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Review

Neurogenic regulation of dendritic cells in the intestine

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ABSTRACT

Antigen presenting cells like dendritic cells (DC) are responsible for the initiation of adaptive immune responses via the T helper cells they activate. The type of T cell responses DC induce is dependant on the local immunological environment where antigen has been taken up. In the gut, resident DC are phenotypically and functionally shaped by epithelial and stromal cell derived signals, the cytokine microenvironment, and neuronal products. These factors can control the activation state of DC thereby inducing tolerance for food and commensal organisms or immunity against pathogenic microbes. The enteric nervous system (ENS) is increasingly recognized as an important regulatory factor in intestinal immune cell control. Neurotransmitters and neuropeptides like acetylcholine (ACh), norepinephrine (NE) and vasoactive intestinal peptide (VIP) are released by neurons of the ENS and can affect the function of DC and subsequent immune responses. The critical balance between tolerance and protective immunity is disrupted in inflammatory bowel disease, which results in an exaggerated immune response against commensal bacteria. In this review we discuss the effects of ACh, VIP, and NE on DC function. DC express various receptors for these neuron derived products and can alter DC co-stimulatory molecule expression, cytokine release and subsequent T cell activation in an anti-inflammatory fashion. Knowledge about these interactions will help find new drug targets and may facilitate the development of specific therapies for diseases like inflammatory bowel disease (IBD).

Contents

1. Introduction

The immune system of the intestine faces the unique challenge of discriminating between self and nonself in order to elicit an immune response against pathogens, but at the same time inducing a state of immunological tolerance toward resident microflora and food antigens. Antigen presenting cells (APC) such as dendritic cells (DC) and macrophages are thought to be critical in maintaining this balance [1]. To date the exact mechanism underlying this process is not completely understood, however, it is becoming clear that the microenvironment consisting of cytokines, chemokines and neuronal products shape the APC function. Modulation of immune function by the central nervous system (CNS) has long been suggested empirically by the observation that emotional or physical stress increases susceptibility to infectious disease. The interaction of the CNS with the immune system can occur via several endocrine pathways like the immuno-inhibitory effects of glucocorticoids resulting from activation of the hypothalamic–pituitary–adrenal axis (HPA axis). However, the presence of various neuropeptide and neurotrans-

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mitter receptors on cells of the immune system suggests a more direct communication.

The concept that neuronal products could influence innate and adaptive immune responses is not new, but more evidence is emerging that the interaction of APC with neuropeptides and neurotransmitters has profound effects on the type of T cells they induce. Local T cell responses are essential for the specific intestinal immune system. DC can either initiate immune responses or control intestinal inflammation and maintain tolerance by programming T cell reactivity [2,3]. An imbalance of this process has consequences and may lead to disease. An example of this is inflammatory bowel disease (IBD) which is caused by an inappropriate and exaggerated mucosal immune response to constituents of the gut flora in genetically predisposed individuals [4]. IBD, which include Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing inflammatory diseases of the gastrointestinal tract. Typical histological features of CD are the involvement of the terminal ileum, macrophage-rich granulomas and patchy transmural inflammation. UC is characterized by mucosal inflammation, begins in the rectum, and spreads up through the colon. Crohn's disease is complicated by perianal fistulas, abscesses, and intestinal strictures leading to obstructions, while UC may predispose to colorectal cancer or evolve to toxic megacolon [5]. There are clear indications of crosstalk between the enteric nervous system (ENS) and inflammatory cells in IBD that may contribute to the perpetuation of disease [6].

Here we will discuss the recent advances in the understanding of the interaction between the extrinsic and enteric nervous system and the immune system (i.e. with DC and the type of T cell responses they influence) in the setting of the intestine.

2. DC in the gut

Antigen presenting cells, including macrophages, conventional DC and plasmacytoid DC are crucial for maintaining tolerance to commensals but must initiate an appropriate immune response during a pathogenic attack. DC are found throughout the intestine, including the lamina propria (LP) of the small and large intestine, the Peyer's patches (PP), intestinal lymphoid follicles and mesenteric lymphnodes (MLN) [7,8]. DC in the lamina propria are ideally situated to monitor the commensal microflora and food antigens. Specialized microfold cells (M-cells) in the Peyer's patches transport organisms and particles from the gut lumen to immune cells across the epithelial barrier [9]. APCs, like macrophages and DC, phagocytose bacteria thus clearing them. DC and some types of macrophages also migrate to the MLN [10] where they present antigen to naïve T cells and depending on the nature of the antigen, initiate pathogenic or tolerance inducing T cell responses [11].

Many DC subtypes in the different intestinal compartments have been described [12–17]. Functionally intestinal CD11c positive DC can be discriminated on the basis of their expression of CX_3CR1 (the receptor for fractalkine) or those that express CD103 (the receptor for epithelial cell adhesion molecule E-catherin). These two main subsets of intestinal DC originate from the bone marrow as a common precursor, the macrophage and dendritic cell precursor, which gives rise to non-monocytic pre-dendritic cells and monocytes [18,19]. Pre-dendritic cells develop into $CD103^{+}CX_3CR1^{-}$ DC under the influence of the growth factor Flt3. Monocytes, reflected by $Ly6C^{hi}$ expression develop into $CD103^{-}CX_3CR1^{+}$ DC dependant on the growth factor GM-CSF [19]. Once inside the intestine, DC acquire mucosal functions via interaction with the local environment. In steady state, intestinal epithelial cells (IECs) can be activated by the commensal microflora to release retinoic acid (RA), transforming growth factor-β (TGF-β) and in humans thymic stromal lymphopoietin (TSLP) [20,21]. These factors condition DC to become tolerogenic by up-regulating CD103 and expression of RA producing enzymes on DC which then are able to induce FoxP3 regulatory T cells under the influence of RA by migrating to MLN. These tolerogenic DC which deliver antigens from both commensal bacteria and apoptotic epithelial cells also induce the expression of the gut homing receptors CCR9 and α4β7-integrin on responding T cells

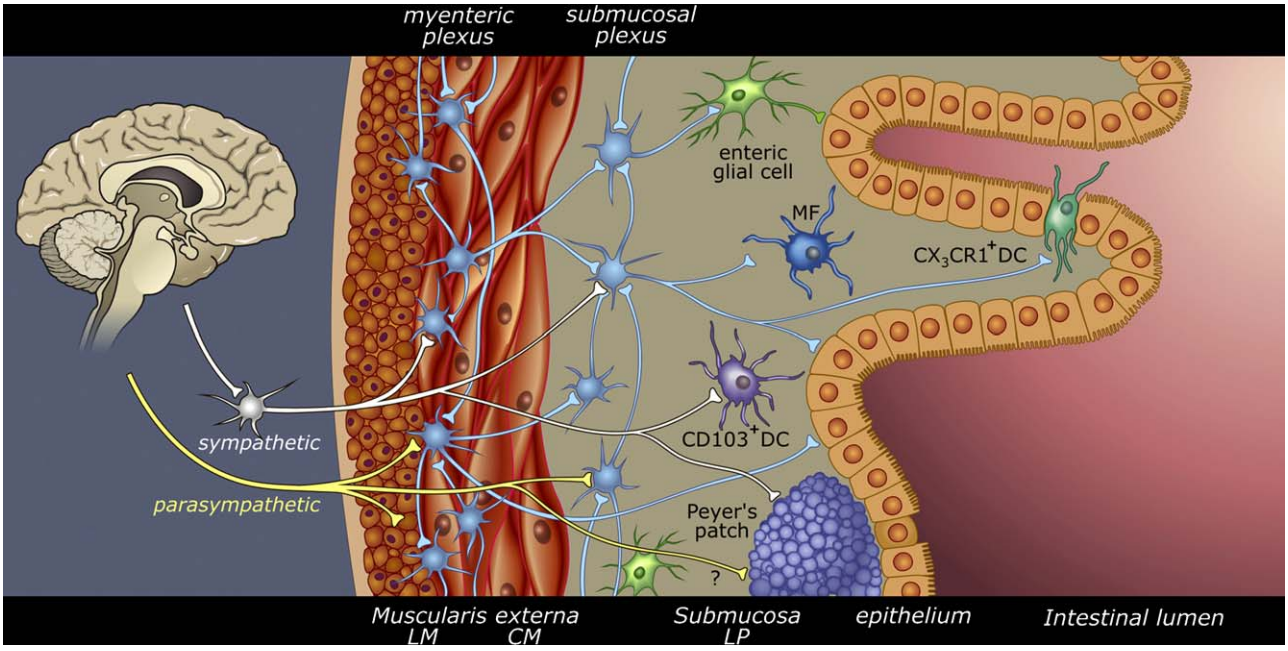

Fig. 1. The ENS. Sympathetic and parasympathetic efferent fibers enter the intestine via the mesentery and form the myenteric and submucosal plexuses. The mucosal layer contains nerve endings that are in close proximity to mucosal APC. The enteric glial cells form a large and widespread network throughout the intestine and serve as intermediaries in the enteric neurotransmission. Together these neurons can produce a large number of neurotransmitters and neuropeptides which are potentially able to affect immune cell function. LM, longitudal muscle; CM, circular muscle; LP, lamina propria; DC, dendritic cell; MF, macrophage.

[22]. On the other hand CX_3CR1^+ DC play a key role in the sampling of luminal antigens. By expressing tight junction proteins CX_3CR1^+ DC extend their dendrites through the epithelial layer into the gut lumen enabling them to directly sample bacteria and other antigens. These cells drive the differentiation of the pro-inflammatory T helper 17 (Th17) cells in the presence of invasive bacteria, probably directly in the LP, as MLN are devoid of CX_3CR1^+ DC [23].

3. DC T cell interaction

The type of T helper cell responses induced by DC strongly depends on the nature and context of the presented antigen. The microenvironment consisting of pro/anti-inflammatory cytokines, Toll like receptor (TLR) ligands, damage-associated molecular pattern molecules and neuropeptides together will determine whether DC will become tolerogenic or immunogenic. In response to pathogens, DC process antigen and migrate to nearby lymphnodes while they undergo a process of phenotypical and functional maturation. DC lose the ability to capture antigen but increase the expression of co-stimulatory molecules like CD80 (B7.1), CD86 (B7.2) and CD40 and produce specific cytokines and chemokines by which they can activate naïve T cells to become effector T helper cells. In steady state DC also migrate at a low rate without undergoing activation. Then they present self-antigens to T cells without up-regulation of co-stimulatory molecules thereby inducing peripheral tolerance. Through the MHC-peptide complex, surface markers they express and cytokines they excrete, DC can polarize naïve T helper (Th) cells into Th1, Th2, Th17 and regulatory T cells (Tregs). Th1 cells releasing interferon-γ (IFN-γ) are inflammatory cells involved in immunity against intracellular pathogens. Th2 cells are involved in B cell help as they release the B cell growth factor interleukin-4 (IL-4). Th17 cells are important to fight bacteria and fungi, but under pathological conditions such as autoimmune disease they exacerbate inflammation. Tregs suppress the function of activated T cells, essential to counteract inflammatory responses. The delicate balance between self-tolerance and immunity can be disrupted leading to autoimmune disorders or cancer [24].

4. The enteric nervous system

The central nervous system communicates with the intestine through what is known as the brain–gut axis, comprising of the HPA axis and the autonomic nervous system. The CNS communicates with the gastrointestinal tract in a bidirectional fashion largely through the enteric nervous system (ENS) (see Fig. 1). The autonomic ENS comprises parasympathetic and sympathetic systems that and can operate without the participation of the CNS, although the ENS interacts directly with the CNS through (para)sympathetic nerves (i.e. spinal/splanchic reflexes). The neural ganglia within the ENS are organized in several plexuses throughout the intestinal wall: the myenteric (or Auerbach's plexus, between circular and longitudinal muscle layer) and submucosal (or Meissner's plexus, in the submocosal) plexuses. The mucosal layer also contains nerve networks known as the mucosal plexus, which contains nerve endings that are potentially in contact with mucosal APC, although the exact nature of such associations is to be determined. The ENS contains sensory neurons, interneurons, motor neurons, which primarily control peristalsis, local changes in blood flow, and secretion of water and electrolytes. An important component of the ENS is the enteric glial cells (EGC), which form a large and widespread network at all levels of the gastrointestinal tract, and serve as intermediaries in the enteric neurotransmission and information processing.

More than 30 different efferent and afferent neurotransmitters exist in the ENS, with most neurons expressing multiple transmitters. Like neurons of the central nervous system, ENS neurons secrete acetylcholine (ACh) and large number of other neurotransmitters and neuropeptides including norepinephrine (NE), ATP, NO, vasoactive intestinal peptide (VIP), Tachykinins, Calcitonin gene related peptide (CGRP), neuropeptide Y and Substance P, for instance reviewed in [25,26]. Many examples exist of immune-modulatory activity of these neurotransmitters, but in this review we will highlight recent data indicating VIP, ACh and NE as modulators of DC function.

5. Vasoactive intestinal peptide

Vasoactive intestinal peptide, a 28-amino-acid peptide was first isolated in 1970s from the intestine for its capacity as a vasodilator. VIP is a neuropeptide that acts as a neurotransmitter and is widely distributed in both central and peripheral nervous system. VIP-ergic nerve fibers have been identified in the bone marrow, gastrointestinal tract and secondary lymphoid organs. The broad spectrum of biologic actions in which VIP is involved also includes immuno-modulatory functions. VIP is released by nerves but is also produced by various immune cells in response to antigen stimulation and under inflammatory conditions, acting as a potent anti-inflammatory factor [27]. VIP exerts its effects by binding to two different receptors namely VPAC1 and VPAC2 [28], which belong to the class II family of guanine nucleotide binding protein (G-protein)-coupled receptors. Activation of these receptors by VIP increases cyclic adenosine 5'phosphate (cAMP), adenylate cyclase and phospholipase C which cause downstream effects on a variety of transcription factors. The different functions mediated by VIP depend on the expression pattern on the various types of immune cells. In vitro generated human monocyte derived DC (Mo-DC) [29], murine bone marrow-derived DC (BMDC) [30] and DC isolated from Peyer's patches [31] express the VIP receptors VPAC1 and 2 in various quantities. VIP released by peptidergic nerve fibers or immune cells in inflammatory conditions is able to alter the differentiation and activation state of DC.

Immature DC (iDC) express high levels of MHC class II but low levels of the co-stimulatory molecules CD80/86, and its up-regulation requires TLR triggering. However, Delgado et al. [30] showed that iDC treated with VIP up-regulated CD86 expression without TLR ligands. This semi-maturation resulted in enhanced iDC capacity to induce proliferation in T cells. Compared to vehicle treated iDC, the VIP treated iDC induced Th2 type (IL-4, IL-5) cytokines instead of high levels of the Th1 cytokine IL-12. When DC were matured with LPS, VIP treatment inhibited CD80/86 expression thereby augmenting T cell proliferation. This anti-inflammatory effect of VIP was dependent on VIP binding to VPAC1, since blocking this receptor could reverse the effect of VIP and blocking of VPAC2 had no effect. Migratory capacity of DC to local lymphnodes is mediated by the chemokine receptor CCR7. VIP dose dependently down-regulates CCR7 expression on LPS stimulated DC thereby inhibiting migration of mature DC (mDC) and preventing the induction of inflammatory responses [32]. In conjunction with these data, human monocytes and murine bone marrow differentiated with GM-CSF and IL-4 in the presence of VIP acquire a tolerogenic phenotype. These VIP-DC express low levels of the co-stimulatory molecules CD80/86 and CD40, produce low levels of pro-inflammatory cytokines and high levels of IL-10 after LPS activation. The endocytic capacity was increased in VIP-DC compared to control. The neuropeptide-induced tolerogenic DC induce anergic T cells, which do not proliferate due to the lack of IL-2 production and do not produce IFN-γ. T cells co-cultured with VIP-DC release the anti-inflammatory cytokines IL-10 and TGF-β. These so called Tr1 cells are able to suppress Th1 proliferation, IFN-

γ and IL-2 production and to a much lesser extent the proliferation and cytokine profile of Th2 cells, thus skewing T cell responses toward a Th2 type [33].

Several reports have recently proposed the use of VIP tolerogenic DC to induce antigen specific regulatory T cells ex vivo and restore immune tolerance in autoimmune disease [33–41]. In murine models of the autoimmune disorders for rheumatic arthritis and multiple sclerosis, these Treg-VIP were injected in mice with established disease. Disease progression was ameliorated in a dose-dependant manner and the effect was mediated through TGF-β and IL-10 as antibodies to these cytokines abrogated the protective effect [35]. Alternatively a single injection of VIP-DC at the onset of disease in a murine model for CD, trinitrobenzene sulphonic acid (TNBS) induced colitis ameliorated the detrimental effect seen in control treated mice [42]. VIP-DC down-regulated Th1 (TNF-α, IFN-γ, IL-6, IL-1β, IL-12) cytokine response of immune cells and stimulated IL-10 and TGF-β production in TNBS induced colitis. Another interesting approach in creating tolerogenic DC is recently reported by the same group [41]. Bone marrow was transduced with lentiviral vectors to genetically engineer VIP-expressing bone marrow-derived DC. The differentiation state, migratory capacity and anti-inflammatory properties of these cells were similar as in tolerogenic DC treated with exogenous VIP. In disease models for multiple sclerosis LentiVIP-DC were pulsed with the disease inducing agent and injected in mice with established disease. In a sepsis model, sepsis was induced by cecal ligation and LentiVIP-DC were injected at the onset of sepsis. In both disease models injection of genetically VIP-expressing DC strongly ameliorated disease progression and survival in models for multiple sclerosis and sepsis respectively.

The use of VIP in engineering DC with tolerogenic properties may be a promising approach for the treatment of several autoimmune disorders such as IBD, and it is tempting to use this experience in the human setting. However, it must be noted that non-antigen specific DC which secrete large amounts of anti-inflammatory mediators could potentially also suppress immune responses to oncogenic cells and pathogens. Therefore the emphasis must lie in creating antigen specific tolerogenic DC.

6. The cholinergic anti-inflammatory pathway

The vagus nerve supplies the internal organs with efferent parasymphatic motor neuron fibers from the neck down to the second segment of the transverse colon. In the abdomen branches enter the stomach, pancreas, small intestine and colon, controlling hormone secretion, gastrointestinal peristalsis and digestion. Besides efferent signaling to various organs in the body the vagus nerve conveys sensory information about the state of the body's organs to the CNS. Evidence is provided that efferent vagus nerve cholinergic activity exerts potent immuno-modulatory properties [43], including the gastrointestinal tract [44].

The so called cholinergic anti-inflammatory pathway was first appreciated by Borovikova et al. in 2000 [43]. They showed that stimulation of the vagus nerve (VNS) ameliorated LPS induced systemic endotoxaemia in rats, inhibited TNF-α production, and prevented the development of shock. On the other hand surgical dissection of the vagal nerve enhanced pro-inflammatory cytokine production and accelerated the development of shock. The anti-inflammatory effect of VNS is mediated by the principal vagal neurotransmitter acetylcholine (ACh), most likely involving the spleen [45]. The group of Tracey claimed that VNS leads to peripheral ACh release which acts on macrophages via the homopentameric α7 nicotinic acetylcholine receptor (nAChR) resulting in a down-regulation of TNF-α production. The molecular mechanism of the anti-inflammatory effect of ACh on macrophages and other immune cells has only recently been revealed [46,47]. In support of this, activation of the cholinergic nervous system ameliorated experimental disease models for ischaemia–reperfusion injury [48], haemorrhagic shock [49], pancreatitis [50], postoperative ileus [51] and dextran sulphate sodium (DSS)-colitis [52].

Which immune cells are responsible for the ameliorative effect of VNS in experimental disease or in vitro stimulation of immune cells with ACh? Several immune cells express various nAChR subtypes [53]. B-lymphocytes express α7 nAChR [54,55] and the heteromeric α4/β2 nAChR [56]. T-lymphocytes express various subunits of nAChR, all known muscarinic acetylcholine receptors (mAChR), M1–M5 and the ACh producing enzyme choline acetyltranferase (ChAT) [54,57]. Macrophages also express various subtypes of nAChR [58], and lamina propria macrophages reside in close proximity of cholinergic fibers [59]. The expression pattern is, however, dependant on the type of macrophage and the tissue were it resides. Macrophages residing in the gut express low levels of CD14, a co-receptor for LPS and low TLR expression, due to the anti-inflammatory microenvironment in the mucosa [60]. Therefore damping immune reactions with vagal activity or nAChR agonists, like nicotine, in experimental models of intestinal colitis would not affect the intestinal macrophages, because they maybe not involved in the production of pro-inflammatory cytokines seen in colitis models. However, it is has been shown that stimulation of the α4β2 nAChR on peritoneal and mucosal macrophages in the mouse results in enhanced endo- and phagocytosis, thereby possibly preventing a sustained inflammatory response by other immune cells [61].

Additionally, immature dendritic cells (iDC) and matured dendritic cells (mDC) also express nAChRs. In vitro studies of monocyte derived DC show constitutive expression of α7 nAChR [62]. In murine BMDC different subtypes of nAChR are expressed (α2, α5, α6, α7, α10, and β2) [63], and expression is up-regulated by maturation with LPS and incubation by its specific ligand nicotine [64]. Nouri-Shirazi and Guinet [65] showed that the specific agonist for nAChR, nicotine, reduced endocytosis of FITC-dextran and phagocytosis of apoptotic cells by immature monocyte derived DC. Upon maturation with LPS, nicotine did not alter general maturation markers like CD80/86 and CD40. However, nicotine treatment of DC during maturation resulted in a significant decrease in the production of pro-inflammatory cytokines like IL-12, IL-1β, and TNF-α. Nicotine treated DC diminished allogenic T cell proliferation compared to control and IFN-γ production by Th1 cells in this assay was significantly lower. In contrast Aicher et al. [62] and Gao et al. [64] showed that nicotine, enhanced endocytosis, can up-regulate co-stimulatory molecules, produce more IL-12 during maturation and increased the ability to induce T cell responses in respectively Mo-DC and BMDC. This nicotinic effect on DC could be blocked by the α7-receptor antagonist α-bungarotoxin and the broad spectrum nicotinic antagonist mecamylamine.

These contrasting effects of nicotine on the functional properties of DC could be due to the timing of nicotine exposure to DC, as maturation status at the time of assay is critical for the studied parameters. The duration of nicotine treatment and concentration also affects the nAChR expression pattern, as these receptors are prone to desensitization. Clearly, the expression of nAChR in DC is suggestive of cholinergic regulation of their activity, but further studies are required to determine a direct role of the vagal nerve in modulating their function in animal models of inflammation. Interestingly both DC and T cell when activated have the ability to synthesize ACh by choline acetyltransferase (ChAT) [66]. Thus the cholinergic pathway seen in immune cells could act as an independent auto/paracrine system, ensuring local control over inflammatory reactions.

7. Sympathetic adrenergic nervous system and DC

The sympathetic nervous system (SNS) plays an important role in several GI functions, including motility, blood flow and inflammation. The SNS begins in the brainstem where preganglionergic efferent fibers originate and leave the central nervous system via spinal nerves. Sympathetic nerve fibers enter the intestinal wall along arteries and terminate in the myenteric and submucosal plexuses, and in the mucosa. In the mucosa norepinephrine is released nonsynaptically, that is, from varicose axon terminals, without synaptic contacts [67]. Lymphoid tissue, and interestingly PP, is also innervated by sympathetic neurons and the axons that innervate the mucosa are in close proximity to immune cells [68]. Finally, circulating catecholamines also elicit sympathetic influences on gut immunocytes. NE acts on adrenergic receptors (ARs) which are G-protein coupled receptors and includes nine different gene products: three α1 (A, B, D), three α2 (A, B, C) and three β (β1, β2, β3) receptor subtypes. At low concentrations (10^{-9} to 10^{-7} M), NE binds to α-adrenoreceptors leading to decreased cAMP levels. At high concentrations (10^{-7} to 10^{-5} M) NE binds to β-adrenoreceptors, increasing cAMP levels [69].

In vitro generated BMDC express the mRNA coding for α1B-, β1-, β2-, α2B-, and α2C-ARs [70,71]. Short (3 h) NE exposure to mimic the physiological situation of iDC prior to maturation with TLR2 and TLR4 ligands results in a significant decrease of IL-12, TNF-α and IL-6 production and an increase in IL-10 production [72]. Even a 15-min incubation with NE followed by a wash of iDC prior to maturation with LPS has this pronounced effect (own unpublished data). This anti-inflammatory cytokine profile is completely neutralized when NE was added together with the β-adrenergic antagonist propranolol [72]. The same effect, a decrease in the production of IL-12 was seen when Mo-DC were activated in the presence of NE. This effect was blocked by salbutamol, a selective β2-AR antagonist. In vivo administration of salbutamol of healthy volunteers and in vitro stimulation IFN-γ and LPS of PBMCs before and after salbutamol administration resulted in a decrease in IL-12 production [73]. Immature DC which express α1b-ARs are recruited to regional lymphnodes upon activation with NE, thereby facilitating antigen presentation to T cells and possible induction of tolerance [70], since that non-activated iDC induce T cell anergy once arrived in the lymphnode [74]. All together these data suggest an anti-inflammatory role for NE on iDC function resulting in mDC inhibiting Th1 and enhancing Th2 differentiation.

In disease models for IBD contrasting roles for the anti-inflammatory effect of the SNS arise. In chronic DSS colitis and the IL-10-knockout model of IBD, sympathetic denervation using 6-hydroxydopamine exacerbated disease [75]. During acute DSS colitis and TNBS induced colitis, sympathetic denervation decreased inflammation [76]. These data suggest that the SNS exerts pro-inflammatory effects at the beginning of tissue inflammation while it confers anti-inflammatory effects in the chronic phase of inflammation. The role of the SNS in chronic inflammation has been indicated some 30 years ago. In surgically resected ileum of patients with CD, Dvorak and Silen found a marked loss of sympathetic nerve fibers compared to control specimens [77]. In contrast, in UC the density of the adrenergic network was significantly pronounced [78].

These interesting observations suggest a pronounced role for the SNS in IBD and disease models for IBD, yet the type of immune cells responsible for these differential effects has to be determined. As it is not known which adrenergic receptors (α-, β-AR) are expressed in the in vivo DC and other immune cells in the gut, the exact immuno-modulatory effect of SNS during inflammation has to be deciphered in the future. Taken together it is clear that the innate and adaptive immune systems are profoundly influenced by the SNS, suggesting a pivotal role for DC.

8. Conclusions and future prospects

We have discussed the role of three important enteric neuron derived products and their effects on DC function as these cells are crucial for maintaining intestinal homeostasis. VIP, ACh and NE act as anti-inflammatory substances which are able to regulate DC function and subsequent T cell differentiation. Current knowledge about the effects of VIP, ACh and NE on DC function, however, is mostly derived from in vitro data. Future research should focus on isolated intestinal DC as these cells are functionally different compared to Mo-DC or BMDC, due to the different origins and local conditioning factors of the intestine. In addition, we should explore the susceptibility of related cell types with APC potential like lamina propria macrophages and enteric glial cells [79] to cholinergic innervation. The principal parasympathetic neurotransmitter ACh and the sympathetic counterpart NE, seem to share the anti-inflammatory effect on DC differentiation suggesting an additive rather than the classical antagonistic function. It has to be determined if this additive effect also holds true for the in vivo situation as it is not known to which concentrations of neurotransmitters DC in the gut are exposed and which specific receptors they express. Now that the different types of DC in the human gut are being described, the question can be raised what DC subtype is influenced by neuronal products. Are the anti-inflammatory neurotransmitters reviewed here acting on the pro-inflammatory CX_3CR1^+ DC resulting in a decrease in their pro-inflammatory function, or do they affect the function of $CD103^+$ DC which are known to induce Tregs? More research is needed to answer these questions. It remains to be shown to what extend such neuro-immunomodulation is relevant for intestinal disease pathology, and whether neurotransmitter and neuropeptide receptors are potential drug targets.

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