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(a) ENTEROENDOCRINE CELLS-SENSORY SENTINELS OF THE INTESTINAL ENVIRONMENT AND ORCHESTRATORS OF MUCOSAL IMMUNITY

(b) John J Worthington; Lancaster University, Faculty of Health and Medicine, Division of Biomedical and Life Sciences, Lancaster, Lancashire, UK.

Frank Reimann; University of Cambridge, Metabolic Research Laboratories, Wellcome Trust/MRC Institute of Metabolic Science & MRC Metabolic Diseases Unit, Addenbrooke's Hospital, Cambridge, UK.

Fiona M Gribble; University of Cambridge, Metabolic Research Laboratories, Wellcome Trust/MRC Institute of Metabolic Science & MRC Metabolic Diseases Unit, Addenbrooke's Hospital, Cambridge, UK.

(c) John J Worthington**;** Lancaster University, Faculty of Health and Medicine, Division of Biomedical and Life Sciences**,** Lancaster, Lancashire, UK; Tel: +44 (0)1524 594 838; j.j.worthington@lancaster.ac.uk

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Text

ABSTRACT

The intestinal epithelium must balance efficient absorption of nutrients with partitioning commensals and pathogens from the bodies' largest immune system. If this crucial barrier fails, inappropriate immune responses can result in inflammatory bowel disease or chronic infection. Enteroendocrine cells represent 1% of this epithelium and have classically been studied for their detection of nutrients and release of peptide hormones to mediate digestion. Intriguingly, enteroendocrine cells are the key sensors of microbial metabolites, can release cytokines in response to pathogen associated molecules and peptide hormone receptors are expressed on numerous intestinal immune cells; thus enteroendocrine cells are uniquely equipped to be crucial and novel orchestrators of intestinal inflammation.

In this review, we introduce enteroendocrine chemosensory roles, summarize studies correlating enteroendocrine perturbations with intestinal inflammation and describe the mechanistic interactions by which enteroendocrine and mucosal immune cells interact during disease; highlighting this immunoendocrine axis as a key aspect of innate immunity.

INTRODUCTION

The intestinal epithelium represents one of the body's most important interfaces with the environment. Not only must it act as a point of nutrient absorption, but also as a barrier against the vast amount of commensal and pathogenic microbes it constantly encounters[1, 2]. As such, the gut hosts the major immune system of the body determining tolerance versus immunity and dysregulation leads to inflammatory bowel disease (IBD) in response to commensals[3], or excessive inflammation in response to infectious pathogens[1]. This single layer of epithelium forms a crucial barrier, but is also believed to play important functions in regulation of the intestinal immune system. Within this epithelium reside the enteroendocrine cells (eecs), specialized trans-

epithelial signal transduction conduits which respond to luminal nutrients by secreting peptide hormones to control gastrointestinal enzyme secretion, motility, and appetite regulation[4, 5]. These key sensory cells comprise just 1% of the epithelium and are dispersed throughout the gut, but collectively form the largest endocrine system in humans. Their elusive nature coupled with a lack of specific surface markers had caused the biology of eecs to remain somewhat enigmatic. However, via the use of transgenic reporter mice[6-12], and the emergence of Claudin-4 as a specific surface marker[13], we are now uncovering novel concepts of eec biology and surprisingly revealing key interactions between these sensory sentinels and the intestinal mucosal immune system.

Enteroendocrine differentiation

Within the intestinal crypt resides the stem cell niche which is responsible for supplying the entire epithelial cell population. These Leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5)-positive stem cells[14] regularly divide providing highly proliferative transit amplifying cells which further differentiate into absorptive or secretory cellular lineages, supplying a constant cascade of epithelial renewal every 3-5 days[15]. Lineage differentiation (Fig.1) is based on Wnt, Notch and Mitogen-activated protein kinases (MAPK)-dependent signaling[16] with the transcription factor hairy and enhancer of split-1 (*Hes1)* required for differentiation into absorptive enterocytes, while Protein atonal homolog 1 (*Atoh1)* expression drives secretory cell fate[17-20]. Growth Factor Independent 1 Transcriptional Repressor (*Gfi-1)* is required for both goblet cells and Paneth cells[21], with Kruppel-like factor 4 (*Klf4)*[22] and *Sox9*[23, 24] essential for each population respectively. Tuft cells require the expression of the Pou domain, class 2, transcription factor 3 (*Pou2f3*)[25, 26], while the development of Microfold (M)-cells is independent of *Hes1*/*Atoh1*, instead relying on *SpiB* transcription factor expression[27] and TNF superfamily member receptor activator of NF-kappaβ ligand (*RankL*) induction[28, 29]. Eecs depend on the transient expression of

Neurogenin3 (*Neurog3)*[30, 31] and micro-RNA-375[32] followed by a variety of overlapping transcription factors[18, 19] (Table 1), including Neurogenic differentiation 1 (*Neurod1)*[33-35], Paired box (*Pax*) 4/6[36-38], Insulin gene enhancer protein (*Isl1)*[39], pancreatic and duodenal homeobox 1 (*Pdx1)*[40-42], *Nkx6-1*[43] and *Nkx2-2*[44, 45], this in turn with spatio-temporal expression of transcription factors[46, 47] *Pdx-1*, caudal type homeobox 2 (*Cdx-2)*[48, 49], *Gata-4*, *Gata-5*, *Gata-6*[50-54], Hepatocyte nuclear factor-1α (*Hnf-1α)*[55], *Hnf-1β*[56] and CCAAT-displacement protein (*Cdp)*[47, 57], determines the eec subset and array of peptide hormones they can secrete. Similar to Paneth cells, in Drosophila eecs have been shown to play an important role in maintaining the stem cell niche[58, 59] , while in both man[60] and mouse[61] quiescent, label retaining cells, have the potential to differentiate into Paneth and eecs. Therefore eecs can potentially play important roles during the modulation of the epithelium in health and disease.

Enteroendocrine subsets

Eecs respond to luminal stimuli by secreting a variety of peptide hormones, including cholecystokinin (CCK), glucagon-like peptide 1 and 2 (GLP-1, GLP-2), glucose dependent insulinotropic peptide (GIP), peptide YY (PYY), gastrin, secretin, somatostatin, motilin, leptin, nesfatin-1 and ghrelin; as well as bioactive amines such as histamine and serotonin (5-HT). The historical dogma of distinct differentiated eec subsets secreting individual hormone peptides mediating biological function (Fig. 2) has been superseded, via the analysis of eecs from transgenic reporter mice[12, 62-65] as well as cell ablation studies[35, 63], to reveal considerable overlap of the eec secretome. It now appears that the secretome “cocktail” secreted by individual eecs is based on tissue location[66], although it is likely that certain peptide hormones remain rarely co-expressed[66, 67].

Once secreted these peptide hormones can act in a traditional endocrine fashion on distant organs, or in a paracrine action to neighboring cells, including other eecs, and to vagal

afferents and enteric neurons communicating at a central or local level respectively. Eecs have classically been studied for their roles in enabling efficient postprandial assimilation of nutrients via alterations in gastrointestinal secretion, motility, pancreatic insulin release and satiety[4, 68] (Fig. 2). However, it is now emerging that eecs have a huge array of chemosensory mechanisms to detect stimuli beyond nutrient intake, further indicating their importance beyond appetite and digestion.

Chemosensory pathways and peptide secretion

Eecs express a broad array of sensory machineries, mirroring their ability to respond to a diversity of ingested nutrients and other components in the gut lumen[5]. Gut hormones are packaged into secretory vesicles, the release of which is mobilized by elevated concentrations of cytoplasmic calcium and enhanced by cyclic adenosine monophosphate (cAMP). Central to the detection of ingested food by eecs is a requirement that macronutrients are first digested to their component parts, including glucose, amino acids and fatty acids. These small molecules are then detected by specific transporters and receptors located on the eecs themselves, and stimulate hormone secretion predominantly at the sites where nutrient absorption is maximal. The essential role of eecs is notably demonstrated by the impaired lipid absorption, reduced weight gain, growth retardation and high frequency of mortality in mice lacking the transcription factor *Neurog3* and hence all intestinal eecs[30].

Important pathways for the detection of glucose, amino acids and dipeptides by eecs are the families of brush border transporters that couple substrate absorption to ionic gradients[69, 70]. Coupling of nutrient fluxes to the movement of sodium or hydrogen ions is an effective mechanism for driving absorption out of the gut lumen against a concentration gradient, but additionally has the consequence of causing small inward movements of positive charge into cells, that in turn can trigger membrane depolarization and voltage gated calcium entry.

Glucose uptake by the sodium glucose cotransporter (SGLT1) is a well-studied example of this mechanism, and underlies the majority of glucose-triggered GIP and GLP-1 secretion[70].

Fatty acids, bile acids and amino acids are detected by specific G-protein coupled receptors (GPCRs) located directly on the eecs[69, 71, 72]. The majority of nutrient-responsive GPCRs are coupled to Gas or Gaq signaling pathways, so their activation results in elevation of cytoplasmic cAMP and/or calcium concentrations, respectively, which in turn enhance vesicle release from the basolateral eec membrane. It has been recognized recently that fatty acids and bile acids, like glucose, must also be absorbed if they are to trigger gut hormone secretion. Thus, both the G-protein coupled bile acid receptor (GPBAR1) and the long chain free fatty acid receptor 1 (FFAR1/GPR40) appear to be localized and functional predominantly on the basolateral membrane of GLP-1 secreting cells[72, 73].

Linking hormone secretion to nutrient absorption generates a robust physiological signal to the body about the quantity and quality of substrates entering the bloodstream at any time. Eecs also, however, respond to a range of non-nutrient stimuli[5], including bacterial metabolites[74-79], hormonal[80], paracrine[81] and neurotransmitter signals[12, 82]. They thus form essential components of a network of complex signaling circuits, linking the gut with the rest of the body.

ENTEROENDOCRINE ALTERATIONS DURING INTESTINAL INFLAMMATION

Intestinal inflammation is often associated with microbial dysbiosis, be it inflammatory bowel disease, infection, colorectal cancer or food allergies[83-86]. Interestingly, eecs are the prime epithelial expressers of the receptors that sense bacterial metabolites[84, 87], such as GPR41/43, and therefore have the unique ability to relay dysbiosis into physiological adaptation, such as modulating energy homeostasis, glucose metabolism, gut barrier function and mucosal immunity[77, 78, 88-102].

Inflammatory bowel disease-Human studies

Inflammatory bowel disease, typified by Crohn's disease (CD) and ulcerative colitis (UC), is often linked to reduced appetite, anorexia and abnormal intestinal contractility[103]. Eecs and the peptide hormones they secrete are now being recognized as potential instigators of these intestinal pathologies, due to their underlying role in mediating these systems during homeostasis. Indeed, genome-wide association studies for CD identified a single nucleotide polymorphism in the eec associated transcription factor Paired-like homeobox 2b (*Phox2B*)[104], while autoantibodies for the eec ubiquitination factor E4A (*UBE4A*) are seen as a biomarker for CD[105]. Moreover, both *Phox2B* and *UBE4A* are seen to increase in ileal CD displaying active inflammation[106]. An accumulation of studies has now begun to enumerate the alterations in eecs and secretions in clinical IBD (Table 2), aiding the ability to properly access their function in disease.

A large number of studies have focused on measuring peptide hormone levels in the serum or plasma of IBD patients. Serum and plasma Chromoagranin A (CgA) levels, a pan-eec-marker[107], strongly increases in IBD patients and correlates to tumor necrosis factor (TNF)α [108, 109], however histological analysis of CgA and mucosal healing are lacking in these studies and are required to allow differentiation between cause and effect. The level of fecal CgA, has been seen to increase in UC but is not associated with disease index[110], while other studies demonstrate differences in microscopic colitis but not in UC or CD[111]. More specifically, numerous studies have measured individual peptide hormone serum and plasma levels during the course of IBD , with significant changes seen in PYY, somatostatin, ghrelin, gastrin, GLP-1, CCK, 5-HT and motilin during IBD (Table 2)[112-129]. Many of these reports also correlate increases of blood detected peptide levels with active disease, with somatostatin[117], ghrelin[115, 120, 122] and gastrin[125] decreasing on remission. Moreover, ghrelin[119, 121] and gastrin[125] correlate with levels of the pro-inflammatory cytokine TNFα and IL-6. However, once again conflicting reports exist within the literature[123, 126] and this is most likely explained by the heterogeneity seen in IBD. Indeed, in studies examining gastric

emptying, post-prandial plasma CCK was seen to increase in CD[128], but not in a follow up study by the same investigators[129]. Another possible explanation for these disparities is that as eec alterations are seen to correlate with markers of inflammation they may be restricted to the inflammatory niche and are hence too localized to be detected via blood sampling.

The availability of patient biopsies and resections has allowed precise examination of tissues from IBD patients and has identified actual alterations in eec peptide hormone storage granules[130]. Immunohistological quantification, in parallel with blood readings, is the most direct measure of eec fluctuation and various reports of changes in PYY, somatostatin, gastrin, GLP-1/2 and 5-HT+ cells exist in the literature (Table 2)[106, 112, 131-137]. Interestingly, similar to Paneth cell occurrence in the colon[138], gastrin+ cells are strangely found in the repairing small intestine of CD patients[131] and subsets of IBD patients have autoantibodies to gastrin[139]. GLP-1[140] and GLP-2[141] are epithelial growth factors, with GLP-2 also having anti-inflammatory action both direct[142] and indirect via Paneth cells[102]. It is therefore a possibility that increases in the glucagon-like peptides during IBD are a possible response to epithelial damage and play a direct role in repair[137]. Indeed, long acting analogs of GLP-2 could potentially be used for the treatment of short-bowel syndrome following CD[143].

Despite the potential benefit that some eec peptide hormones may offer during IBD, they are also likely responsible for the reduced appetite, anorexia and nausea that accompanies inflammation. Indeed, increases in plasma GLP-1[129] and CCK[128] are thought to be responsible for changes in gastric emptying, while decreased appetite and nausea in small bowel CD correlate with increased PYY levels[115]. Plasma motilin also increases in IBD and is related to altered contractility[144, 145], with a polymorphism of the motilin gene interestingly seen in subsets of patients with CD[146]. Although the majority of these human studies rely on small population sizes, collectively, these data strongly correlate alterations in eec peptide release with inflammation in IBD. Going forward, future studies should report the precise location of biopsy sampling, given the spatio-temporal expression of eec peptides. There is also an urgent need for more mechanistic approaches as overall there remains a lack of

human data, besides co-localization, demonstrating direct cross-talk between intestinal inflammation and eecs. The varying and often clinically unknown burden in IBD has led to the use of animal models to decipher possible pathogenic mechanisms at play.

Inflammatory bowel disease-animal models

In rodents, chemically induced and genetically prone models of IBD are well associated with reduced feeding and weight loss, which is linked to eec function (Table 3)[147-152]. Similar to the observations in human IBD, eec changes are often correlative to inflammation. PYY+ cell decreases in the dextran sulfate sodium (DSS) colitis model are restored with prednisolone treatment[144], while, the interleukin (IL)-2-/- colitis model reductions in PYY+ cells occur on activation of inflammation[153]. Animal models have also begun to demonstrate that alterations in eec function are likely to be key factors in disease. Blocking CCK receptors in an acetic acid model of colitis reduces TNFα levels and ameliorates pathology[154], while 2,4,6-trinitrobenzenesulfonic acid (TNBS) colitis is inhibited with a CCKB receptor antagonist[155]. Interestingly CCK was a novel and verified hit in a recent zebrafish enterocolitis small molecule screen[156]. Additionally, the regulatory peptide nesfatin-1[157] and somatostatin have been shown to be anti-inflammatory in the acetic acid model of colitis[158, 159]. Indeed, somatostatin agonists are able to increase intestinal tight junctions in models of dextran sulfate sodium (DSS) and *Citrobacter rodentium* induced colitis[160] and modulate the water and sodium uptake protein NHE8, associated with UC pathology, via MAPK signaling[161]. Neurotensin+ cells are seen to increase in the mouse DSS model and blocking signaling via antagonists increases pathology via a cyclooxygenase (COX)-2 mediated pathway[162], indicating a protective effect. Indeed, therapeutic use of peptides or agonists has been beneficial in mouse models, GLP-2 can rescue DSS colitis[163] and small intestinal enteritis[164, 165] possibly by reducing bacterial translocation[166], while nanodelivery of GLP-1 is also

protective[167]. Taken together this suggests that eecs play an essential and varied role in the pathology of IBD and are strong candidates for therapeutic intervention[168].

As is often the case, the majority of initial observations have arisen from readily available chemical models of IBD, and while these results remain valid, new scientific knowledge is likely to arise by examining the influence of eecs in more complex models which better relate to IBD. It is therefore imperative to begin to examine alterations of eec biology in models such as the T-cell transfer model and *Helicobacter hepaticus* induced models of colitis[169]. Furthermore, given the high concentration of eecs in the small intestine, examining eec changes in the SAMP1/YitFc model[170], which most closely resembles human ileal CD, should be a priority.

Non-infectious enteropathies

Beyond IBD, there is strong evidence that eecs are involved in multiple inflammatory driven diseases of the gut and may again be potential therapeutic targets. Coeliac disease is associated with changes in eec number[171, 172] as well as peptide granule storage[130]. Serum levels of GLP-1, GIP[173] and plasma CCK, thought to be responsible for the pancreatic dysfunction seen in celiac patients[174], are seen to be reduced in celiac blood. However, increases in CgA+ cells are also observed[174], with increased ghrelin+ cells seen in the duodenum that correlate with inflammation[175, 176]. Increased serum somatostatin[177] and GLP-2[178], plasma oxyntomodulin[179], neurotensin[180] and motilin[181] are also reported despite the villous blunting seen in the disease. In particular, 5-HT+ cell increases are thought to prolong inflammation via increased IFN-y in tissue samples of refractory celiac patients[174], again pointing to a direct role for eecs in pathology.

With their close links to intestinal function it is unsurprising that eec alterations are also linked to irritable bowel syndrome (IBS). CD remission patients with IBS-like symptoms have increased levels of markers for 5-HT biosynthesis, rather than an increase in actual

enterochromaffin cells[182]. Somatostatin also increases in IBS post-IBD[183], while post-infectious IBS is strongly linked to changes in nerve sensitivity to peptide hormones[184-187]. Interestingly, high correlations of Chlamydia antigens are associated with eecs in IBS sufferers[188], further linking eecs not only to inflammation but also to intestinal infection.

Infection models and human correlation

Helminth infections in particular show alterations in eec function, perhaps due to the close association of helminths with the epithelium. Initial correlations were revealed in the livestock industry, with increases in serum CCK levels correlating with weight loss in pigs and lambs infected with the helminths *Ascaris suum* and *Trichostrongylus colubriformis* respectively[189, 190]. Calves infected with *Ostertagia ostertagi* have elevated gastrin[191] while sheep infected with *Ostertagia circumcincta* have reduced gastrin and somatostatin+ cells and this is linked to the development of hypergastrin~~a~~emia in parasitized animals[192]. Furthermore, helminth induced alterations are not limited to mammal livestock with increases in CCK cells seen in *Eubothrium crassum* infected trout[193] and *Anisakis simplex* infected flounders[194]; while CCK and gastrin+ cell increase, but GLP-1/2 reduce in *Eubothrium crassum* infected trout[193]. Experimental murine models have been used to further dissect the association of helminth infection with alterations in eec function.

CCK+ cell hyperplasia[195] and hypersecretion[196] are seen during *Trichinella spiralis* mouse infection and this correlates with hypophagia during enteritis. Furthermore, mice lacking CCK display no period of hypophagia associated with inflammation, identifying CCK as the sole mediator of hypophagia during this infection[195]. This does not seem to be the case in all helminth infections as serum CCK levels are reduced in *Nippostrongylus brasilliensis* infection in rats[197], while increased serum gastrin is seen during *T. spiralis*, but not tape worm infection[198]; furthermore decreased somatostatin+ cells are seen during intestinal inflammation resulting from intestinal schistomiasis in mice[199].

Importantly, alterations in eec function during infection are also reported in the clinic and are not limited to helminth infection, with increases in CCK+ cells occurring in patients with upper intestinal infection, such as *Giardia lambia*[200]. Alterations are also seen in bacterial and viral infection with reduced CgA+ cells seen in *Helicobacter pylori* patients[201]. In particular reductions in ghrelin are associated with disease pathology[202], with eradication of *H*. *pylori* associated with increased ghrelin which correlates with abatement of dyspepsia[203]. Importantly, in mouse models, changes occur prior to any general epithelial damage caused by the infection[204], while reduced 5-HT and somatostatin+ cells in HIV-1 infected individuals are associated with lower survival prognosis[205], again correlating alterations in eec function to pathology. Indeed, upon sensing chlamydia infection, eecs respond via a distinct transcript alteration[206], supporting their role as innate sensors of disease.

Collectively, the specific alterations of peptide secretion during inflammation indicate~~s~~ an uncoupling of eec subtype differentiation in disease, which holds promising therapeutic potential given the diverse functional roles of individual eec peptide hormones. In the case of infection, it will be interesting to resolve if peptide hormone release is driven by a detection of the parasites themselves or the microbial dysbiosis that often accompanies disease.

Intestinal neoplasia

As eec precursor cells are label retaining, Lgr5+ quiescent cells that have the potential to be recalled to the stem cell fate, they have a potential role in neoplasia[61]. Indeed, increased eec numbers in UC have been suggested to act as promoters for the neoplasia associated with IBD[207], with animal models demonstrating GLP-1 agonists as regulators of intestinal tumorigenesis[140]. Moreover, at rest a subset of eecs express the cancer-associated transcription factor Brachyury[208] and although rare, neuroendocrine tumors (NETs) are the most common cancer of the small intestine. Around 29% of small intestinal NETs carry amplifications or activating mutations in the PI3K/AKT/ mammalian target of rapamycin

(mTOR) pathway[209] and recent data demonstrating that EGF signaling is inhibited during eec differentiation[16], suggests it is reactivated during NET neoplasia[210]. Therefore, the current targeting of the mTOR pathway in intestinal neoplasia[211] is perhaps suggestive of a future focus on eecs in tumor pathology. Beyond the well-defined NETs, eecs have a long observed differentiation with sporadic colorectal cancer, occurring in 35% of colorectal carcinomas[212, 213] and are often associated with the proliferative compartments of adenocarcinomas[214, 215]. There is much debate regarding the clinical impact of eec differentiation on colorectal cancer, reviewed in[216]. Of particular interest is the production of VEGF from eecs during cancer[212, 217], a factor whose targeting has been shown to prolong survival in colorectal cancer patients[218, 219], and promising results are again coming from drug trials blocking mTOR[220, 221]. In line with the observations in IBD, the heterogeneity of intestinal neoplasia may account for some of the discrepancies seen, but beyond a strong correlation we are again in need of mechanistic studies, as well as stricter terminology within the intestinal cancer field[222].

MECHANISTIC CROSS-TALK BETWEEN ENTEROENDOCRINE CELLS AND IMMUNE CELLS DURING INTESTINAL INFLAMMATION

Inflammatory driven alterations in enteroendocrine cells

Numerous of the above studies correlate inflammation to alterations in eecs, and changes in IBD-mouse models are prevented with prior treatment of NFκβ or AP-1 inhibitors, which although not exclusively activated by immune cells, suggests the changes as immune driven[148, 223]. There is a close physical association of immune cells with eecs[224] and infection driven 5-HT+ cell hyperplasia observed during *Citrobacter rodentium* infection is absent in severe combined immunodeficiency (SCID) mice[225], as is the CCK and 5-HT+ cell hyperplasia seen in helminth infection[195, 226]. 5-HT+ cell increases seen during *T. muris* infection are also driven by specific T-helper (Th)2 CD4+ T-cell responses[227, 228]. Recent

studies have shown that the pro-inflammatory cytokines interferon (IFN)γ and TNFα increase CgA+ eecs in an autophagy and protein kinase B (Akt) dependent manner[229]. Bromodeoxyuridine (BrdU) pulse-chase labelling of proliferative cells has demonstrated that increases in 5-HT+ cells during TNBS-colitis are due to alterations in the stem cell niche rather than division of existing eecs[230]. Collectively this points to cytokine mediated alterations of specific eec subsets via adaptation at the stem cell niche as opposed to proliferation of existing eecs. Indeed, IL-33 derived from pericryptal fibroblasts during Salmonella infection has been shown to downregulate notch signaling in epithelial progenitors and increase CgA+ cells[231]. Due to the high turnover of intestinal epithelial cells eec hyper/hypoplasia can therefore quickly influence the inflammatory state. Cytokines can also directly mediate peptide hormone secretion with TNFα decreasing GLP-2 expression by up-regulating G-protein-coupled receptor 120 in CD[232], IL-6 increasing GLP-1 release[233], while IL-1β has been shown to cause 5-HT secretion from CD enterochromaffin cells *ex vivo*[234]. Immune cells and cytokines therefore directly influence eec biology and can mediate anorexia, which is now seen as a key modulator of specific immune responses[195, 235]. Furthermore, eec signaling can be protective to the gut, with peptide hormones shown to modulate barrier function and therefore potentially limit antigenic load (Fig. 3A). Moreover, this immunoendocrine crosstalk is unidirectional with chemosensory eecs able to mediate mucosal immunity, both direct and indirectly, acting as “cytokines” (Fig.3B) and~~or~~ initiating vagal anti-inflammatory pathways.

Direct Immune Modulation

Enteroendocrine production of cytokines

Similar to recent findings in the chemosensory Tuft cells subset[26, 236-238], eecs are a source of cytokines and play roles in intestinal disease progression. Enteroendocrine cells have functional toll-like receptors and secrete cytokines following toll-like receptor (TLR) 1, 2 and

4 stimulation resulting in increased NF-κβ, MAPK signaling, as well as Ca^{2+} flux culminating in TNFα, transforming growth factor (TGF)β,macrophage inflammatory protein-2 and CCK release[74]. Importantly, eecs are able to modulate their secretome in response to pathogenic detection, secreting chemokine (CXC-motif) 1/3 and IL-32 in response to flagellin and lipopolysaccharide (LPS), but not to fatty acids[239]. In the case of IBD eecs are key producers of the pro-inflammatory cytokine IL-17C and therefore are involved in the pathogenesis of active disease[240]. Mice lacking the exopeptidase carboxypeptidase E (CPE), an eec specific processing peptide, demonstrate reduced levels of PYY and are more susceptible to DSS-induced colitis[241]. Moreover, at rest these mice display elevated IL-6 and KC levels from the epithelium as a whole, suggesting a CPE mediated immunosuppressive effect on intestinal barrier function by influencing the processing of specific neuropeptides[241].

Enteroendocrine peptide modulation of barrier function

Further to producing cytokines, peptide hormones themselves have innate roles in maintaining barrier function (Fig. 3A). At the most basic level they play a role in detecting toxins, with eecs releasing CCK following activation of the T2R38 bitter receptor limiting the absorption of toxic substances through modulation of gut efflux membrane transporters in neighboring epithelium[242]. Moreover, chemotherapy drug induced emesis is dependent on 5-HT release and 5-HT3 receptor triggering[243], while more recently rotavirus toxin induced emesis was hypothesized to act via a similar mechanism[244]. Interestingly, CCK and motilin can alter the behavior and movement of the liver fluke *Fasciola hepatica* [245] , while ghrelin also has direct anti-parasitic[246] and anti-bacterial effects[247], although the basolateral release of peptide hormones brings this suggested anti-microbial function into question. Moreover, eecs modulate production and secretion of classical anti-microbials, Drosophila have been shown to respond to *Pseudomonas entomophila* by expressing the peptide hormone allatostatin A which in turn regulates epithelial cell antimicrobial peptides and survival[248]. The

process of peptide hormones influencing anti-microbial production also extends to Paneth cells. GLP-2 receptor null mice have increased bacterial colonization of the small intestine and reduced expression of Paneth cell antimicrobial gene products[102], although it remains to be ascertained if this is a result of other cellular phenotypes arising in the GLP-2 receptor null mouse[102].

Beyond anti-microbial effects, GLP-2 has been seen to maintain barrier function in mouse[97, 249], and human[250] models, via the modulation of intestinal tight junction mechanisms and hence directly influences intestinal permeability. The most well studied role of peptide hormones influencing barrier function is that of GLP-2[141], and more recently GLP-1[140], as potent epithelial growth factors. GLP-2s trophic affects act via myofibroblast produced insulin-like growth factor[141] and keratinocyte growth factor[251] as well as the ErbB signaling network in intestinal tissue[252]; while GLP-1 mediates growth via fibroblast growth factor 7[140].

Enteroendocrine peptides as "cytokines"

Intriguingly, immune cells express a vast array of receptors for eec secreted hormone peptides[253] suggesting the potential for peptide hormones to act as "cytokines" (Fig. 3B). Most notably the adipokine leptin and the amines histamine and 5-HT, although not exclusively produced from eecs, have well established direct immunomodulatory roles on numerous innate and adaptive cell types; reviewed in[254-256].

Similarly to leptins role in influencing CD4+ T-cell responses, eec peptides have been shown to modulate T-cell polarization; nesfatin-1 has been linked to Th17 cell activation[257], while conversely ghrelin inhibits Th17 formation[258] via mTOR[259], being beneficial in EAE models[260, 261]. CCK has been shown to promote a Th2[262] and regulatory T-cell (Treg) phenotype *in vitro*[262], as does GLP-1[263] via decreased MAPK activation[264]. As well as influencing T-cell differentiation, peptide hormones can also shape T-cell proliferation and migration. The orexigenic peptide hormone ghrelin increases T-cell proliferation via Phosphatidylinositol-

4,5-bisphosphate 3-kinase, extracellular signal–regulated kinases and protein kinase C[265] and has an anti-inflammatory effect in DSS colitis[266]; with CD patients interestingly demonstrating a reduction of the ghrelin receptor GHSR-1a on T-cells[267]. Somatostatin is also inhibitory to T-cell proliferation [268], downregulates LFA-1 expression[269] and is ultimately involved in thymus development[270]. Apart from CD4+ T-cells, GLP-1 signals to intraepithelial lymphocytes ameliorating the inflammation in DSS induced colitis[271] and signals to fat resident invariant NKT-cells mediating weight loss[272] and psoriasis at the skin barrier[273]. A number of these effects seem to be tissue specific with somatostatin inhibiting Peyer's patch, but not splenic natural killer activity[274]; and CCK altering lamina propria but not blood sourced cells[275].

B-cells are also under the control of peptide hormones with CCK driving acetylcholine (Ach) production to recruit neutrophils independently of vagal stimulation[276]. CCK[277] and somatostatin[278] can reduce B-cell activation, while ghrelin[279] and neurotensin[280] are able to enhance B-cell activation and proliferation respectively. CCK[277], somatostatin[278] and GLP-2[281] also influence immunoglobulin production and strikingly, the huge reduction in Immunoglobulin A production, seen during parenteral feeding can be rescued via the infusion of CCK[253, 282], although the mechanism remains undefined.

Eec peptide hormones also modulate innate immunity and hence quickly relay chemosensory detection of microbial metabolites and pathogens to the immune system. CCK has been shown to inhibit TLR9 stimulation of plasmacytoid DCs via TNF receptor associated factor 6 signaling[283], while somatostatin[284] and neurotensin[285] are also reported to be inhibitory to DC activation. Conversely CCK can promote IL-12 production[286] and secretin acts as a chemoattractant to DCs[287] suggesting more than a simple, global peptide hormone anti-inflammatory signal. Similarly, macrophages and monocytes are influenced by peptide hormones. CCK can inhibit macrophage activation[288-290], including inducible nitric oxide synthase production[291], and cause monocytes to produce inflammatory cytokines and eicosanoids[292]. Several studies have importantly also deciphered the intracellular pathways

involved,GLP-1 receptor agonists reduce endoplasmic reticulum stress and decrease inflammation-associated gene expression in macrophages[293, 294], while GLP-2 inhibits macrophage LPS stimulation via reduced NFκβ[295] in an IL-10 independent manner[142]. Discrepancies in these *in vitro* studies exist, with monocytes releasing IL-6 in response to somatostatin[296], while it can be anti-inflammatory in other settings[297], similar to GLP-1[298] and ghrelin[299, 300]. Peptide hormones appear to play an important role in transferring luminal signals during obesity, be it nutritional or microbial, to the immune system. GLP-1 agonists can inhibit monocyte to foam cell transition via altering autophagy, but this occurs only in obese patients[301], placing eecs under the spot light in this growing epidemic.

Granulocytes are generally inhibited by peptide hormone signaling; with basophils and eosinophils immunosuppressed by somatostatin[113] and GLP-1[302] respectively. Neutrophil phagocytosis[303-305], elastase release[306] and adhesion[305, 307] are all inhibited by multiple peptide hormones, of particular interest is the role of GIP in ameliorating obesity-induced adipose tissue inflammation via modulation of neutrophil function[308]. Most notably mast cells are strongly responsive to peptide hormones, with CCK[309], gastrin[310] and somatostatin[311] inhibitory for degranulation, while ghrelin[312] and PYY[313] increase histamine release. CCK also induces intestinal contraction via mast cells during *Giardia* infection[314], demonstrating distinct fine tuning of mast cell function over other granulocytes. Interestingly, mast cells can populate 5-HT+ producing cells in the *Neurog3* null mouse[315], and under homeostatic conditions share a transcriptome similar to mast cells[316], presenting an evolutionary link between these cellular populations. Eecs therefore have a unique ability to sense the intestinal environment and directly interact with the underlying innate and adaptive immune system through cytokines and peptide hormone signaling.

The purest evidence of peptide hormone immune cell influence is via *in vitro* assays, especially given the numerous pathways and tissues these hormones may affect. However,

older studies may have been susceptible to endotoxin contamination[317] and cell specific peptide receptor-null studies are required to fully decipher the overall importance of the immunoendocrine axis.

Indirect immune modulation

Vagal anti-inflammatory reflex

Eec released peptide hormones may also influence immunity via signaling to vagal afferents and influence the intestinal cholinergic anti-inflammatory pathway[318] via the release of Ach from vagal efferents. Recent evidence has demonstrated that eecs possess a direct contact with neurons and this “neuropod” allows direct neuroepithelial communication[319], a portal that pathogens may have evolved to target infection of the nervous system[320-322].. This anti-inflammatory pathway was originally highlighted in an LPS model of hemorrhagic shock; prior nutritional stimulation of mice with a high-fat diet induced a vagal reflex and Ach release which inhibited LPS-induced cytokine secretion and reduced pathology. This was seen to be dependent on vagal CCK stimulation and resulting Ach stimulation of macrophage alpha7-nAch receptor[323]. This pathway is also dependent on post-absorptive chylomicron formation, lipoprotein formations shown to release endogenous CCK[324] and also requires GLP-1 receptor activation[325] and potentially ghrelin[326]. GLP-2 also acts via enteric nerves to increase the secretion of immunomodulatory vasoactive intestinal peptide during animal models of IBD[327].

Others have demonstrated similar CCK-induced vagal anti-inflammatory pathways in a variety of inflammatory settings, such as post-operative ileus[328] and lung damage during endotoxemia[329]. Furthermore, interfering with the vagal reflex has also been shown to exacerbate DSS colitis[330]. Although not thought to be B or T-cell dependent[331], CCK induced Ach release has also been shown to influence other innate cells such as mast cells[332]. Recently vagally released Ach has been shown to influence the level of a key host-

protective mediator, PCTR1, in group 3 innate lymphoid cells (ILCs) regulating tissue resolution tone and myeloid cell responses in an *E.coli* peritonitis model[333]. However, it remains to be seen if eec peptides can influence Ach production to effect intestinal specific cell types or directly modulate ILC function. This anti-inflammatory role of the vagus nerve, and therefore eec peptide hormone stimulation, is an exciting and growing area of research[334].

Control of appetite

Beyond the vagal reflex response is the concept of altered feeding itself as an immune modulator. This is not a new concept with the adage “starve a fever, feed a cold” familiar to many, however growing evidence has demonstrated that anorexia is an essential aspect of certain[335-337] , but not all[338], acute infections. Most recently, Medzhitov and colleagues have confirmed that although anorexia is beneficial in *Listeria monocytogenes* infection, it is detrimental during influenza. This was shown to be due to the differing stress pathways elicited during the distinct immunopathology associated with each disease, and therefore explains why anorexia does not always supply the correct metabolic requirements for tolerance in each disease setting[235]. This offers the intriguing hypothesis that feeding behavior induced by altered eec dynamics is an attempt to influence immunity and minimize immunopathology.

Utilizing the helminth *T. spiralis* model of T-cell induced eec driven hypophagia[196], Worthington and colleagues investigated the possible molecular mechanisms and actual purpose of the hypophagia seen during this parasitic infection. During infection CD4+ T-cells hijack classical cholecystokinin feeding pathways to reduce food intake during enteritis[195, 196]. Increased c-Fos brain expression during helminth infection[339, 340], supports that hypophagia relies on increased gut-brain axis signaling, as opposed to intestinal hypomotility. This hypophagia results in significant weight loss and visible reduction of visceral fat pads, which

are a key source of adipokines such as leptin[255, 341]. As T-cells express functional leptin receptors[342] and leptin stimulation polarizes T-cells towards a pro-inflammatory Th1 state[343], it was postulated that the immune driven reduction in leptin driven by CCK during *T. spiralis* infection, would be beneficial in allowing a helminth expelling Th2 immune response to develop. Indeed, delayed expulsion of *Heligmosomoides bakeri* is seen in protein deficient mice and is linked to higher levels of leptin[344]. Restoration via recombinant leptin treatment, resulted in a significant reduction in CD4+ Th2 cytokine production and accompanying mastocytosis, which is essential for worm expulsion[345]. This restoration of basal leptin levels and shift in immune response culminated in a significant delay in parasite expulsion. Hence, identifying immune driven alterations in eec mediated feeding mechanisms, as a novel mechanism in helminth expulsion[195].

CONCLUSIONS

In summary, the eec secretome encompasses cytokines as well as peptide hormones that have the ability to directly and indirectly influence the majority of the intestinal mucosal immune system. Novel transgenic reporter models are now allowing the scientific community to fully investigate this exciting crosstalk between our intestinal endocrine and immune systems, opening up the possibility to repurpose current drugs used for metabolic syndromes in wider immune inflammatory settings such as IBD, infection and cancer. Indeed, as eecs transpose microbial signals it may be possible to utilize eec peptide agonist/antagonists over and above microbial interventions in the treatment of disease. Moreover, the expression and role of epithelial endocrine cells at other mucosal sites such as the lung is hugely understudied. Indeed, this potential may go beyond diseases of the intestine with peptide agonists showing potential in models of psoriasis, multiple sclerosis and rheumatoid arthritis[260, 273, 286], highlighting the huge therapeutic potential of the immunoendocrine axis.

AUTHOR CONTRIBUTIONS

JJW, FR and FMG wrote the article

DISCLOSURE

F.M.G. and F.R. have research collaborations with AstraZeneca/MedImmune. F.M.G. has received honoraria for speaking at symposia organized by Novo Nordisk and is a member of the external scientific advisory board of BioKier. F.R. has received honoraria for speaking at symposia organized by MSD.

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Figure 1. Intestinal epithelial cell differentiation. Epithelial cells arise from the same LGR-5+ pluripotent stem cell found in the crypt niche and based on the expression of the Notch-dependent basic helix loop helix transcription factors *Hes-1* or *Atoh-1* develop into absorptive enterocytes or secretory epithelial lineages, or via SpiB transcription factor expression to antigen-sampling M-cells. The secretory cells further differentiate into mucin secreting goblet cells, anti-microbial peptide secreting Paneth cells, opioid and alarmin secreting Tuft cells and peptide hormone secreting enteroendocrine cells, whose peptide hormone secretome further depends on spatio-temporal expression of further transcription factors.

Figure 2. Spatio-temporal expression of enteroendocrine peptide hormones. The dogma of terminally differentiated enteroendocrine cells secreting individual peptide hormones has been superseded with a secretome that contains a comprehensive array of peptide hormones altering based on their location within the gut. However, the traditional lettering nomenclature helps to demonstrate the role and function of individual peptide hormones.

Figure 3. Enteroendocrine cell influence on epithelial barrier function and immune cells. (A) Enteroendocrine cells possess multiple chemosensory apparatus and are uniquely equipped to sense microbial metabolites and PAMPs. In response they secrete both peptide hormones and cytokines which directly influence barrier function. **(B)** Furthermore, as mucosal immune cells have numerous receptors for peptide hormones they can act as “cytokines” and can therefore be directly influenced by enteroendocrine cells. Reference numbers are indicated in superscript and black arrows indicate increase or decrease in specified cell activation.

Table 1. Transcription factors required for enteroendocrine differentiation. The following table has been produced from published literature based on observations from genetic knockdown of specific transcription factors in mice. Reference numbers are indicated in superscript. X indicates non-present, arrows indicate increase or decrease in detection, NE= not examined, NC= No change, If only specific tissues are examined brackets indicate which, with, st, d, j, i identifying stomach, duodenum, jejunum and ileum respectively.

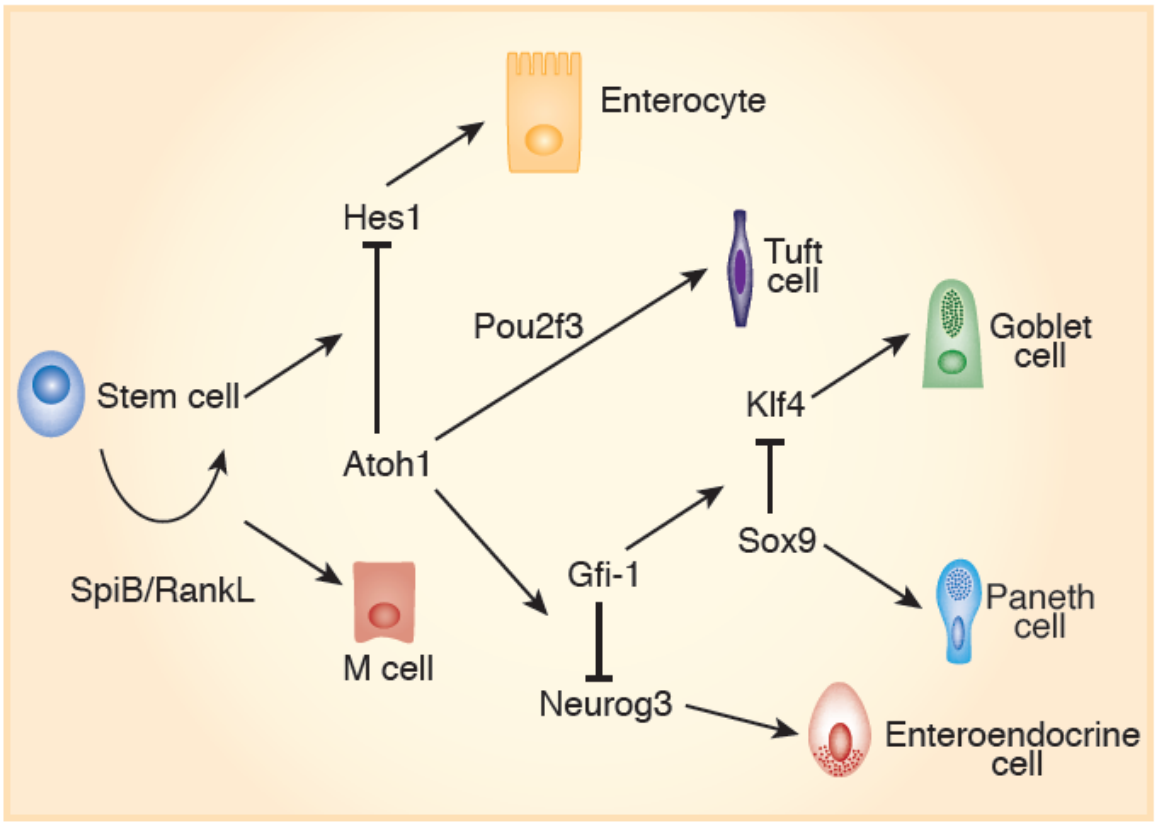
Table 2. Alterations in enteroendocrine peptides during IBD. The following table has been produced from published literature based on observations in the clinic. Reference numbers are indicated in superscript and arrows indicate increase or decrease in measured parameter for specified peptide hormone. * importantly in all of these studies patients were free from the use of protein pump inhibitors.

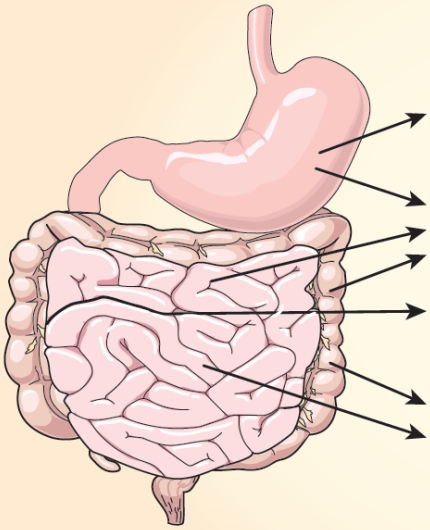
Table 3. Alterations in enteroendocrine peptides during murine models of IBD. The following table has been produced from published literature based on observations in indicated IBD models. Reference numbers are indicated in superscript and arrows indicate increase or decrease in measured parameter for specified peptide hormone.

	Neurog3	*Neurod1*	*Pax4*	*Pax6*	*Isl1*	*Pdx1*	*Nkx2-2*	*Cdx-2*	*GATA4*	*GATA6*	*HNF1-α*
Ghrelin	X (NC st) [31]	NE	NE	NE	NC [39]	NE	↑(d, j, i) [44]	↑(d, j, i) [48]	NE	NC [50]	↑(d, j, i) [55]
Histamine	X (NC st) [31]	NE	NE	NE	NE	NE	NE	NE	NE	NC [50]	NE
Gastrin	X [30]	NC [35]	NC [36]	↓ [36]	NE	X [40]	↓(d, j, i) [44]	NE	NE	NC [50]	NE
Somatostatin	X [30]	↓(d, i) [35]	X (st) [36]	X (st) [36]	↓(d) [39]	NC [40, 42]	↓(d, j, i) [44]	NE	NE	↓(i) [50]	↓(d, j, i) [55]
5-HT	X (NC st) [31]	↓(d, i) [35]	↓ (st,d) [36]	NC [36, 38]	↑(d) [39]	↑(st) [40] ↓(d) [42]	↓(d, j, i) [44]	NE	NE	NC [50]	NE
CCK	X [30]	X(d, j, i) [34, 35]	↓ (d) [36]	X (d) [36]	↓(d) [39]	↓(d) [42]	↓(d, j, i) [44]	NE	↓(d, j) [51]	↓(i) [50]	NE
GIP	X [30]	↓(d, i) [35]	↓ (d) [36]	↓ (d) [36]	↓(d) [39]	↓(d) [40]	↓(d, j, i) [44]	NE	NE	NC [50]	↓(d, j, i) [55]
Secretin	X [30]	X(d, j, i) [34, 35]	↓ (d) [36]	NC [36, 38]	NE	↓(d) [40]	NC [44]	NE	NE	NC [50]	NE
GLP-1	X [30]	↓(d, i) [35]	NC [36]	X [38]	↓(d) [39]	NC [42]	↓(d, j, i) [44]	NE	NE	↓(i) [50]	NC [55]
GLP-2	X [30]	↓ (d, i) [35]	NC [36]	X [38]	↓(d) [39]	NE	↓(d, j, i) [44]	NE	NE	↓(i) [50]	NE
PYY	X [30]	↓ (d, i) [35]	↓(d) [36]	NC [36, 38]	NE	↓(st) [40]	NC [44]	NE	↑(d, j) [51]	↓(i) [50]	NE
Neurotensin	X [30]	NC [34]	NE	NE	NE	↓(d) [40]	↓(d, j, i) [44]	NE	NE	↓(i) [50]	NE

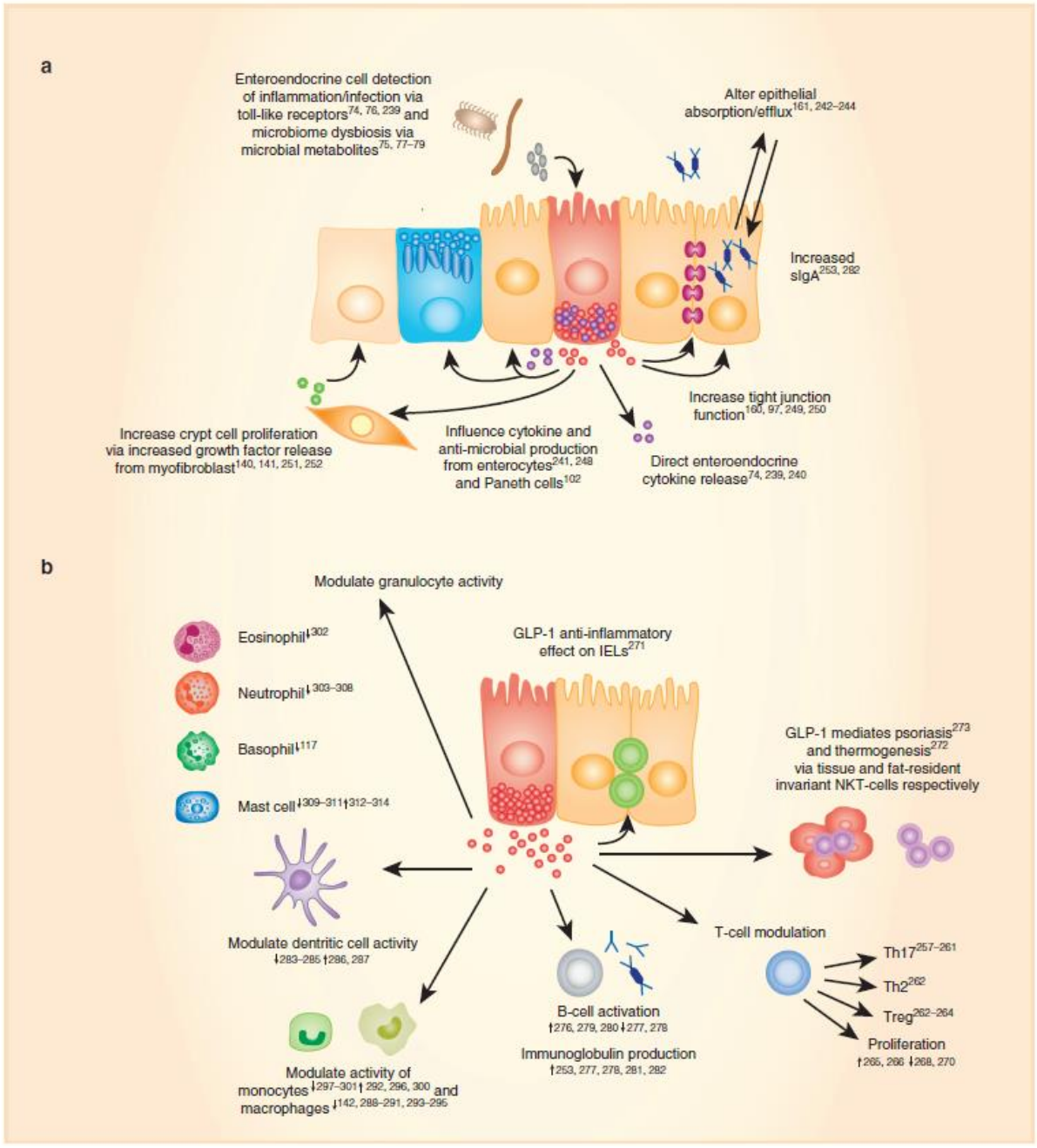
	Ulcerative colitis			Crohn's Disease			Microscopic colitis
	Serum	Plasma	Histology	Serum	Plasma	Histology	Histology
Ghrelin	↑[118-121]			↑[115, 118—121]			
Gastrin*	↑[124]			↑[123]	↑[125]	↑[131]	
Somatostatin		↑[116, 117]	↓[136]			↓[136]	
5-HT			↓[134]			↓[134]	↑[135]
CCK					↑[127, 128]		
GLP-1	↑[126]	↑[128,129]		↑[126]		↑[106]	
GLP-2			↑[137]			↑[137]	
PYY	↓[112]		↓[112, 133]	↑[112, 114, 115]		↓[132]	↑[135]

	Chemical		Genetically prone		Immunocompromised
	TNBS	DSS	TCRα-/-	IL-2-/-	T-cell transfer
CgA	↓[148]				
Somatostatin	↑[148]	↓[160]			
5-HT	↑[148, 149]		↓[152]	↓[153]	
Neurotensin		↑[162]	↓[152]		
CCK			↓[152]		
GLP-1					↑[151]
GLP-2	↑[149]				↓[150]
PYY	↓[148]	↓[144]		↓[153]	
Oxyntomodulin	↑[148]				


Enterocyte
Hes1
Tuft cell
Pou2f3
Goblet cell
Stem cell
Klf4
Atoh1
Sox9
SpiB/RankL
Gfi-1
Paneth cell
M cell
Neurog3
Enteroendocrine cell



Traditional nomenclature and associated peptide hormone	Function
A (X-like) cells (Ghrelin, nesfatin-1)	Appetite, growth hormone release
Enterochromaffin-like-cell (histamine)	Acidity
G cells (Gastrin)	Acidity
P cells (Leptin)	Appetite
D cells (Somatostatin)	Acidity and insulin
Enterochromaffin cell (5-HT)	Appetite and motility
I cells (CCK)	Appetite, motility, bile acid and enzyme release
K cells (GIP)	Insulin
S cells (Secretin)	Acidity
M cells (Motilin)	Motility
L cells (GLP-1, GLP-2, PYY, oxyntomodulin)	Appetite, Insulin, motility
N cells (Neurotensin)	Motility


a
Enteroendocrine cell detection of inflammation/infection via toll-like receptors[74, 76, 239] and microbiome dysbiosis via microbial metabolites[75, 77–79]
Alter epithelial absorption/efflux[161, 242–244]
Increased sIgA[253, 282]
Increase tight junction function[160, 97, 249, 250]
Direct enteroendocrine cytokine release[74, 239, 240]
Influence cytokine and anti-microbial production from enterocytes[241, 248] and Paneth cells[102]
Increase crypt cell proliferation via increased growth factor release from myofibroblast[140, 141, 251, 252]
b
Modulate granulocyte activity
Eosinophil↓[302]
Neutrophil↓[303–308]
Basophil↓[117]
Mast cell↓[309–311]↑[312–314]
GLP-1 anti-inflammatory effect on IELs[271]
GLP-1 mediates psoriasis[273] and thermogenesis[272] via tissue and fat-resident invariant NKT-cells respectively
Modulate dentritic cell activity ↓[283–285]↑[286, 287]
T-cell modulation
Th17[257–261]
Th2[262]
Treg[262–264]
Proliferation ↑[265, 266]↓[268, 270]
B-cell activation ↑[276, 279, 280]↓[277, 278]
Immunoglobulin production ↑[253, 277, 278, 281, 282]
Modulate activity of monocytes ↓[297–301]↑[292, 296, 300] and macrophages ↓[142, 288–291, 293–295]