. Maternal retinoids control type 3 innate lymphoid cells and set the offspring immunity. Nature. 2014; 508:123-127.
41. Van de Pavert SA. Chemokine CXCL13 is essential for lymph node initiation and is induced by retinoic acid and neuronal stimulation. Nat. Immunol. 2009; 10:1193-1199.
42. Sato Y, Heuckeroth RO. Retinoic acid regulates murine enteric nervous system precursor proliferation, enhances neuronal precursor differentiation, and reduces neurite growth *in vitro*. Dev. Biol. 2008; 320:185-198.
43. Kioussis D, Pachnis V. Immune and nervous systems: more than just a superficial similarity? Immunity. 2009; 31:705-710.
44. Louveau A. Structural and functional features of central nervous system lymphatic vessels. Nature. 2015; 523:337-341.
45. Llorens-Bobadilla E. Single-cell transcriptomics reveals a population of dormant neural stem cells that become activated upon brain injury. Cell Stem Cell. 2015; 17:329-340.
46. Filiano AJ. Unexpected role of interferon-γ in regulating neuronal connectivity and social behaviour. Nature 2016; 535:425-429.
47. Arendt D. The evolution of cell types in animals: emerging principles from molecular studies. Nat. Rev. Genet. 2008; 9:868-882.
48. Schuchardt A, D'Agati V, Larsson-Blomberg L, Costantini F, Pachnis V. Defects in the kidney and enteric nervous system of mice lacking the tyrosine kinase receptor Ret. Nature. 1994; 367:380-383.
49. Almeida AR. RET/GFRα signals are dispensable for thymic T cell development *in vivo*. PLoS One 7, e52949, 2012.
50. Almeida AR. The neurotrophic factor receptor RET regulates IL-10 production by *in vitro* polarised T helper 2 cells. Eur. J. Immunol. 2014; 44:3605-3613.
51. Fonseca-Pereira D. The neurotrophic factor receptor RET drives haematopoietic stem cell survival and function. Nature. 2014; 514:98-101.
52. Airaksinen MS, Saarma M. The GDNF family: signalling, biological functions and therapeutic value. Nat. Rev. Neurosci. 2002; 3:383-394.
53. Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat. Rev. Cancer. 2014; 14:173-186.
54. Ibiza S. Glial-cell-derived neuroregulators control type 3 innate lymphoid cells and gut defence. Nature. 2016; 535:440-443.
55. Heanue TA, Pachnis V. Ret isoform function and marker gene expression in the enteric nervous system is conserved across diverse vertebrate species. Mech. Dev. 2008; 125:687-699.
56. Taraviras S. Signalling by the RET receptor tyrosine kinase and its role in the development of the mammalian enteric nervous system. Development. 1999; 126:2785-2797.

57. Uesaka T, Enomoto H. Neural precursor death is central to the pathogenesis of intestinal aganglionosis in Ret hypomorphic mice. J Neurosci. 2010; 30:5211-5218.
58. Gianino S, Grider JR, Cresswell J, Enomoto H, Heuckeroth RO. GDNF availability determines enteric neuron number by controlling precursor proliferation. Development. 2003; 130:2187-2198.
59. Katayama Y. Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. Cell. 2006; 124:407-421.
60. Méndez-Ferrer S. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. Nature. 2010; 466:829-834.
61. Méndez-Ferrer S, Lucas D, Battista M, Frenette PS. Haematopoietic stem cell release is regulated by circadian oscillations. Nature. 2008; 452:442-447.
62. Spiegel A. Catecholaminergic neurotransmitters regulate migration and repopulation of immature human CD34+ cells through Wnt signaling. Nat. Immunol. 2007; 8:1123-1131.
63. Vantourout P, Hayday A. Six-of-the-best: unique contributions of γδ T cells to immunology. Nat. Rev. Immunol. 2013; 13:88-100.
64. Cheroutre H, Lambolez F, Mucida D. The light and dark sides of intestinal intraepithelial lymphocytes. Nat. Rev. Immunol. 2011; 11:445-456.
65. Sawa S. Lineage relationship analysis of RORγt+ innate lymphoid cells. Science. 2010; 330:665-669.
66. Atarashi K. Induction of colonic regulatory T cells by indigenous Clostridium species. Science. 2011; 331:337-341.
67. Round JL. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science. 2011; 332:974-977.
68. Geuking MB. Intestinal bacterial colonization induces mutualistic regulatory T cell responses. Immunity. 2011; 34:794-806.
69. Veldhoen M, Veiga-Fernandes H. Feeding immunity: skepticism, delicacies and delights. Nat. Immunol. 2015; 16:215-219.
70. Goverse G. Vitamin A controls the presence of RORγ+ innate lymphoid cells and lymphoid tissue in the small intestine. J. Immunol. 2016; 196:5148-5155.
71. Spencer SP. Adaptation of innate lymphoid cells to a micronutrient deficiency promotes type 2 barrier immunity. Science. 2014; 343:432-437.
72. Iwata M. Retinoic acid production by intestinal dendritic cells and its role in T-cell trafficking. Semin. Immunol. 2009; 21:8-13.
73. Kim MH, Taparowsky EJ, Kim CH. Retinoic acid differentially regulates the migration of innate lymphoid cell subsets to the gut. Immunity. 2015; 43:107-119.
74. Hall JA. Essential role for retinoic acid in the promotion of CD4+ T cell effector responses via retinoic acid receptor alpha. Immunity. 2011; 34:435-447.
75. Mucida D. Retinoic acid can directly promote TGF-β-mediated Foxp3+ Treg cell conversion of naive T cells. Immunity. 2009; 30:471-472.
76. Mora JR, von Andrian UH. Role of retinoic acid in the imprinting of gut-homing IgA-secreting cells. Semin. Immunol. 2009; 21:28-35.
77. Veldhoen M. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature. 2008; 453:106-109.
78. Kiss EA. Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. Science. 2011; 334:1561-1565.
79. Li Y. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. Cell. 2011; 147:629-640.
80. Zaid A. Persistence of skin-resident memory T cells within an epidermal niche. Proc. Natl. Acad. Sci. USA. 2014; 111:5307-5312.
81. Liu MT, Kuan YH, Wang J, Hen R, Gershon MD. 5-HT4 receptor-mediated neuroprotection and neurogenesis in the enteric nervous system of adult mice. J Neurosci. 2009; 29:9683-9699.
82. Joseph NM. Enteric glia are multipotent in culture but primarily form glia in the adult rodent gut. J. Clin. Invest. 2011; 121:3398-3411.
83. Roberts RR, Murphy JF, Young HM, Bornstein JC. Development of colonic motility in the neonatal mouse-studies using spatiotemporal maps. Am. J. Physiol. Gastrointest. Liver Physiol. 2007; 292:930-938.
84. Kabouridis PS, Pachnis V. Emerging roles of gut microbiota and the immune system in the development of the enteric nervous system. J Clin. Invest. 2015; 125:956-964.
85. Pham TD, Gershon MD, Rothman TP. Time of origin of neurons in the murine enteric nervous system: sequence in relation to phenotype. J. Comp. Neurol. 1991; 314:789-798.
86. Collins J, Borojevic R, Verdu EF, Huizinga JD, Ratcliffe EM. Intestinal microbiota influence the early postnatal development of the enteric nervous system. Neurogastroenterol. Motil. 2014; 26:98-107.
87. Foster JA, McVey Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. Trends Neurosci. 2013; 36:305-312.
88. McVey Neufeld KA, Mao YK, Bienenstock J, Foster JA, Kunze WA. The microbiome is essential for normal gut intrinsic primary afferent neuron excitability in the mouse. Neurogastroenterol. Motil. 2013; 25:183-e88.
89. Anitha M, Vijay-Kumar M, Sitaraman SV, Gewirtz AT, Srinivasan S. Gut microbial products regulate murine gastrointestinal motility via Toll-like receptor 4 signaling. Gastroenterology. 2012; 143:1006-1016.
90. Barajon I. Toll-like receptors 3, 4, and 7 are expressed in the enteric nervous system and dorsal root ganglia. J. Histochem. Cytochem. 2009; 57:1013-1023.
91. Meseguer V. TRPA1 channels mediate acute neurogenic inflammation and pain produced by bacterial endotoxins. Nat. Commun. 2014; 5:3125.
92. Brun P. Toll-like receptor 2 regulates intestinal inflammation by controlling integrity of the enteric nervous system. Gastroenterology. 2013; 145:1323-1333.
93. Brun P. Toll like receptor-2 regulates production of glial-derived neurotrophic factors in murine intestinal smooth muscle cells. Mol. Cell. Neurosci. 2015; 68:24-35.
94. Rumio C. Activation of smooth muscle and myenteric plexus cells of jejunum via Toll-like receptor 4. J. Cell. Physiol. 2006; 208:47-54.
95. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010; 140:805-820.
96. Muller PA. Crosstalk between muscularis macrophages and enteric neurons regulates gastrointestinal motility. Cell. 2014; 158:300-313.
97. Gabanyi I. Neuroimmune interactions drive tissue programming in intestinal macrophages. Cell. 2016; 164:378-391.

98. Schemann M, Camilleri M. Functions and imaging of mast cell and neural axis of the gut. Gastroenterology. 2013; 144:698-704.
99. Rosas-Ballina M. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science. 2011; 334:98-101.
100. Wang H. Nicotinic acetylcholine receptor α7 subunit is an essential regulator of inflammation. Nature. 2003; 421:384-388.
101. De Jonge WJ. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. Nat. Immunol. 2005; 6:844-851.
102. Van Diest SA, Stanisor OI, Boeckxstaens GE, de Jonge WJ, van den Wijngaard RM. Relevance of mast cell-nerve interactions in intestinal nociception. Biochim. Biophys. Acta. 2012; 1822:74-84.
103. Stead RH. Intestinal mucosal mast cells in normal and nematode-infected rat intestines are in intimate contact with peptidergic nerves. Proc. Natl. Acad. Sci. USA. 1987; 84:2975-2979.
104. Stead RH, Dixon MF, Bramwell NH, Riddell RH, Bienenstock J. Mast cells are closely apposed to nerves in the human gastrointestinal mucosa. Gastroenterology. 1989; 97:575-585.
105. Liu YA. 3-D imaging, illustration, and quantitation of enteric glial network in transparent human colon mucosa. Neurogastroenterol. Motil. 2013; 25:e324-e338.
106. Neunlist M. The digestive neuronal-glial-epithelial unit: a new actor in gut health and disease. Nat. Rev. Gastroenterol. Hepatol. 2013; 10:90-100.
107. Renz H, Brandtzaeg P, Hornef M. The impact of perinatal immune development on mucosal homeostasis and chronic inflammation. Nat. Rev. Immunol. 2011; 12:9-23.
108. Sharkey KA. Emerging roles for enteric glia in gastrointestinal disorders. J. Clin. Invest. 2015; 125:918-925.
109. Cirillo C. Increased mucosal nitric oxide production in ulcerative colitis is mediated in part by the enteroglial-derived S100B protein. Neurogastroenterol. Motil. 2009; 21:1209-e112.
110. Cirillo C. Proinflammatory stimuli activates human-derived enteroglial cells and induces autocrine nitric oxide production. Neurogastroenterol. Motil. 2011; 23:e372-e382.
111. Esposito G. Enteric glial-derived S100B protein stimulates nitric oxide production in celiac disease. Gastroenterology. 2007; 133:918-925.
112. Xiao WD. The protective effect of enteric glial cells on intestinal epithelial barrier function is enhanced by inhibiting inducible nitric oxide synthase activity under lipopolysaccharide stimulation. Mol. Cell. Neurosci. 2011; 46:527-534.
113. Geboes K. Major histocompatibility class II expression on the small intestinal nervous system in Crohn's disease. Gastroenterology. 1992; 103:439-447.
114. Koretz K, Momburg F, Otto HF, Möller P. Sequential induction of MHC antigens on autochthonous cells of ileum affected by Crohn's disease. Am. J Pathol. 1987; 129:493-502.
115. Bush TG. Fulminant jejuno-ileitis following ablation of enteric glia in adult transgenic mice. Cell. 1998; 93:189-201.
116. Cornet A. Enterocolitis induced by autoimmune targeting of enteric glial cells: a possible mechanism in Crohn's disease? Proc. Natl. Acad. Sci. USA 2001; 98:13306-13311.
117. Veiga-Fernandes H, Pachnis V. Neuroimmune regulation during intestinal development and homeostasis. Nature Immunology. 2017; 18(2):116-22.
118. Alexander GM. Remote control of neuronal activity in transgenic mice expressing evolved G protein-coupled receptors. Neuron. 2009; 63:27-39.
119. Prakash R. Two-photon optogenetic toolbox for fast inhibition, excitation and bistable modulation. Nat. Methods. 2012; 9:1171-1179.
120. Yano JM. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015; 161:264-276.