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Enteroendocrine cells regulate intestinal homeostasis and epithelial function

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ABSTRACT

Enteroendocrine cells (EECs) are well-known for their systemic hormonal effects, especially in the regulation of appetite and glycemia. Much less is known about how the products made by EECs regulate their local environment within the intestine. Here, we focus on paracrine interactions between EECs and other intestinal cells as they regulate three essential aspects of intestinal homeostasis and physiology: 1) intestinal stem cell function and proliferation; 2) nutrient absorption; and 3) mucosal barrier function. We also discuss the ability of EECs to express multiple hormones, describe *in vitro* and *in vivo* models to study EECs, and consider how EECs are altered in GI disease.

1. The GI tract is organized to maximize nutrient absorption

The gut is responsible for acquiring the nutrients required to fuel the whole body and is essential for the survival of all vertebrate and invertebrate animals (Hartenstein and Martinez, 2019). Some invertebrates, like insects and worms, and all vertebrate animals have developed a specialized gastrointestinal (GI) tract that is remarkably conserved among species. In mammals, nutrient absorption begins with secretion of salivary enzymes, mastication of food, and transport to the stomach. The stomach prepares macronutrients for absorption by churning the masticated food with gastric acid and digestive enzymes to form chyme. Chyme flows into the duodenum where it is mixed with pancreatic enzymes and bile to further break down into absorbable sugars, di- and tri-peptides, and free fatty acids. The proximal small intestine, including the duodenum and jejunum, absorb the vast majority of dietary nutrients, with the ileum responsible for reclaiming and recycling unused bile acids. The surface area of the small intestine is increased by coiling the tube, folding the epithelium into crypt-villus units, and the presence of microvilli on the brush border membrane of enterocytes, together increasing the absorptive surface 60–120 times (Helander and Fändriks, 2014). The microbial colonization of the gut increases distally, feeding on unabsorbed nutrients, and produces metabolites which are recognized by the intestinal epithelial cells. The colon extracts water from the luminal contents, and any unabsorbed nutrients are excreted. In healthy individuals, the GI tract is ~90–98% efficient at absorbing ingested nutrients (Lund et al., 2020), but GI disease can dramatically reduce absorptive efficiency. Many factors contribute to absorptive efficiency, including epithelial homeostasis, nutrient density, nutrient-nutrient interactions, gut motility, epithelial damage, and microbial diversity. One underappreciated regulator of nutrient absorption and intestinal homeostasis is the enteroendocrine cell (EEC), which participates in every aspect of gut function and systemic nutrient handling.

2. EECs are rare but widely diversified and distributed throughout the GI tract

EECs are sensory cells within the intestine that secrete biologically active peptides, neurotransmitters, and metabolites in response to environmental stimuli like nutrients and microbes. The sensory receptors and secretory machinery of EECs have recently been reviewed (Barton et al., 2023), as has the intimate relationship between EECs and the microbiome (Masse and Lu, 2023; Worthington et al., 2018; Yu et al., 2019). EECs are evolutionarily ancient cells that serve as a functional link between nutrient input and systemic responses to ingestion of a meal, and have been identified in all species of animals, from sea stars and sea cucumbers (García-Arrarás et al., 2019) to axolotl (Maake et al., 2001), fish (Wallace et al., 2005; Z. Wang et al., 2010), flies (Guo et al., 2022; Jang et al., 2021; Medina et al., 2022), frogs and reptiles (Trandaburu and Ali, 1998; Trandaburu and Nürnberger, 1995; Trandaburu

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and Trandaburu, 2007), and mammals (Beumer and Clevers, 2021). EECs are required for proper gut function as genetic loss of EECs severely impairs its absorptive capacity, resulting in failure to thrive and malabsorptive diarrhea in mouse models (Mellitzer et al., 2010) and human children (Wang et al., 2006).

Despite comprising only ~1% of the intestinal epithelium, EECs and their derived products regulate systemic nutrient handling by signaling via G-protein coupled receptors (GPCRs) located on target tissues. For example, peptide YY (PYY) and cholecystokinin (CCK) signal satiety to the brain (Batterham et al.; Gibbs et al., 1973); glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) augment insulin secretion from the pancreas (Drucker et al., 1987; Ebert and Creutzfeldt, 1982; Kreymann et al., 1987); CCK and secretin promote bile, bicarbonate, and digestive enzyme release (Bayliss and Starling, 1902; Denton et al., 1950; Liddle et al., 1986); and serotonin (5-HT) and somatostatin regulate smooth muscle contractions driving intestinal motility (Mawe et al., 1989; Ormsbee et al., 1978). While EECs are traditionally known for their endocrine functions, EEC receptors are abundant on enteric neurons (Egerod et al., 2018) and many EEC-derived products directly influence enteric neuronal activity (L. Ye et al., 2021). Moreover, some EECs directly synapse with enteric neurons via a long cytoplasmic process termed the neuropod (Bohorquez et al., 2015), and can transmit the presence of sugar to the brain in milliseconds (Kaelberer et al., 2018). Beyond the enteric nervous system, the paracrine role of EECs in regulating local functions within the intestinal mucosa itself has been largely overlooked and is the subject of this review.

The intestinal epithelium is maintained by intestinal stem cells (ISCs), which are highly proliferative, replenishing the entire epithelium every ~5 days, and give rise to both the absorptive and secretory cell lineages. ISC proliferation, differentiation, and homeostasis are regulated in part by levels of classical signaling pathways, including Wnt (wingless-related integration site), Notch, and BMP (bone morphogenetic protein), which are conserved in flies (Hartenstein et al., 2010), fish (Crosnier et al., 2005; Flasse et al., 2013; Roach et al., 2013), and mammals (Beumer and Clevers, 2021; Hartenstein et al., 2010). In mammals, high Wnt signaling in the crypts supports its proliferative capacity, whereas increasing BMP signaling toward the villus tip promotes terminal differentiation of most migrating progenitors (Beumer and Clevers, 2021). Paneth cells remain in the low BMP crypt to support ISC function. Differentiated EECs can be found in both crypts and villi, with some hormone expression responsive to BMP signaling (Beumer et al., 2018) (discussed in depth below).

In all animals, the diversity of EEC subtypes is driven by a hierarchical cascade of transcription factors acting in a combinatorial fashion (Guo et al., 2022a,b; Sanchez et al., 2022). In mammals, secretory progenitors which express the basic helix-loop-helix transcription factor *neurogenin 3* (*Neurog3*) will differentiate into EECs, with loss of Neurog3 preventing EEC formation in mouse (Jenny et al., 2002; Mellitzer et al., 2010) and human (Cortina et al., 2007; Wang et al., 2006). While some Neurog3+ progenitors can also give rise to the other cell types (discussed in depth in section 4.2), expression of the basic helix-loop-helix transcription factor *neuronal differentiation 1 (NeuroD1)* restricts Neurog3+ cells to the EEC fate (Li et al., 2019). Subsequent action of signaling networks and combinatorial transcription factors acting downstream of Neurog3/NeuroD1 segregate EEC progenitors into broad subtypes and have recently been reviewed (Beumer et al., 2020; Sanchez et al., 2022). Lineage tracing experiments and single-cell RNA sequencing demonstrate that mRNA expression and peptide translation of multiple hormones within the same cell are common, and can change with migration and age of the cell (Bai et al., 2022; Beumer et al., 2018; Beumer et al., 2020; Billing et al., 2018; Egerod et al., 2012; Fazio Coles et al., 2019; Fothergill and Furness, 2018; Gehart et al., 2019; Glass et al., 2017; Grunddal et al., 2016; Habib et al., 2012; Roberts et al., 2019). Recent advances in intersectional genetic and chemogenetic approaches to activate certain subtypes of EECs have also demonstrated how a single cell type secretes multiple products to drive whole-body metabolism (Bai et al., 2022; Hayashi et al., 2023; Lewis et al., 2020). These findings render traditional classification systems obsolete (Beumer et al., 2020; Fothergill and Furness, 2018), and highlight a need to focus on the regulation and functions of individual EEC-derived products.

EECs are broadly distributed from the stomach to the rectum. In this review, we focus on EECs found in the mammalian small intestine as they relate to homeostasis and nutrient absorption. Most EEC-derived peptides are enriched in one segment of the intestine and emanate a gradient of expression either proximally or distally (Fig. 1). EECs in the proximal small intestine express high levels of CCK, motilin, secretin, ghrelin, gastrin, and GIP, whereas EECs in the distal small intestine express high levels of GLP-1, GLP-2, PYY, and neurotensin. GLP-1 and PYY also populate the proximal small intestine with less frequency. Somatostatin, serotonin (5-HT), and Tac1 are abundant throughout the length of the small intestine (Beumer et al., 2018; Billing et al., 2018; Burclaff et al., 2022; Egerod et al., 2012; Haber et al., 2017; Hayashi et al., 2023; Roth and Gordon, 1990; Svendsen et al., 2016).

Some EECs are also spatially enriched in either the crypt or the villus of the small intestine (Grunddal et al., 2016; Roth and Gordon, 1990), often replacing the expression of one hormone for another as they migrate up the villus and are exposed to increased BMP signaling (Beumer et al., 2018) (Fig. 1). For example, GLP-1 and PYY are often co-expressed in the crypt, but villus cells expressing PYY rarely co-express GLP-1 (Beumer et al., 2018). Similarly, 5-HT expressing EECs are represented in both the crypt and the villus, but predominantly co-express Tac1 in the crypt and secretin in the villus (Beumer et al., 2018). Manipulation of BMP levels in enteroids *in vitro* (discussed in section 3.3) followed by bulk RNA sequencing revealed that expression of some spatially-enriched hormones, like secretin, GLP-1, PYY, and neurotensin, were responsive to BMP signaling, whereas hormones that are found in both the crypt and villus, like Tph1 (5-HT), CCK, and GIP, were insensitive to BMP (Beumer et al., 2018).

The spatial and regional distribution of diverse EEC-derived products support the myriad of digestive and metabolic functions regulated by this rare cell type. In this review, we focus on the local interactions of EECs with their surrounding environment that maintain intestinal homeostasis and enable nutrient absorption.

3. Models to study EECs

Because EECs are quite rare, it has been difficult to study them, especially in human intestine where investigations have been historically limited to immunostaining and measuring serum hormone levels. Genetic manipulation of *Drosophila,* zebrafish, and mouse have been essential tools to begin to understand EEC biology. More recently, 3D human intestinal organoids have become a useful platform for mechanistic insights into human EEC formation and function.

3.1. Genetic manipulation in model organisms

The development and function of EECs is evolutionarily conserved, allowing for critical insights into EEC biology in model organisms such as *Drosophila*, zebrafish, and mice. In mouse, genetic loss of various transcription factors has helped narrow down the transcriptional networks that drive diversity in EECs. Many of these transcription factors had originally been described as regulating endocrine differentiation in the pancreas, which shares developmental origins with the intestine. Loss of function experiments have demonstrated that combinatorial expression of transcription factors downstream of the master endocrine regulator Neurog3, along with positional patterning across the proximal-distal axis, result in the variety of products expressed by EECs.

Mice with loss of Neurog3 do not form any EECs (Jenny et al., 2002; Mellitzer et al., 2010), which was also observed in human patients with mutations in NEUROG3 (Cortina et al., 2007; Wang et al., 2006). Loss of

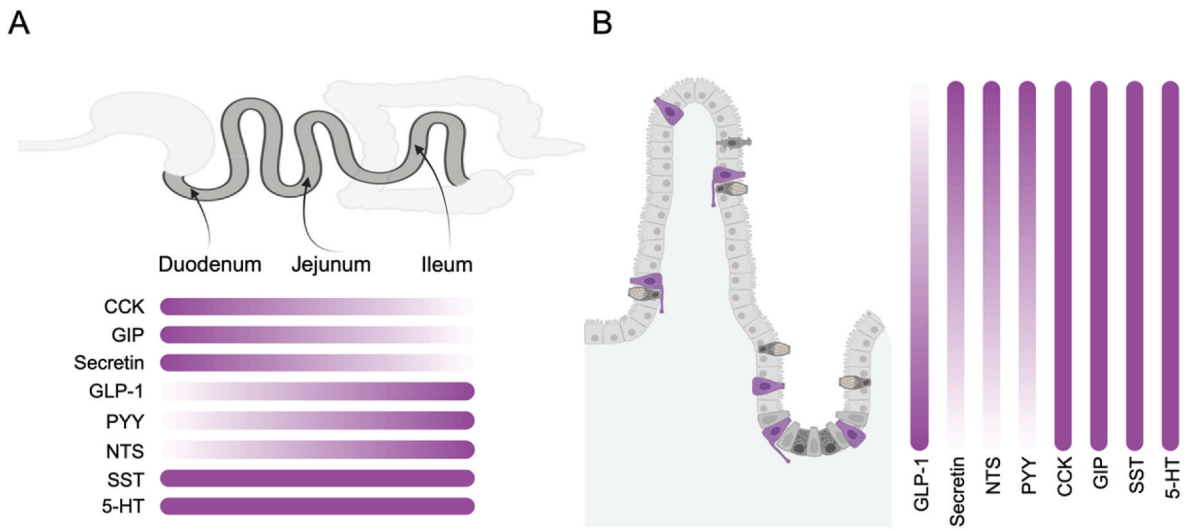

Fig. 1. EEC hormone expression varies along the proximal-distal and crypt-villus axes of the mammalian GI tract. A. Different EEC-derived products are enriched in the proximal small intestine compared to the distal small intestine. B. Within these regions, EEC-derived products can be enriched either in the crypt region or in the villus. Figure generated using BioRender.com.

function of other endocrine transcriptional regulators only results in loss of subsets of EECs, demonstrating the complex regulation by which one Neurog3+ progenitor can generate so many different EEC subtypes. Many of these transcription factors act as decision points between subtypes of EECs, as loss of one subset drives the concomitant increase in expression of the others. This leads to difficulty in interpreting the results of some genetic experiments, as observed phenotypes may be due to loss of certain EEC-derived products or caused by the de-repression and increase of others. One of first decision points is whether an EEC progenitor will express peptidergic hormones or 5-HT. This decision is regulated by expression of *regulatory factor 6 (Rfx6)*, which promotes the expression of peptidergic hormones while repressing 5-HT synthesis (Piccand et al., 2019). Downstream of *Rfx6*, *aristaless-related homeobox (Arx)* (Beucher et al., 2012; Du et al., 2012; Terry et al., 2015) and *pancreatic and duodenal homeobox 1 (Pdx1)* (Chen et al., 2009), further refine EEC subtypes in a combinatorial manner. These transcription factor networks are evolutionarily conserved, with human patients harboring mutation in these transcription factors recapitulating endocrine phenotypes observed in mouse (Krishnamurthy et al., 2022; Sanchez et al., 2024). The transcriptional networks that govern EEC differentiation have recently been reviewed (Sanchez et al., 2022).

Recent advances in intersectional genetic and chemogenetic approaches have enabled researchers to specifically activate subpopulations of EECs. These approaches have firmly established the roles of several EEC-derived products in the central control of feeding and metabolism (Bai et al., 2022; Hayashi et al., 2023; Lewis et al., 2020). Future work adapting these tools to demonstrate how activation of specific types of EECs impacts local gut function will greatly enhance our understanding of EEC biology. The combination of transcriptional regulation and exposure to the extracellular signaling microenvironment enable the full repertoire of EEC-derived products that mediate the myriad of EEC-controlled functions.

3.2. Lineage tracing and reporter experiments

Murine lineage tracing and reporter models have been essential in studying rare EECs and are especially useful for isolating populations of EECs by flow cytometry for further analysis. The *glucagon*-Venus transgenic mouse was the first fluorescent EEC reporter model and enabled isolation of EECs expressing the *proglucagon* gene, from which GLP-1 and GLP-2 are translated (Reimann et al., 2008). *Gcg*-Venus+ cells were observed throughout the proximal and distal small intestine. These isolated, fluorescent cells were then used to demonstrate electrical activity via patch-clamping and GLP-1 secretion in response to glucose (Reimann et al., 2008). Similarly, GIP-expressing cells were isolated from the *Gip*-Venus reporter mouse and demonstrated functional secretion *in vitro* when stimulated by glucose, glutamine, and linoleic acid (Parker et al., 2009). Transcriptional profiling of these EEC populations was the first experiment that revealed substantial overlap in hormonal mRNA expression, with both populations expressing *Gip, Gcg, Sct, Cck,* and *Pyy*, but differential expression of *Sst* (only in *Gip*-Venus+ cells) and *Nts* (only in *Gcg*-Venus+ cells) (Habib et al., 2012). Single-cell RNA sequencing subsequently identified that there are three distinct populations of *Gcg*-Venus+ cells in the upper small intestine: a dominant population that co-expresses *Pyy*, a second population that has high overlap with *Gip*-expressing cells, and a third population that highly expresses *Tph1*, the enzyme responsible for 5-HT (serotonin) production (Glass et al., 2017). Fluorescent labeling using other EEC hormone genes reveals similar patterns; for example, *Cck*-GFP+ cells are observed throughout the proximal and distal small intestine, and can coexpress GLP-1, GIP, PYY, NTS, and secretin, but not somatostatin (Egerod et al., 2012).

Generation of a time-resolved, dual reporter system revealed many mechanisms by which a *Neurog3*+ progenitor cell gives rise to these abundant cell types with overlapping hormone expression (Gehart et al., 2019). The *Neurog3*Chrono mouse incorporates a novel strategy to pulse-label Neurog3+ cells with a rapidly degrading mNeonGreen protein and a long-lived tdTomato protein and monitor the fluorescent shift from green to yellow to red over several days as progenitors differentiate (Gehart et al., 2019). Sequencing these early, mid, and late EEC populations revealed over 1400 differentially expressed genes, including 172 transcriptional regulators, some of which are only transiently expressed (Gehart et al., 2019). Moreover, analysis at a single-cell level revealed that more than 70% of EECs express multiple hormones, in diverse combinations based on the age of the cell and crypt-villus localization (Gehart et al., 2019).

Together, these murine studies reveal that EECs display remarkable plasticity and reinforce the need to study the roles of individual EEC-derived products at spatial and temporal resolution.

3.3. Human intestinal organoids and enteroids

The transcriptome and secretome of mouse and human EECs are broadly similar (Roberts et al., 2019). However, with EECs emerging as

pharmacological targets for human disease, human model systems are essential for drug development, high-throughput screening, and identifying non-target effects on the intestine itself. Two methods have been developed for modeling human intestine in 3D: human pluripotent stem cell (PSC)-derived organoids (HIOs) and crypt-derived epithelial organoids (enteroids).

Intestinal stem cells (ISCs), housed within the crypt, proliferate and differentiate to repopulate all cell types in the intestinal epithelium. This is also true *in vitro*, when mouse and human crypts are maintained in supportive media conditions (Sato et al., 2009, 2011). The resulting 3D structures (enteroids) contain all intestinal epithelial cell types and can grow indefinitely. Enteroids are routinely established from intestinal biopsies from patients undergoing endoscopy, colonoscopy, or resection, and have the advantage of being a patient-specific avatar to be used for disease modeling and drug screening. When stimulated to differentiate by removing Wnt from the media, enteroids form differentiated cells at physiological frequency, meaning ~1% will become EECs. Several strategies have been developed to increase the proportion of EECs to enable their study using enteroids. Inducing quiescence of Lgr5+ ISCs by inhibiting EGF (epithelial growth factor) or MAPK (mitogen-activated protein kinase) signaling results in these cells adopting an EEC signature, which, when combined with Wnt and Notch inhibition, results in a dramatic expansion of EECs (Basak et al., 2017). In a parallel approach, inhibition of cannabinoid signaling, JNK (c-Jun N-terminal kinase), and FOXO1 (forkhead box protein O1) also promotes EEC differentiation in enteroids, with differing ratios of hormones produced depending on the combination of inhibitors used (Zeve et al., 2022). Perhaps most excitingly, administering short chain fatty acids (SCFAs) to enteroid cultures increases the population of GLP-1 expressing cells (Petersen et al., 2014), suggesting dietary approaches may be capable of modulating EEC production. Recently, methods to stably transfect human enteroids with lentiviral constructs have enabled the inducible overexpression of NEUROG3, resulting in increased EEC formation (Chang-Graham et al., 2019; Zhang et al., 2019).

PSC-derived HIOs are generated by directing the differentiation of human embryonic or induced PSCs through the developmental steps that occur during embryogenesis to create a spherical structure lined with intestinal epithelial cells and surrounded by supporting mesenchymal cells (Spence et al., 2011). These HIOs can be further matured by xenograft into an immunocompromised mouse, with robust crypt-villus architecture, smooth muscle and supporting stromal cells, and physiologic functions developing after 2–3 months (Watson et al., 2014). HIOs also contain functional Lgr5+ ISCs and can be used as the starting material to generate enteroid cultures, negating the need for a surgical biopsy. It has become relatively straightforward to edit the genome of human PSCs to create stable lines to study the function of genes through human organ development and function. PSC lines with loss- and gain-of function of NEUROG3 have created HIOs which can be used to investigate the roles of individual EEC-derived hormones on intestinal function (McCauley et al., 2020), or to increase the population of EECs to enable meaningful study in their local environment (Sinagoga et al., 2018).

Bioengineering approaches are continually evolving to improve the capacity of these human *in vitro* model systems to faithfully recapitulate intestinal biology in a dish. One approach is to increase complexity of *in vitro* systems by adding in additional cell types, such as enteric neurons and glia (Eicher et al., 2022; Workman et al., 2016) or macrophages (Jurickova et al., 2024; Noel et al., 2017). These models improve the functional capacity of the intestinal epithelium, demonstrating the importance of a complex system to accurately model intestinal function. Increased intestinal function has also been achieved by introducing stretch (Poling et al., 2018) and luminal flow (Kasendra et al., 2020), modeling the dynamic nature of the intestinal lumen. Finally, extracellular scaffolds improve the ability of organoids to self-organize to mimic *in vitro* architecture (Nikolaev et al., 2020; Wang et al., 2017). Together, these next-generation tissue culture models will be invaluable tools for investigating how EECs interact with their local environment.

4. EECs and intestinal stem cell homeostasis

4.1. In response to nutrient availability

One way by which EECs regulate gut homeostasis is by influencing ISC function (Fig. 2). ISCs are rapidly cycling cells that proliferate and differentiate to form all epithelial cell types within the intestine. Despite residing deep in the intestinal crypts with limited access to luminal nutrients, ISCs and their niche are sensitive to changes in diet, such as high-fat (Beyaz et al., 2016) or fasting (Yilmaz et al., 2012). Within days of switching to a high-fat diet, intestinal stem and progenitor cells shift their metabolic pathways from glycolysis to fatty acid oxidation and increase proliferation (Enriquez et al., 2022). Increased fatty acid oxidation and ISC activity is also observed when mice are fasted (Mihaylova et al., 2018), suggesting rapid adaptation of the stem cell niche to change in nutrient availability. This suggests that nutrient-sensing cells, such as EECs, may be relaying luminal cues to the stem cell niche which is spatially restricted from sensing such cues itself.

Indeed, the crypts of fed EEC-deficient animals are reprogrammed to upregulate lipid metabolism pathways, consistent with fasting models (Blot et al., 2023; McCauley et al., 2023). This was associated with increased mitochondrial activity and oxygen consumption in intestinal crypts, demonstrating functional metabolic adaptation of ISCs to loss of EECs (McCauley et al., 2023). While one study did not detect transcriptional changes in proliferative or stem cell markers in EEC-deficient intestinal tissue (Blot et al., 2023), another demonstrated a slight, but significant, increase in cellular proliferation and expanded capacity of ISCs to form enteroids at the same levels as those of fasting mice (McCauley et al., 2023) (Fig. 2). Together, these studies suggest that EECs influence crypt metabolism and ISC function in the presence of nutrients, but additional work needs to be done to assign roles of individual EEC-derived products as positive or negative regulators of proliferation.

The effects of individual EEC-derived products on intestinal homeostasis and function have been difficult to elucidate, largely due to functional overlap (McCauley, 2019). While loss of a single EEC-derived hormone has limited effects on the health of the mouse, the roles of some EECs have been identified by nutritional challenge. Loss of neurotensin is well-tolerated by mice on a standard chow diet, with no difference in gut length, villus height, crypt number, or ability to form enteroids, despite a reduction in *Lgr5* and *Olfm4* transcripts (Li et al., 2016; Rock et al., 2022). However, loss of neurotensin reduces crypt cell proliferation in distal, but not proximal, small intestine, which is exacerbated by fasting and associated with reduction in canonical Wnt signaling (Rock et al., 2022). Together, these data describe a role for neurotensin in positively regulating proliferation in the distal small intestine via canonical Wnt signaling during periods of nutrient deprivation. This is consistent with the increased abundance of neurotensin-expressing EECs in the distal small intestine and supports a role for local regulation of crypt cell activity by EECs.

Serotonin (5-HT) also promotes intestinal epithelial proliferation, potentially through both enteric (enterochromaffin) and neuronal 5-HT sources (Fig. 2). While genetic gain- and loss-of function studies in mice suggested a dominant role for neuronal 5-HT in mediating proliferation (Gross et al., 2012), *in vitro* human enteroid models demonstrate that enteric 5-HT production by EECs is both necessary and sufficient to stimulate epithelial proliferation (Poplaski et al., 2023). These findings support a disease mechanism by which patients with Cronkhite-Canada syndrome exhibit increased intestinal 5-HT expression and intestinal polyposis (Poplaski et al., 2023).

Perhaps the best-known and most potent positive regulator of intestinal proliferation is GLP-2, which is now in clinical use for the treatment of short bowel syndrome. While GLP-2 is not required for normal gut development or homeostasis (Lee et al., 2012), exogenous

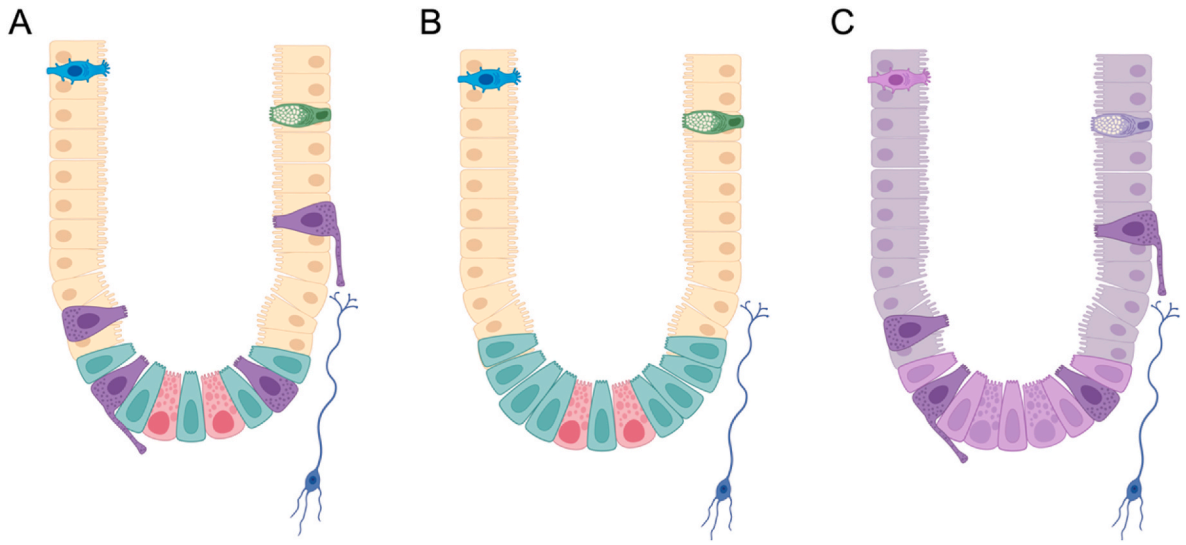

Fig. 2. EECs regulate ISC homeostasis. A. EECs are essential regulators of ISC homeostasis, both directly and indirectly via enteric neurons. B. Loss of all EECs disrupts ISC homeostasis and increases ISC activity. C. EECs can give rise to all intestinal epithelial cell types, including ISCs. The quiescent, +4 reserve stem cell expresses markers of EECs and is activated upon loss of actively cycling ISCs. Figure generated using BioRender.com.

GLP-2 stimulates crypt cell proliferation, elongates villus height and microvillus length, and overall increases intestinal mass (Drucker et al., 1996) . This involves a complex mechanism which requires insulin-like growth factor receptor and is assisted by protein kinase B (Akt), EGF, and ErbB receptor tyrosine kinase signaling to increase canonical Wnt signaling in ISCs (Dubé et al., 2008; Fesler et al., 2020; Markovic and Brubaker, 2019; Yusta et al., 2009). Together, GLP-2 utilizes these pathways to induce Lgr5+ ISCs to enter S-phase of the cell cycle, increasing the overall ISC population that contribute to intestinal growth (Chen et al., 2022). The GLP-2 receptor is required to mediate these actions but is absent on intestinal epithelial cells. Instead, GLP-2 exerts its intestinotrophic actions via stromal cells, enteric neurons, and/or mesenteric veins (Yusta et al., 2019), or potentially via signaling to other EECs (Yusta et al., 2000) that do act on the epithelium. Similarly, in *Drosophila*, EECs regulate intestinal stem cell proliferation by signaling to cells within the subepithelial niche (Amcheslavsky et al., 2014; Scopelliti et al., 2014).

Additional studies are needed to gain a better understanding of the complex ways in which EECs and their products influence intestinal homeostasis in the epithelium and in surrounding non-epithelial cell populations.

4.2. In injury and regeneration

The first clue that EECs or their progenitors may have stem cell potential was revealed in an effort to lineage trace EECs by using *Neurog3* to drive Cre expression (Schonhoff et al., 2004). While all GI EECs were labeled, a subset of other secretory cells including goblet and Paneth cells also traced from *Neurog3*. Additionally, while not frequent, labeled ribbons emerged, indicating that a Neurog3+ cell could populate all the cells comprising a crypt-villus unit (Schonhoff et al., 2004) (Fig. 2). Labeled ribbons also emerged in Nkx2.2 (Gross et al., 2015) and Isl1 (Bai et al., 2022) reporter animals, suggesting that EEC progenitors downstream of Neurog3 maintain multipotency and supporting the notion that EECs may act as reserve stem cells. Single-cell sequencing confirmed that *Neurog3*+ cells give rise to all known intestinal epithelial cell types, including enterocytes and proliferative stem cells with classical ISC markers (Enriquez et al., 2022).

While the actively cycling, Lgr5+, crypt-base columnar intestinal stem cells (active ISCs, aISCs) maintain the intestinal epithelium in homeostatic conditions, multiple populations of cells are capable of facultative or reserve ISC activity. Reserve ISCs are long-lived and have the plasticity to revert to an actively dividing state to assist epithelial regeneration upon injury, and have been reviewed thoroughly elsewhere (Bankaitis et al., 2018). Three techniques have been used to identify these cells: 1) label retention; 2) lineage tracing; and 3) activation in response to epithelial damage and loss of aISCs. The intestinal epithelium is remarkably plastic, with both absorptive (Tetteh et al., 2016) and secretory (Buczacki et al., 2013; Sei et al., 2011; van Es et al., 2012; Van Landeghem et al., 2012; Yan et al., 2017) cell lineages able to function as reserve ISCs. The classical "+4" quiescent ISC that expresses Bmi1 also expresses markers of mature EECs, suggesting that EECs are particularly plastic in their ability to revert to an active state (Sei et al., 2018; Yan et al., 2017) (Fig. 2). As sensory cells, it is tempting to consider that EECs integrate environmental cues to trigger regeneration after injury. This is in concert with the recent finding that loss of the nutrient-sensing EEC drives intestinal proliferation and stem cell activity that recapitulates the absence of nutrients during fasting (McCauley et al., 2023).

5. EECs are important for intestinal epithelial nutrient absorption

As nutrient-sensing cells, EECs play a key role in coordinating absorption of dietary sugars, proteins, and fats by enterocytes (Fig. 3). As many EEC-derived products are being targeted for the treatment of obesity, specifically for their satiety-inducing actions within the central nervous system, it is essential to understand how EECs may also participate in the physical act of absorption of ingested nutrients. The knowledge gained from these experiments also has implications for augmenting nutrient absorption in populations with malabsorptive disorders. Some EEC-derived peptides act directly on enterocytes via their cognate GPCRs, whereas others act via intermediary cell types, like enteric neurons. In many studies, particularly those done *in vivo*, it is difficult to determine whether the effect of EEC-derived peptides is truly direct. Many studies of glucose and dipeptide transport rely on *ex vivo* experiments conducted in the Ussing chamber, in which ion-coupled nutrient absorption results in a measurable increase in the short-circuit current (Clarke, 2009). To determine the role of enteric neurons in mediating this electrogenic response, the muscle layer can be stripped and/or tetrodotoxin added to the tissue, with the remaining response to nutrients assumed to be driven by the intestinal epithelial

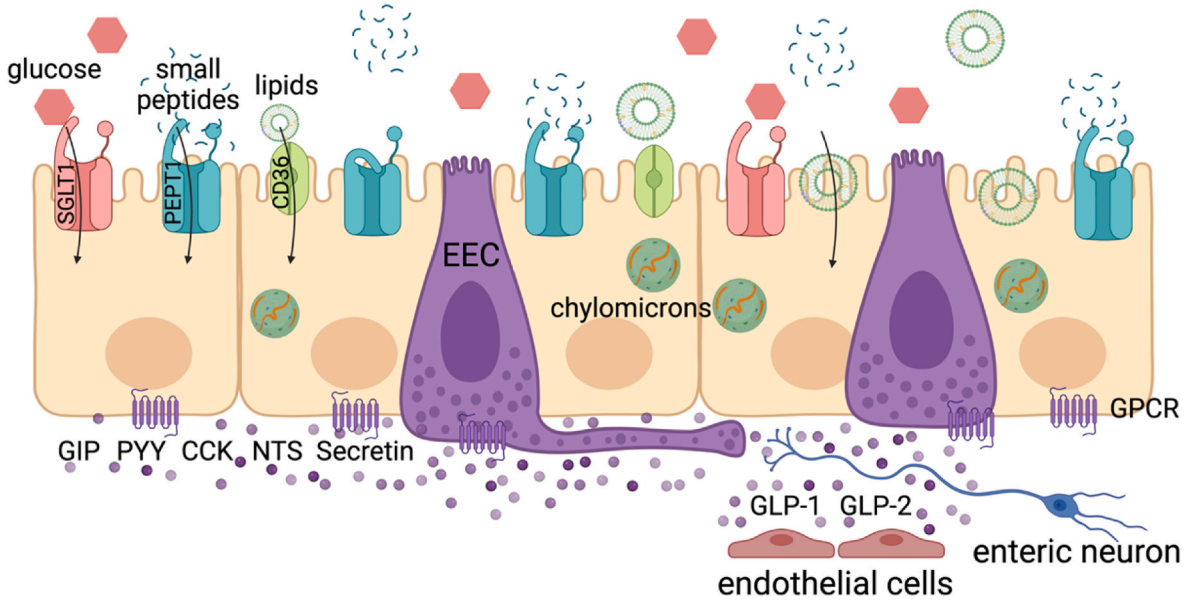

Fig. 3. EECs participate in epithelial absorption of glucose, peptides, and lipids. Many EEC-derived products influence the efficiency of nutrient absorption. PYY, GIP, CCK, secretin, and neurotensin act directly on enterocytes, whereas GLP-1 and GLP-2 act via enteric neurons, endothelial cells, or other EECs to augment nutrient absorption. Glucose is imported via SGLT1, small peptides are imported via PEPT1, and lipids can freely diffuse through the brush border or be imported via CD36. Figure generated using BioRender.com.

cells.

5.1. Glucose

Once dietary carbohydrates are hydrolyzed in the lumen into simple sugars, sodium-glucose co-transporter 1 (SGLT1) imports one glucose molecule with two sodium molecules into the enterocyte. This process is driven by the inward gradient of sodium, established by the basolateral Na^+/K^+ ATPase and maintained by a series of apical and basal ion transporters that work in concert to maintain homeostatic electrophysiology (Koepsell, 2020). Glucose is then exported basolaterally via the electroneutral GLUT2. At very high glucose concentrations, GLUT2 can translocate to the apical membrane to assist glucose handling along with increased brush border expression of SGLT1 (Koepsell, 2020). SGLT1 expression and activity is driven by cyclic AMP (cAMP) and its downstream effectors, activated in part by stimulatory G_s-coupled GPCRs. While EECs are not required for SGLT1-mediated glucose absorption, loss of EECs disrupts its kinetics suggesting EECs participate in regulation and function of SGLT1 (McCauley et al., 2020). Accordingly, administration of PYY(1–36) to EEC-deficient human intestinal organoids and *ex vivo* mouse jejunum slowed the rate of glucose import to normal levels (McCauley et al., 2020). The PYY(1–36) receptor NPY1R is G_i-coupled (inhibitory), dampening cAMP and downstream signaling. NPY1R is widely expressed on intestinal epithelial cells as well as enteric neurons, but blockade of enteric neuron activity with tetrodotoxin and action in human intestinal organoids which lack enteric neurons suggest a direct effect on enterocytes (McCauley et al., 2020).

Conversely, the GIP, GLP-1, GLP-2 receptors are G_s-coupled (stimulatory) resulting in increased cAMP in their target cells. The GIP receptor GIPR is expressed on intestinal epithelial cells and stimulates SGLT1 activity in muscle-stripped mouse jejunum (Singh et al., 2008). Intriguingly, *in vivo* administration of GIP reduced glucose absorption in an SGLT1-independent manner (Ogawa et al., 2011), suggesting involvement of other factors, such as insulin. GLP-2 also stimulates SGLT1 activity but its receptor GLP2R is not expressed on epithelial cells, requiring enteric neurons to mediate this interaction (Cheeseman, 1997; Moran et al., 2018).

Alongside cAMP regulation of SGLT1 activity, there are other mechanisms regulating glucose absorption in the small intestine. In rat, *in vivo* perfusion experiments suggest CCK reduces glucose absorption by reducing the abundance of SGLT1 protein at the brush border (Hirsh and Cheeseman, 1998; Hirsh et al., 1996). While it is difficult to isolate direct versus indirect action on enterocytes in this model, data suggest this occurs via a CCKAR dependent mechanism that does not require enteric neurons (Hirsh and Cheeseman, 1998; Hirsh et al., 1996). On the other hand, at high luminal glucose concentrations brush border expression of the electroneutral GLUT2 is increased. *In vivo* perfusion experiments demonstrated similarly increased apical GLUT2 in the presence of GLP-2 (Au et al., 2002; Cheeseman and O'Neill, 1998; Cheeseman and Tsang, 1996), although GLP2 receptor localization indicates this cannot be a direct effect on enterocytes.

5.2. Protein

Dietary protein is broken down in the lumen into small di- and tripeptides, as well as single amino acids, for import into the enterocyte. There are a number of amino acid transporters on both the apical and basolateral membranes of enterocytes, which are typically H^+, Na^+, K^+, or Cl^- coupled and function as uniporters, symporters, or antiporters (Bröer, 2008). However, most dietary protein is absorbed as di- and tripeptides via the H^+-coupled PEPT1 transporter (Adibi, 1971; Hu et al., 2008).

In contrast to glucose, EECs are required for di- and tri-peptide absorption via PEPT1. In EEC-deficient mice, there was virtually no electrogenic response to the non-hydrolyzable dipeptide Gly-Sar, which can only be absorbed by PEPT1 (McCauley et al., 2020). Similarly, over 80% of ingested protein was recovered in the stool of a patient with NEUROG3 mutation, indicating the importance of EECs and their products in protein absorption (Wang et al., 2006). When EEC-deficient mouse intestine or human intestinal organoids were given PYY *ex vivo* in Ussing chamber experiments, there was no immediate improvement in electrogenic response to Gly-Sar, unlike that which was seen for glucose via SGLT1. However, when EEC-deficient organoids or mice were given PYY over several days, PEPT1-mediated dipeptide absorption was restored to normal, accompanied by a restoration of the intracellular pH supporting PEPT1 function (McCauley et al., 2020).

PEPT1 activity is regulated in part by cAMP signaling. Similar to what was observed for glucose, administering GIP to mouse jejunum *ex vivo* stimulated PEPT1-mediated absorption of Gly-Sar (Coon et al., 2013). *In vitro* studies suggest that GIP acts directly on intestinal epithelial cells to augment PEPT1 expression and function via AKT/PI3K signaling (Coon et al., 2015). GLP-2 also activates AKT/PI3K signaling to augment amino acid transport in the small intestine; however, this is blocked by treatment with tetrodotoxin, a neurotoxin that blocks neuronal firing, indicating that enteric neurons are required to mediate this interaction (Lee et al., 2017).

5.3. Lipids

Dietary fat is mostly composed of triacylglycerides which must first be emulsified and hydrolyzed by digestive enzymes and bicarbonate from the exocrine pancreas into 2-monoacylglycerol and free fatty acids. These then combine with phospholipids, cholesterol, and bile acids to form micelles. Enterocytes can absorb micelles actively and passively, through the fatty acid binding proteins (FABP) and CD36 at low concentrations, and directly through the cell membrane by diffusion at high concentrations. The enterocyte then repackages free fatty acids to be retained within the cell as cytoplasmic lipid droplets or combined with apolipoproteins to form chylomicrons, which are exported to the lacteal and subsequently enter the bloodstream. Lipid absorption is a complex process, and has been recently reviewed in detail (Ko et al., 2020).

EECs are involved with nearly every step of this process and are essential for lipid absorption. Nearly all EEC-deficient mice die within the first week or two of life, suffering from diarrhea and lipid malabsorption (Mellitzer et al., 2010). The few EEC-deficient mice which survive weaning and the transition from high-fat milk to low-fat standard chow will typically reach normal life span, despite remaining underweight and continuing persistent diarrhea (McCauley et al., 2020; Mellitzer et al., 2010). Conversely, adult mice with tamoxifen-inducible loss of EECs do not present a gross phenotype within the first 4 weeks of tamoxifen treatment, but start to lose weight, specifically fat mass, over time (Blot et al., 2023; McCauley et al., 2023). This is dramatically exacerbated when adult EEC-deficient mice are placed on a high fat diet, in which all EEC-deficient mice either died or required a humane endpoint by 5 weeks due to severe weight loss associated with lipid malabsorption (Blot et al., 2023).

The loss of individual EEC subtypes or their receptors has limited impact on postnatal survival or lipid absorption on a standard chow diet, suggesting functional compensation between EEC peptides. However, loss of a subset of peptidergic EECs, driven by mutation in the pro-EEC transcription factors *Rfx6* (Piccand et al., 2019) or *Arx* (Beucher et al., 2012; Du et al., 2012; Terry et al., 2015), recapitulates the phenotype of neonatal mice and humans with total loss of EECs, suggesting that multiple hormones converge to regulate lipid absorption.

Secretion of bile acids from the gallbladder and bicarbonate and digestive enzymes from the exocrine pancreas is stimulated by CCK and secretin (Afroze et al., 2013; Rehfeld, 2017). On a standard chow diet, loss of only CCK (Lo et al., 2008) or only of the secretin receptor (Sekar and Chow, 2014) had no effect on postnatal survival, body weight, or lipid absorption. However, loss of CCK (Lo et al., 2010) or the secretin receptor (Sekar and Chow, 2014) partially protected adult mice from gaining weight on a high fat diet by reducing fat absorption by 8–10%. This occurred despite high levels of pancreatic lipase in the CCK knockout animals (Lo et al., 2010), suggesting that 1) there are redundant mechanisms for regulating digestive enzyme release, and 2) these hormones must be acting at another step of the fat digestion and absorption pathway. While secretin is not required for normal lipid absorption, it does directly promote fatty acid uptake and expression of CD36 and FABP in isolated jejunal cells (Sekar and Chow, 2014).

Similar to CCK and secretin, neurotensin is not required for normal lipid absorption on a standard chow diet, but is required to maximize fat absorption upon acute challenge with fat bolus or upon prolonged high-fat diet (Armstrong et al., 1986; Li et al., 2016). In the presence of fat, neurotensin acts through its receptor NTSR1 to inhibit the phosphorylation of the key metabolic fuel sensor, AMPK, which promotes lipid absorption in an intestinal epithelial cell line *in vitro* (Li et al., 2016).

GLP-2 also promotes lipid absorption and postprandial lipemia, primarily by increasing chylomicron production. The rapid appearance of lipemia after GLP-2 administration suggests that GLP-2 stimulates chylomicron production from pre-synthesized and stored ApoB lipoproteins (Dash et al., 2014; Hsieh et al., 2015). This has been attributed to two mechanisms: 1) increased CD36 expression at the brush border (Hsieh et al., 2009); and 2) endothelial nitric oxide signaling (Hsieh et al., 2015). Because the GLP-2 receptor is not expressed on enterocytes, the mechanism connecting GLP-2 and CD36 remains unclear but could involve enteric neurons or other intermediate EECs like secretin, CCK, or neurotensin.

GLP-1 and GLP-2 are co-secreted in equal concentrations from the same cell, but have opposite effects on lipid absorption (Hein et al., 2013). While GLP-2 promotes lipid absorption, GLP-1 inhibits lipid absorption by decreasing intestinal lymph flow and appearance of labeled fat and lipoproteins in the lymph (Qin et al., 2005). At baseline, the pro-absorptive effects of GLP-2 overshadow the anti-absorptive effects of GLP-1 because of the longer half-life of GLP-2 (Hein et al., 2013). Increasing GLP1R agonism by DPP4 inhibition or administration of synthetic GLP1R agonists increases the anti-absorptive action of GLP-1, resulting in improvement in the dyslipidemia seen in people with metabolic disease (Hein et al., 2013).

6. EECs are important for barrier integrity

The intestinal epithelium functions as a surface barrier that allows the uptake of nutrients while excluding bacteria and pathogenic molecules. In addition to the epithelial cell layer, the outer mucus layer and the inner lamina propria housing immune cells comprise the mucosal defense system (Turner, 2009). Disruptions in barrier integrity are common in GI diseases like inflammatory bowel disease (IBD), helping drive the inflammatory response. Emerging evidence supports the role of some EEC-derived products in maintaining all three layers of the mucosal barrier (Fig. 4).

6.1. Mucus

The mucus layer is the initial line of defense for incoming molecules

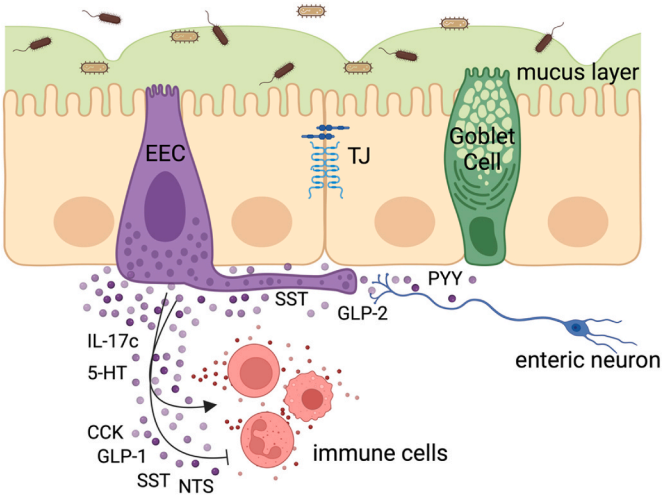

Fig. 4. EECs influence barrier function. EEC-derived products have been shown to influence mucus secretion, junctional proteins, and immune activation. While some factors secreted from EECs are proinflammatory, many are anti-inflammatory. Figure generated using BioRender.com.

and mucin 2 (Muc2), produced by goblet cells, is essential for the formation of the intestinal mucus barrier (Pelaseyed et al., 2014). Reduced numbers of goblet cells and decreased mucus are common in IBD, particularly in ulcerative colitis (Kim and Ho, 2010). Loss of Muc2 causes spontaneous colitis in mice, which is associated with increased serum levels of PYY (J. Ye et al., 2021). In turn, loss of PYY results in increased *Muc2* expression (Farzi et al., 2021), suggesting a potential interaction between EECs and goblet cells. Conversely, in mice and in a goblet cell line, treatment with somatostatin or its analog octreotide increases *Muc2* expression (Song et al., 2020). It is possible that EECs participate in maintaining goblet cell function and mucus barrier homeostasis either directly or indirectly via enteric neurons. The neuropeptide vasoactive intestinal polypeptide (VIP) is a potent stimulator of *Muc2* expression and mucus secretion (Hokari et al., 2005). Enteric neurons, including those that secrete VIP, express nearly all EEC hormone receptors (Egerod et al., 2018) and their function can be modulated by EECs (Abot et al., 2018).

6.2. Epithelial barrier proteins

Maintaining tight junctions between epithelial cells is essential for barrier integrity (Suzuki, 2013; Turner, 2009). Tight junctions are selectively permeable, allowing ions and water to pass but restricting paracellular permeability of pro-inflammatory triggers, such as microbes and toxins (Lee, 2015). Tight junctions are comprised of four families of junctional proteins: claudins, occludin, junctional adhesion molecules (JAM), and tricelluin (Lee, 2015). These proteins are supported by intracellular scaffolding proteins, like zona occludens (ZO), which connect the tight junctions to the actin cytoskeleton (Lee, 2015). Tight junctions are classically regulated by cytokines and growth factors, with some evidence suggesting EECs may also regulate epithelial barrier proteins. Somatostatin levels are reduced in experimental models of colitis, and treatment with somatostatin or its analog octreotide increased levels of barrier-forming claudins 1 and 3 in mouse and in Caco-2 cells (Li et al., 2014). Claudin 2 is a pore-forming claudin, increasing paracellular permeability (Günzel and Yu, 2013). Its expression is upregulated in mice lacking PYY (Farzi et al., 2021), suggesting PYY is important in preventing a leaky barrier. GLP-2 has been shown to improve barrier function in healthy mice (Benjamin et al., 2000) and in models of colitis (L'Heureux and Brubaker, 2003) by modulating expression and localization of the barrier-forming claudins 3 and 7 in a manner dependent on insulin-like growth factor 1 (IGF-1) (Dong et al., 2014). Serum levels of GLP-2 are often increased in patients with IBD, suggesting an adaptive response to intestinal injury and an attempt to restore normal mucosal integrity (Xiao et al., 2000).

6.3. Immune regulation

Cytokines are well-established regulators of barrier integrity, and can be produced by immune cells or intestinal epithelial cells, including EECs (Yu et al., 2019). For example, during active colonic inflammation EECs secrete the interleukin IL-17C which is a chemoattractant for Th17 cells (Friedrich et al., 2015). Moreover, many EECs can directly act on macrophages, dendritic cells, T cells, and intraepithelial lymphocytes to influence immune cell activation and cytokine production (Yu et al., 2019). 5-HT activates macrophages (Ghia et al., 2009), induces proliferation of lymphocytes (Stefulj et al., 2001), and promotes recruitment and activation of T cells (Laberge et al., 1996) to drive an inflammatory environment that decreases barrier integrity. Conversely, CCK (Jia et al., 2014; Zhang et al., 2011, 2014), GLP-1 (Hadjiyanni et al., 2010; Yusta et al., 2015), somatostatin (Kao et al., 2006), and neurotensin (da Silva et al., 2011) reduce the proliferation, pro-inflammatory activation, and cytokine production of B cells, T cells, intraepithelial lymphocytes, and dendritic cells, suggesting these hormones likely have a positive impact on barrier integrity. The role of EECs in mucosal immunology, termed the immunoendocrine axis, has recently been reviewed (Worthington et al., 2018).

7. EECs are altered in GI disease

As sensory cells interfacing between the outside environment and the body's response, EECs are often dysregulated in metabolic and GI disease. In humans, it is impossible to determine whether changes in EECs predicate disease or arise in response to other pathogenic processes, like inflammation and wound healing. People with metabolic and GI disease also often present with microbial dysbiosis (Singh et al., 2021), and it is possible that this is an inciting event for changes in the sensory EEC population. Regardless of the cause-and-effect nature of EEC alterations, many studies in humans with GI disease report changes in serum or plasma levels of EEC-derived products and histological changes in the EEC composition within the epithelium (Table 1). Some studies report conflicting information about changes in EECs or their secretion, which may be attributable to changes in study design, improvements in detection, fasting versus postprandial sampling, or the inherent heterogeneity in disease presentation between individuals. The symptoms of many GI diseases are alleviated by dietary interventions, which reproducibly normalize changes in EEC number, distribution, or secretion. Here, we consider that alterations in EECs contribute to worsened disease symptoms in several common GI diseases, and that targeting EEC-derived peptides may be an underappreciated therapeutic avenue.

7.1. Crohn's disease

Crohn's disease is a chronic inflammatory bowel disease (IBD) characterized by patches of inflammatory cells infiltrating the mucosa. These inflammatory patches can occur anywhere along the GI tract but are most common in the terminal ileum and colon. In addition to local mucosal damage, inflamed areas may lead to stricture or fistula formation. People with Crohn's disease often display changes in the microbiome, reduced barrier integrity, and poor absorption of nutrients and vitamins, all processes influenced by EECs. Histological analysis of the terminal ileum revealed increased numbers of CHGA+ EECs, including increased numbers of GLP-1-expressing cells (Moran et al., 2012). Colonic biopsies revealed an increase in GLP-1 and 5-HT+ cells, but a decrease in PYY+ cells in people with Crohn's (El-Salhy et al., 1997). The histological appreciation of increased EECs in Crohn's disease is supported by increased serum/plasma levels of gastrin (Triantafillidis et al., 2003), ghrelin (Ates et al., 2008; Cekic et al., 2014), CCK (Keller et al., 2009), GIP (Besterman et al., 1983), motilin (Besterman et al., 1983), GLP-1 (Bendet et al., 2004; Besterman et al., 1983), and GLP-2 (Xiao et al., 2000), compared to controls. Strangely, despite fewer PYY+ cells (El-Salhy et al., 1997), circulating levels are elevated (Moran et al., 2012) in Crohn's patients. It is possible that the damaged mucosa in Crohn's disease upregulates EECs in an attempt to improve absorption of nutrients and maintain an intact barrier. Conversely, other studies described reduced numbers of somatostatin-positive cells in the colon, correlating with the severity of inflammation (Koch et al., 1988; Watanabe et al., 1992). As PYY (L. Wang et al., 2010) and somatostatin (Farthing, 1996) decrease motility and epithelial ion secretion, it is possible that reduction in the number of SST+ and PYY+ cells in the colon contributes to the diarrhea experienced by people with Crohn's disease. Clinical management of Crohn's disease typically involves strong anti-inflammatory drugs; however, treatment of mucosal damage by administering GLP-2 analogs rapidly improves symptoms (Blonski et al., 2013; Buchman et al., 2006; Pizzoferrato et al., 2022), suggesting a role for EECs in mediating disease severity.

7.2. Ulcerative colitis

In contrast to Crohn's disease, ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) restricted to the colon and typically involves widespread, continuous inflammation rather than the patches

Table 1
EECs are altered in GI disease. Overview of studies analyzing EECs in human GI disease. Some studies evaluated circulating levels in serum/plasma, while others performed histological analysis on biopsy sections. Arrows indicate change from humans without GI disease. Details and references are reported in the text. nd = no data found during our literature search.

	ChgA	Gastrin	Ghrelin	SST	5-HT	SCT	CCK	GIP	GLP-1	GLP-2	PYY	NTS
Crohn's Disease	↑	↑	↑	↓	↑	nd	↑	↑	↑	↑	↑↓	nd
Ulcerative Colitis	↑	↑	↑	↓	↑	nd	=	↑	↑	↑	↑	nd
Microscopic Colitis	↑	nd	nd	↓	↑	nd	nd	nd	nd	nd	↑	nd
Irritable Bowel Syndrome – constipation	↓	↑	↓	↓	↓	=	=	↓	↓	nd	↑	nd
Irritable Bowel Syndrome – diarrhea	↓	=	↑	↓	↑↓	↓	↑↓	↓	nd	nd	↓	nd
Celiac Disease	↑	=	↑	↑	↑	↓	↓	↓	↑	↑	↑	↑

observed in patients with Crohn's. Ulceration of the colonic mucosa results in bloody diarrhea characteristic of UC. Few studies have evaluated the EEC population in colonic biopsies from people with UC, and those are conflicting. One study noted no change in somatostatin-expressing cells in the colon of people with UC (Watanabe et al., 1992), whereas another demonstrated a significant decrease (Koch et al., 1988). Analysis of EEC hormones in the blood of UC patients indicate increased levels of gastrin (Besterman et al., 1983), ghrelin (Ates et al., 2008; Cekic et al., 2014), 5-HT (Sikander et al., 2015), GIP (Besterman et al., 1983), motilin (Besterman et al., 1983), GLP-1 (Keller et al., 2009), and GLP-2 (Xiao et al., 2000), decreased PYY (Tari et al., 1988), and no change in gastrin (Triantafillidis et al., 2003) or CCK (Keller et al., 2009). In an experimental model of colitis, administration of dextran sulfate sodium (DSS) leads to a reduction in small intestinal EECs, and manipulation of EEC levels correlates with disease severity (Raouf et al., 2024). Interestingly, the changes were most prominent in the distal ileum, not colon, whereas histological analysis of human patients with UC relies solely on colonic biopsies, potentially obscuring the role of small intestinal EECs in disease pathogenesis. This suggests that EECs likely play a protective role in IBD.

7.3. Microscopic colitis

While Crohn's disease and UC are typically diagnosed in young adults, microscopic colitis is frequently diagnosed in older patients and presents primarily with diarrhea. Microscopic colitis requires histological examination of a colonic biopsy and reveals lymphocyte infiltration into the mucosa, which may occur with a thickened band of collagen. Despite requiring biopsy for diagnosis, few studies have used these specimens to interrogate the role of EECs in the pathogenesis of microscopic colitis (El-Salhy et al., 2017). While there are no studies evaluating the number of GLP-1 or GLP-2 expressing cells or circulating levels, one case study reports improvement in microscopic colitis after treatment with the GLP-2 analog teduglutide (Rim et al., 2023). Immunohistochemistry does reveal decreased somatostatin+ (Koch et al., 1988) but increased CHGA+, 5-HT+, and PYY+ cells in the colon of patients with microscopic colitis (Chojnacki et al., 2021; El-Salhy et al., 2012; El-Salhy et al., 2011), with increased levels of 5-HT in the blood (Chojnacki et al., 2021; Sikander et al., 2015). 5-HT acts as a pro-inflammatory signal as well as a potent stimulator of intestinal motility, and is associated with diarrhea in other diseases like irritable bowel syndrome (IBS).

7.4. Irritable bowel syndrome

IBS shares many clinical presentations with IBD but lacks the presence of mucosal inflammation upon biopsy. People with IBS complain of abdominal pain and bloating that occurs with either constipation (IBS-C), diarrhea (IBS-D) or mixed (IBS-M) and is often associated with changes in the microbiome that affect the gut-brain axis. Duodenal, ileal, and colonic biopsies reveal an overall decrease in the numbers of CHGA + EECs in people with all types of IBS, although there are differences in hormone expression between people with constipation and those with diarrhea (El-Salhy et al., 2014; El-Salhy et al., 2012; El-Salhy et al., 2015; El-Salhy et al., 2010; El-Salhy et al., 2010; El-Salhy et al., 2013).

Gut motility is, in part, regulated by motilin. People with IBS have reduced levels of circulating motilin compared to healthy controls (Sjölund et al., 1996), which may contribute to altered bowel frequency. 5-HT is also an important regulator of motility and visceral hypersensitivity, and circulating levels of 5-HT appear to distinguish between types of IBS, with decreased concentration in IBS-C and increased concentration in IBS-D (Sikander et al., 2009). Unexpectedly, both types of IBS are associated with fewer 5-HT expressing cells in the ileum and colon, suggesting that changes in the ability of EECs to secrete 5-HT or in 5-HT reuptake may contribute to disease pathogenesis.

People with IBS-C have elevated circulating gastrin levels but decreased circulating ghrelin and no change in CCK secretion from control patients (Furgała et al., 2023). This correlates with an increase in antral gastrin+ and 5-HT+ cells and decrease in ghrelin+ and somatostatin+ cells that potentially leads to elevated gastric acid secretion (El-Salhy et al., 2014; El-Salhy et al., 2009). This also correlates with no change in the abundance of CCK+ cells in the duodenum between people with IBS-C and controls, although duodenal CCK+ cells are reduced in IBS-D (El-Salhy et al., 2010). Biopsies from people with IBS-C also reveal reduced duodenal GIP, duodenal somatostatin, and colonic PYY expression (El-Salhy et al., 2012; El-Salhy et al., 2010), but increased PYY+ cells in the ileum compared to controls (El-Salhy et al., 2014). This is consistent with the pro-absorptive role of PYY and is not observed in people with IBS-D, suggesting PYY may contribute to the constipation experienced in IBS-C. Biopsies from people with IBS-D reveal a different composition of EECs, suggesting that EECs may participate in pathogenesis. In IBS-D, fewer GIP+, somatostatin+, secretin+, and CCK+ cells are found in the duodenum (El-Salhy et al., 2010), but circulating CCK is increased (Qin et al., 2020).

Circulating GLP-1 is reduced in people with IBS-C compared to controls, and negatively correlates with abdominal pain (Li et al., 2017), suggesting that GLP-1 mimetics may be an effective treatment for people with IBS. This is consistent with the well-described action of GLP-1 on enteric and vagal neurons. Indeed, treatment with a GLP1R agonist significantly reduced pain in people with IBS-C and IBS-M, although it did not improve pain in people with IBS-D (Touny et al., 2022).

Dietary intervention by reducing fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) often successfully relieves symptoms, and this is associated with increased levels of secretin, CCK, GIP, 5-HT, and somatostatin in the duodenum and increased 5-HT and PYY in the colon compared to the time of diagnosis (Mazzawi and El-Salhy, 2017; Mazzawi et al., 2016). This suggests that alterations in nutritional intake and microbiome composition can influence the differentiation of EECs and provides proof of concept for EEC-based and dietary treatments of GI disease.

7.5. Celiac disease

Celiac disease is an autoimmune condition in which inflammatory cells destroy enterocytes in the presence of gluten. This results in villus blunting and a dramatic reduction in absorptive surface area. Histological studies in human small intestinal biopsies reveal a decrease in secretin+ cells but an increase in CHGA+ (Pietroletti et al., 1986),

5-HT+ (Di Sabatino et al., 2014; Sjölund et al., 1982), somatostatin+, GIP+, CCK+, motilin+ and proglucagon+ cells (Sjölund et al., 1979) in active celiac disease. Due to the damaged and blunted villi in people with celiac disease, these EECs are enriched in the crypt compared to healthy controls and may not exhibit a normal secretory response to nutrients. While patients with active celiac disease have elevated levels of circulating 5-HT (Sjölund and Nobin, 1985), somatostatin (Fraquelli et al., 1999), ghrelin (Peracchi et al., 2003) proglucagon (Besterman et al., 1978), neurotensin (Besterman et al., 1978; Iorfida et al., 2020), PYY (Sjölund and Ekman, 1988), and GLP-2 (Caddy et al., 2006), they have reduced levels of circulating secretin (Besterman et al., 1978), GIP (Besterman et al., 1978), and CCK (Maton et al., 1985) despite the presence of abundant hormone-positive cells in the duodenum (Sjölund et al., 1979). Loss of these proximally-enriched hormones contributes to impaired gallbladder function and bile secretion in patients with celiac disease (Maton et al., 1985), which further exacerbates nutrient malabsorption. In every study to date, the alterations in EEC abundance and function have been completely restored by adherence to a gluten-free diet accompanied by restoration of normal mucosal architecture.

8. Conclusions and future perspectives

While EECs have been studied for over 100 years (Wabitsch, 2017), new technologies like single-cell RNA sequencing, CRISPR-mediated gene editing, chemo- and optogenetics, and human intestinal organoid culture systems continue to define new roles for EECs and their secreted products in homeostasis and disease. While the function of circulating EEC-derived hormones has been well-studied, their roles in governing the function of the intestine itself are only recently appreciated. These include proliferation and intestinal stem cell homeostasis, intestinal crypt metabolism, absorption of dietary nutrients, and barrier maintenance. The specific mechanisms by which EECs and EEC-derived products exert these functions are still elusive and an active area of research fueled by these modern tools. With a firm understanding of how EECs manipulate local cells in response to environmental cues, off-target GI effects of pharmaceuticals that augment EEC signaling can be minimized. Moreover, EECs can be targeted to improve intestinal function in diseases like IBD and IBS.

The role of EECs in maintaining the mucosal barrier is particularly exciting, as EECs have been associated with changes in mucus production, tight junction integrity, and immune cell recruitment and activation. The mechanisms by which EEC transmit microbial signals to other cell types that maintain the intestinal barrier is a major gap in the field. While many studies have reported alterations in EEC populations or levels of circulating hormone in GI disease, elucidating specific mechanisms by which EECs participate in pathology is essential for human health.

EECs are stimulated by the natural physiology of the gut, via mechanosensation of a food bolus, the presence of nutrients, and the composition of the microbiome. Because adherence to special diets improves many symptoms of GI diseases, it is tempting to consider these improvements are mediated by EECs. As researchers continue to identify novel sensory receptors on different subtypes of EECs (Beumer et al., 2020), more targeted approaches can be developed to augment the secretion of specific EEC-derived products that have distinct effects on their target cells. It is possible that the secretion of certain hormones may be augmented by pharmaceutical, dietary, or pre/probiotic interventions that could drive improvements in nutrient absorption, barrier function, and overall gut health.

CRediT authorship contribution statement

Jennifer G. Nwako: Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Heather A. McCauley:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

None.

Data availability

No data was used for the research described in the article.

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