

## **Title Page**

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

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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<sup>1,2</sup>. 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<sup>3</sup>, or excessive inflammation in response to infectious pathogens<sup>1</sup>. 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<sup>4,5</sup>. 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<sup>6-12</sup>, and the emergence of Claudin-4 as a specific surface marker<sup>13</sup>, 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<sup>14</sup> 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<sup>15</sup>. Lineage differentiation (Fig.1) is based on Wnt, Notch and Mitogen-activated protein kinases (MAPK)-dependent signaling<sup>16</sup> 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<sup>17-20</sup>. Growth Factor Independent 1 Transcriptional Repressor (*Gfi-1*) is required for both goblet cells and Paneth cells<sup>21</sup>, with Kruppel-like factor 4 (*Klf4*)<sup>22</sup> and *Sox9*<sup>23, 24</sup> essential for each population respectively. Tuft cells require the expression of the Pou domain, class 2, transcription factor 3 (*Pou2f3*)<sup>25, 26</sup>, while the development of Microfold (M)-cells is independent of *Hes1/Atoh1*, instead relying on *SpiB* transcription factor expression<sup>27</sup> and TNF superfamily member receptor activator of NF- $\kappa$ B ligand (*RankL*) induction<sup>28, 29</sup>. Eecs depend on the transient expression of

Neurogenin3 (*Neurog3*)<sup>30, 31</sup> and micro-RNA-375<sup>32</sup> followed by a variety of overlapping transcription factors<sup>18, 19</sup> (Table 1), including Neurogenic differentiation 1 (*Neurod1*)<sup>33-35</sup>, Paired box (*Pax*) 4/6<sup>36-38</sup>, Insulin gene enhancer protein (*Isl1*)<sup>39</sup>, pancreatic and duodenal homeobox 1 (*Pdx1*)<sup>40-42</sup>, *Nkx6-1*<sup>43</sup> and *Nkx2-2*<sup>44, 45</sup>, this in turn with spatio-temporal expression of transcription factors<sup>46, 47</sup> *Pdx-1*, caudal type homeobox 2 (*Cdx-2*)<sup>48, 49</sup>, *Gata-4*, *Gata-5*, *Gata-6*<sup>50-54</sup>, Hepatocyte nuclear factor-1 $\alpha$  (*Hnf-1 $\alpha$* )<sup>55</sup>, *Hnf-1 $\beta$* <sup>56</sup> and CCAAT-displacement protein (*Cdp*)<sup>47, 57</sup>, 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<sup>58, 59</sup>, while in both man<sup>60</sup> and mouse<sup>61</sup> 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<sup>12, 62-65</sup> as well as cell ablation studies<sup>35, 63</sup>, to reveal considerable overlap of the eec secretome. It now appears that the secretome “cocktail” secreted by individual eecs is based on tissue location<sup>66</sup>, although it is likely that certain peptide hormones remain rarely co-expressed<sup>66, 67</sup>.

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<sup>4, 68</sup> (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<sup>5</sup>. 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<sup>30</sup>.

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<sup>69, 70</sup>. 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<sup>70</sup>.

Fatty acids, bile acids and amino acids are detected by specific G-protein coupled receptors (GPCRs) located directly on the eecs<sup>69, 71, 72</sup>. The majority of nutrient-responsive GPCRs are coupled to Gas or G<sub>q</sub> 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<sup>72, 73</sup>.

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<sup>5</sup>, including bacterial metabolites<sup>74-79</sup>, hormonal<sup>80</sup>, paracrine<sup>81</sup> and neurotransmitter signals<sup>12, 82</sup>. 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<sup>83-86</sup>. Interestingly, eecs are the prime epithelial expressers of the receptors that sense bacterial metabolites<sup>84, 87</sup>, 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<sup>77, 78, 88-102</sup>.

## 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<sup>103</sup>. 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*)<sup>104</sup>, while autoantibodies for the EEC ubiquitination factor E4A (*UBE4A*) are seen as a biomarker for CD<sup>105</sup>. Moreover, both *Phox2B* and *UBE4A* are seen to increase in ileal CD displaying active inflammation<sup>106</sup>. 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 assess 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 Chromogranin A (CgA) levels, a pan-EEC marker<sup>107</sup>, strongly increases in IBD patients and correlates to tumor necrosis factor (TNF) $\alpha$ <sup>108, 109</sup>, 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<sup>110</sup>, while other studies demonstrate differences in microscopic colitis but not in UC or CD<sup>111</sup>. 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)<sup>112-129</sup>. Many of these reports also correlate increases of blood detected peptide levels with active disease, with somatostatin<sup>117</sup>, ghrelin<sup>115, 120, 122</sup> and gastrin<sup>125</sup> decreasing on remission. Moreover, ghrelin<sup>119, 121</sup> and gastrin<sup>125</sup> correlate with levels of the pro-inflammatory cytokine TNF $\alpha$  and IL-6. However, once again conflicting reports exist within the literature<sup>123, 126</sup> 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<sup>128</sup>, but not in a follow up study by the same investigators<sup>129</sup>. 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<sup>130</sup>. 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)<sup>106, 112, 131-137</sup>. Interestingly, similar to Paneth cell occurrence in the colon<sup>138</sup>, gastrin+ cells are strangely found in the repairing small intestine of CD patients<sup>131</sup> and subsets of IBD patients have autoantibodies to gastrin<sup>139</sup>. GLP-1<sup>140</sup> and GLP-2<sup>141</sup> are epithelial growth factors, with GLP-2 also having anti-inflammatory action both direct<sup>142</sup> and indirect via Paneth cells<sup>102</sup>. 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<sup>137</sup>. Indeed, long acting analogs of GLP-2 could potentially be used for the treatment of short-bowel syndrome following CD<sup>143</sup>.

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<sup>129</sup> and CCK<sup>128</sup> are thought to be responsible for changes in gastric emptying, while decreased appetite and nausea in small bowel CD correlate with increased PYY levels<sup>115</sup>. Plasma motilin also increases in IBD and is related to altered contractility<sup>144, 145</sup>, with a polymorphism of the motilin gene interestingly seen in subsets of patients with CD<sup>146</sup>. 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)<sup>147-152</sup>. 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<sup>144</sup>, while, the interleukin (IL)-2-/- colitis model reductions in PYY+ cells occur on activation of inflammation<sup>153</sup>. 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 TNF $\alpha$  levels and ameliorates pathology<sup>154</sup>, while 2,4,6-trinitrobenzenesulfonic acid (TNBS) colitis is inhibited with a CCKB receptor antagonist<sup>155</sup>. Interestingly CCK was a novel and verified hit in a recent zebrafish enterocolitis small molecule screen<sup>156</sup>. Additionally, the regulatory peptide nesfatin-1<sup>157</sup> and somatostatin have been shown to be anti-inflammatory in the acetic acid model of colitis<sup>158, 159</sup>. Indeed, somatostatin agonists are able to increase intestinal tight junctions in models of dextran sulfate sodium (DSS) and *Citrobacter rodentium* induced colitis<sup>160</sup> and modulate the water and sodium uptake protein NHE8, associated with UC pathology, via MAPK signaling<sup>161</sup>. 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<sup>162</sup>, indicating a protective effect. Indeed, therapeutic use of peptides or agonists has been beneficial in mouse models, GLP-2 can rescue DSS colitis<sup>163</sup> and small intestinal enteritis<sup>164</sup>,<sup>165</sup> possibly by reducing bacterial translocation<sup>166</sup>, while nanodelivery of GLP-1 is also

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

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<sup>169</sup>. Furthermore, given the high concentration of eecs in the small intestine, examining eec changes in the SAMP1/YitFc model<sup>170</sup>, 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<sup>171, 172</sup> as well as peptide granule storage<sup>130</sup>. Serum levels of GLP-1, GIP<sup>173</sup> and plasma CCK, thought to be responsible for the pancreatic dysfunction seen in celiac patients<sup>174</sup>, are seen to be reduced in celiac blood. However, increases in CgA+ cells are also observed<sup>174</sup>, with increased ghrelin+ cells seen in the duodenum that correlate with inflammation<sup>175, 176</sup>. Increased serum somatostatin<sup>177</sup> and GLP-2<sup>178</sup>, plasma oxyntomodulin<sup>179</sup>, neurotensin<sup>180</sup> and motilin<sup>181</sup> 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- $\gamma$  in tissue samples of refractory celiac patients<sup>174</sup>, 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<sup>182</sup>. Somatostatin also increases in IBS post-IBD<sup>183</sup>, while post-infectious IBS is strongly linked to changes in nerve sensitivity to peptide hormones<sup>184-187</sup>. Interestingly, high correlations of Chlamydia antigens are associated with eecs in IBS sufferers<sup>188</sup>, 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<sup>189, 190</sup>. Calves infected with *Ostertagia ostertagi* have elevated gastrin<sup>191</sup> while sheep infected with *Ostertagia circumcincta* have reduced gastrin and somatostatin+ cells and this is linked to the development of hypergastrinemia in parasitized animals<sup>192</sup>. Furthermore, helminth induced alterations are not limited to mammal livestock with increases in CCK cells seen in *Eubothrium crassum* infected trout<sup>193</sup> and *Anisakis simplex* infected flounders<sup>194</sup>; while CCK and gastrin+ cell increase, but GLP-1/2 reduce in *Eubothrium crassum* infected trout<sup>193</sup>. Experimental murine models have been used to further dissect the association of helminth infection with alterations in eec function.

CCK+ cell hyperplasia<sup>195</sup> and hypersecretion<sup>196</sup> 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<sup>195</sup>. This does not seem to be the case in all helminth infections as serum CCK levels are reduced in *Nippostrongylus brasiliensis* infection in rats<sup>197</sup>, while increased serum gastrin is seen during *T. spiralis*, but not tape worm infection<sup>198</sup>; furthermore decreased somatostatin+ cells are seen during intestinal inflammation resulting from intestinal schistomiasis in mice<sup>199</sup>.

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 lamblia*<sup>200</sup>. Alterations are also seen in bacterial and viral infection with reduced CgA+ cells seen in *Helicobacter pylori* patients<sup>201</sup>. In particular reductions in ghrelin are associated with disease pathology<sup>202</sup>, with eradication of *H. pylori* associated with increased ghrelin which correlates with abatement of dyspepsia<sup>203</sup>. Importantly, in mouse models, changes occur prior to any general epithelial damage caused by the infection<sup>204</sup>, while reduced 5-HT and somatostatin+ cells in HIV-1 infected individuals are associated with lower survival prognosis<sup>205</sup>, again correlating alterations in eec function to pathology. Indeed, upon sensing chlamydia infection, eecs respond via a distinct transcript alteration<sup>206</sup>, supporting their role as innate sensors of disease.

Collectively, the specific alterations of peptide secretion during inflammation indicates 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<sup>61</sup>. Indeed, increased eec numbers in UC have been suggested to act as promoters for the neoplasia associated with IBD<sup>207</sup>, with animal models demonstrating GLP-1 agonists as regulators of intestinal tumorigenesis<sup>140</sup>. Moreover, at rest a subset of eecs express the cancer-associated transcription factor Brachyury<sup>208</sup> 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<sup>209</sup> and recent data demonstrating that EGF signaling is inhibited during eec differentiation<sup>16</sup>, suggests it is reactivated during NET neoplasia<sup>210</sup>. Therefore, the current targeting of the mTOR pathway in intestinal neoplasia<sup>211</sup> 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<sup>212, 213</sup> and are often associated with the proliferative compartments of adenocarcinomas<sup>214, 215</sup>. There is much debate regarding the clinical impact of eec differentiation on colorectal cancer, reviewed in<sup>216</sup>. Of particular interest is the production of VEGF from eecs during cancer<sup>212, 217</sup>, a factor whose targeting has been shown to prolong survival in colorectal cancer patients<sup>218, 219</sup>, and promising results are again coming from drug trials blocking mTOR<sup>220, 221</sup>. 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<sup>222</sup>.

## **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<sup>148, 223</sup>. There is a close physical association of immune cells with eecs<sup>224</sup> and infection driven 5-HT+ cell hyperplasia observed during *Citrobacter rodentium* infection is absent in severe combined immunodeficiency (SCID) mice<sup>225</sup>, as is the CCK and 5-HT+ cell hyperplasia seen in helminth infection<sup>195, 226</sup>. 5-HT+ cell increases seen during *T. muris* infection are also driven by specific T-helper (Th)2 CD4+ T-cell responses<sup>227, 228</sup>. Recent

studies have shown that the pro-inflammatory cytokines interferon (IFN) $\gamma$  and TNF $\alpha$  increase CgA+ eecs in an autophagy and protein kinase B (Akt) dependent manner<sup>229</sup>.

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<sup>230</sup>. 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<sup>231</sup>. 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 TNF $\alpha$  decreasing GLP-2 expression by up-regulating G-protein-coupled receptor 120 in CD<sup>232</sup>, IL-6 increasing GLP-1 release<sup>233</sup>, while IL-1 $\beta$  has been shown to cause 5-HT secretion from CD enterochromaffin cells *ex vivo*<sup>234</sup>. 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<sup>195, 235</sup>.

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<sup>26, 236-238</sup>, 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- $\kappa$ B, MAPK signaling, as well as Ca<sup>2+</sup> flux culminating in TNF $\alpha$ , transforming growth factor (TGF) $\beta$ , macrophage inflammatory protein-2 and CCK release<sup>74</sup>. 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<sup>239</sup>. 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<sup>240</sup>. 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<sup>241</sup>. 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<sup>241</sup>.

### ***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<sup>242</sup>. Moreover, chemotherapy drug induced emesis is dependent on 5-HT release and 5-HT<sub>3</sub> receptor triggering<sup>243</sup>, while more recently rotavirus toxin induced emesis was hypothesized to act via a similar mechanism<sup>244</sup>. Interestingly, CCK and motilin can alter the behavior and movement of the liver fluke *Fasciola hepatica*<sup>245</sup>, while ghrelin also has direct anti-parasitic<sup>246</sup> and anti-bacterial effects<sup>247</sup>, 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<sup>248</sup>. 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<sup>102</sup>, although it remains to be ascertained if this is a result of other cellular phenotypes arising in the GLP-2 receptor null mouse<sup>102</sup>.

Beyond anti-microbial effects, GLP-2 has been seen to maintain barrier function in mouse<sup>97, 249</sup>, and human<sup>250</sup> 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<sup>141</sup>, and more recently GLP-1<sup>140</sup>, as potent epithelial growth factors. GLP-2s trophic effects act via myofibroblast produced insulin-like growth factor<sup>141</sup> and keratinocyte growth factor<sup>251</sup> as well as the ErbB signaling network in intestinal tissue<sup>252</sup>; while GLP-1 mediates growth via fibroblast growth factor 7<sup>140</sup>.

### ***Enteroendocrine peptides as “cytokines”***

Intriguingly, immune cells express a vast array of receptors for eec secreted hormone peptides<sup>253</sup> 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<sup>254-256</sup>.

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<sup>257</sup>, while conversely ghrelin inhibits Th17 formation<sup>258</sup> via mTOR<sup>259</sup>, being beneficial in EAE models<sup>260, 261</sup>. CCK has been shown to promote a Th2<sup>262</sup> and regulatory T-cell (Treg) phenotype *in vitro*<sup>262</sup>, as does GLP-1<sup>263</sup> via decreased MAPK activation<sup>264</sup>. 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<sup>265</sup> and has an anti-inflammatory effect in DSS colitis<sup>266</sup>; with CD patients interestingly demonstrating a reduction of the ghrelin receptor GHSR-1a on T-cells<sup>267</sup>. Somatostatin is also inhibitory to T-cell proliferation<sup>268</sup>, downregulates LFA-1 expression<sup>269</sup> and is ultimately involved in thymus development<sup>270</sup>. Apart from CD4+ T-cells, GLP-1 signals to intraepithelial lymphocytes ameliorating the inflammation in DSS induced colitis<sup>271</sup> and signals to fat resident invariant NKT-cells mediating weight loss<sup>272</sup> and psoriasis at the skin barrier<sup>273</sup>. A number of these effects seem to be tissue specific with somatostatin inhibiting Peyer's patch, but not splenic natural killer activity<sup>274</sup>; and CCK altering lamina propria but not blood sourced cells<sup>275</sup>.

B-cells are also under the control of peptide hormones with CCK driving acetylcholine (ACh) production to recruit neutrophils independently of vagal stimulation<sup>276</sup>. CCK<sup>277</sup> and somatostatin<sup>278</sup> can reduce B-cell activation, while ghrelin<sup>279</sup> and neurotensin<sup>280</sup> are able to enhance B-cell activation and proliferation respectively. CCK<sup>277</sup>, somatostatin<sup>278</sup> and GLP-2<sup>281</sup> 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<sup>253, 282</sup>, although the mechanism remains undefined.

Intestinal 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<sup>283</sup>, while somatostatin<sup>284</sup> and neurotensin<sup>285</sup> are also reported to be inhibitory to DC activation. Conversely CCK can promote IL-12 production<sup>286</sup> and secretin acts as a chemoattractant to DCs<sup>287</sup> 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<sup>288-290</sup>, including inducible nitric oxide synthase production<sup>291</sup>, and cause monocytes to produce inflammatory cytokines and eicosanoids<sup>292</sup>. 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<sup>293, 294</sup>, while GLP-2 inhibits macrophage LPS stimulation via reduced NF $\kappa$ B<sup>295</sup> in an IL-10 independent manner<sup>142</sup>. Discrepancies in these *in vitro* studies exist, with monocytes releasing IL-6 in response to somatostatin<sup>296</sup>, while it can be anti-inflammatory in other settings<sup>297</sup>, similar to GLP-1<sup>298</sup> and ghrelin<sup>299, 300</sup>. 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<sup>301</sup>, 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<sup>113</sup> and GLP-1<sup>302</sup> respectively. Neutrophil phagocytosis<sup>303-305</sup>, elastase release<sup>306</sup> and adhesion<sup>305, 307</sup> 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<sup>308</sup>. Most notably mast cells are strongly responsive to peptide hormones, with CCK<sup>309</sup>, gastrin<sup>310</sup> and somatostatin<sup>311</sup> inhibitory for degranulation, while ghrelin<sup>312</sup> and PYY<sup>313</sup> increase histamine release. CCK also induces intestinal contraction via mast cells during *Giardia* infection<sup>314</sup>, 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<sup>315</sup>, and under homeostatic conditions share a transcriptome similar to mast cells<sup>316</sup>, 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<sup>317</sup> 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<sup>318</sup> 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<sup>319</sup>, a portal that pathogens may have evolved to target infection of the nervous system<sup>320-322</sup>.. 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<sup>323</sup>. This pathway is also dependent on post-absorptive chylomicron formation, lipoprotein formations shown to release endogenous CCK<sup>324</sup> and also requires GLP-1 receptor activation<sup>325</sup> and potentially ghrelin<sup>326</sup>. GLP-2 also acts via enteric nerves to increase the secretion of immunomodulatory vasoactive intestinal peptide during animal models of IBD<sup>327</sup>.

Others have demonstrated similar CCK-induced vagal anti-inflammatory pathways in a variety of inflammatory settings, such as post-operative ileus<sup>328</sup> and lung damage during endotoxemia<sup>329</sup>. Furthermore, interfering with the vagal reflex has also been shown to exacerbate DSS colitis<sup>330</sup>. Although not thought to be B or T-cell dependent<sup>331</sup>, CCK induced Ach release has also been shown to influence other innate cells such as mast cells<sup>332</sup>. 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<sup>333</sup>. 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<sup>334</sup>.

### ***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<sup>335-337</sup>, but not all<sup>338</sup>, 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<sup>235</sup>. 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<sup>196</sup>, 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<sup>195, 196</sup>. Increased c-Fos brain expression during helminth infection<sup>339, 340</sup>, 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<sup>255, 341</sup>. As T-cells express functional leptin receptors<sup>342</sup> and leptin stimulation polarizes T-cells towards a pro-inflammatory Th1 state<sup>343</sup>, 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<sup>344</sup>. Restoration via recombinant leptin treatment, resulted in a significant reduction in CD4+ Th2 cytokine production and accompanying mastocytosis, which is essential for worm expulsion<sup>345</sup>. 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<sup>195</sup>.

## 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<sup>260, 273, 286</sup>, 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.

## REFERENCES

1. Artis D, Grencis RK. The intestinal epithelium: sensors to effectors in nematode infection. *Mucosal Immunology* 2008; **1**(4): 252-264.
2. Peterson LW, Artis D. Intestinal epithelial cells: regulators of barrier function and immune homeostasis. *Nat Rev Immunol* 2014; **14**(3): 141-153.
3. Pastorelli L, De Salvo C, Mercado JR, Vecchi M, Pizarro TT. Central role of the gut epithelial barrier in the pathogenesis of chronic intestinal inflammation: lessons learned from animal models and human genetics. *Frontiers in immunology* 2013; **4**: 280.
4. Begg DP, Woods SC. The endocrinology of food intake. *Nat Rev Endocrinol* 2013; **9**(10): 584-597.
5. Gribble FM, Reimann F. Enteroendocrine Cells: Chemosensors in the Intestinal Epithelium. *Annu Rev Physiol* 2016; **78**: 277-299.
6. Liou AP, Lu X, Sei Y, Zhao X, Pechhold S, Carrero RJ *et al*. The G-protein-coupled receptor GPR40 directly mediates long-chain fatty acid-induced secretion of cholecystokinin. *Gastroenterology* 2011; **140**(3): 903-912.
7. Bohorquez DV, Chandra R, Samsa LA, Vigna SR, Liddle RA. Characterization of basal pseudopod-like processes in ileal and colonic PYY cells. *J Mol Histol* 2011; **42**(1): 3-13.

8. Parker HE, Habib AM, Rogers GJ, Gribble FM, Reimann F. Nutrient-dependent secretion of glucose-dependent insulinotropic polypeptide from primary murine K cells. *Diabetologia* 2009; **52**(2): 289-298.
9. Reimann F, Habib AM, Tolhurst G, Parker HE, Rogers GJ, Gribble FM. Glucose sensing in L cells: a primary cell study. *Cell Metab* 2008; **8**(6): 532-539.
10. Engelstoft MS, Lund ML, Grunddal KV, Egerod KL, Osborne-Lawrence S, Poulsen SS *et al.* Research Resource: A Chromogranin A Reporter for Serotonin and Histamine Secreting Enteroendocrine Cells. *Molecular endocrinology (Baltimore, Md)* 2015; **29**(11): 1658-1671.
11. Sakata I, Nakano Y, Osborne-Lawrence S, Rovinsky SA, Lee CE, Perello M *et al.* Characterization of a novel ghrelin cell reporter mouse. *Regul Pept* 2009; **155**(1-3): 91-98.
12. Adriaenssens A, Lam BY, Billing L, Skeffington K, Sewing S, Reimann F *et al.* A Transcriptome-Led Exploration of Molecular Mechanisms Regulating Somatostatin-Producing D-Cells in the Gastric Epithelium. *Endocrinology* 2015; **156**(11): 3924-3936.
13. Nagatake T, Fujita H, Minato N, Hamazaki Y. Enteroendocrine cells are specifically marked by cell surface expression of claudin-4 in mouse small intestine. *PLoS One* 2014; **9**(6): e90638.
14. Barker N, van Es JH, Kuipers J, Kujala P, van den Born M, Cozijnsen M *et al.* Identification of stem cells in small intestine and colon by marker gene Lgr5. *Nature* 2007; **449**(7165): 1003-1007.
15. Barker N. Adult intestinal stem cells: critical drivers of epithelial homeostasis and regeneration. *Nature reviews Molecular cell biology* 2014; **15**(1): 19-33.
16. Basak O, Beumer J, Wiebrands K, Seno H, van Oudenaarden A, Clevers H. Induced Quiescence of Lgr5+ Stem Cells in Intestinal Organoids Enables Differentiation of Hormone-Producing Enteroendocrine Cells. *Cell stem cell* 2017; **20**(2): 177-190.e174.
17. Shroyer NF, Helmrath MA, Wang VYC, Antalffy B, Henning SJ, Zoghbi HY. Intestine-specific ablation of mouse atonal homolog 1 (Math1) reveals a role in cellular homeostasis. *Gastroenterology* 2007; **132**(7): 2478-2488.
18. Li HJ, Ray SK, Singh NK, Johnston B, Leiter AB. Basic helix-loop-helix transcription factors and enteroendocrine cell differentiation. *Diabetes, obesity & metabolism* 2011; **13 Suppl 1**: 5-12.
19. May CL, Kaestner KH. Gut endocrine cell development. *Mol Cell Endocrinol* 2010; **323**(1): 70-75.

20. Yang Q, Bermingham NA, Finegold MJ, Zoghbi HY. Requirement of Math1 for secretory cell lineage commitment in the mouse intestine. *Science* 2001; **294**(5549): 2155-2158.
21. Shroyer NF, Shultz DW, Venken KJ, Bellen HJ, Zoghbi HY. Gfi1 functions downstream of Math1 to control intestinal secretory cell differentiation. *Gastroenterology* 2005; **128**(4): A127-A127.
22. Katz JP, Perreault N, Goldstein BG, Lee CS, Labosky PA, Yang VW *et al.* The zinc-finger transcription factor Klf4 is required for terminal differentiation of goblet cells in the colon. *Development* 2002; **129**(11): 2619-2628.
23. Bastide P, Darido C, Pannequin J, Kist R, Robine S, Marty-Double C *et al.* Sox9 regulates cell proliferation and is required for Paneth cell differentiation in the intestinal epithelium. *The Journal of cell biology* 2007; **178**(4): 635-648.
24. Mori-Akiyama Y, van den Born M, van Es JH, Hamilton SR, Adams HP, Zhang J *et al.* SOX9 is required for the differentiation of paneth cells in the intestinal epithelium. *Gastroenterology* 2007; **133**(2): 539-546.
25. Gerbe F, van Es JH, Makrini L, Brulin B, Mellitzer G, Robine S *et al.* Distinct ATOH1 and Neurog3 requirements define tuft cells as a new secretory cell type in the intestinal epithelium. *The Journal of cell biology* 2011; **192**(5): 767-780.
26. Gerbe F, Sidot E, Smyth DJ, Ohmoto M, Matsumoto I, Dardalhon V *et al.* Intestinal epithelial tuft cells initiate type 2 mucosal immunity to helminth parasites. *Nature* 2016; **529**(7585): 226-230.
27. Kanaya T, Hase K, Takahashi D, Fukuda S, Hoshino K, Sasaki I *et al.* The Ets transcription factor Spi-B is essential for the differentiation of intestinal microfold cells. *Nat Immunol* 2012; **13**(8): 729-736.
28. Knoop KA, Kumar N, Butler BR, Sakthivel SK, Taylor RT, Nochi T *et al.* RANKL is necessary and sufficient to initiate development of antigen-sampling M cells in the intestinal epithelium. *J Immunol* 2009; **183**(9): 5738-5747.
29. de Lau W, Kujala P, Schneeberger K, Middendorp S, Li VS, Barker N *et al.* Peyer's patch M cells derived from Lgr5(+) stem cells require SpiB and are induced by RankL in cultured "miniguts". *Mol Cell Biol* 2012; **32**(18): 3639-3647.
30. Mellitzer G, Beucher A, Lobstein V, Michel P, Robine S, Kedinger M *et al.* Loss of enteroendocrine cells in mice alters lipid absorption and glucose homeostasis and impairs postnatal survival. *J Clin Invest* 2010; **120**(5): 1708-1721.



31. Jenny M, Uhl C, Roche C, Duluc I, Guillermin V, Guillemot F *et al.* Neurogenin3 is differentially required for endocrine cell fate specification in the intestinal and gastric epithelium. *The EMBO journal* 2002; **21**(23): 6338-6347.
32. Knudsen LA, Petersen N, Schwartz TW, Egerod KL. The MicroRNA Repertoire in Enteroendocrine Cells: Identification of miR-375 as a Potential Regulator of the Enteroendocrine Lineage. *Endocrinology* 2015; **156**(11): 3971-3983.
33. Mutoh H, Fung BP, Naya FJ, Tsai MJ, Nishitani J, Leiter AB. The basic helix-loop-helix transcription factor BETA2/NeuroD is expressed in mammalian enteroendocrine cells and activates secretin gene expression. *Proc Natl Acad Sci U S A* 1997; **94**(8): 3560-3564.
34. Naya FJ, Huang HP, Qiu Y, Mutoh H, DeMayo FJ, Leiter AB *et al.* Diabetes, defective pancreatic morphogenesis, and abnormal enteroendocrine differentiation in BETA2/neuroD-deficient mice. *Genes Dev* 1997; **11**(18): 2323-2334.
35. Rindi G, Ratineau C, Ronco A, Candusso ME, Tsai M, Leiter AB. Targeted ablation of secretin-producing cells in transgenic mice reveals a common differentiation pathway with multiple enteroendocrine cell lineages in the small intestine. *Development* 1999; **126**(18): 4149-4156.
36. Larsson LI, St-Onge L, Hougaard DM, Sosa-Pineda B, Gruss P. Pax 4 and 6 regulate gastrointestinal endocrine cell development. *Mech Dev* 1998; **79**(1-2): 153-159.
37. Trinh DK, Zhang K, Hossain M, Brubaker PL, Drucker DJ. Pax-6 activates endogenous proglucagon gene expression in the rodent gastrointestinal epithelium. *Diabetes* 2003; **52**(2): 425-433.
38. Hill ME, Asa SL, Drucker DJ. Essential requirement for Pax6 in control of enteroendocrine proglucagon gene transcription. *Molecular endocrinology (Baltimore, Md)* 1999; **13**(9): 1474-1486.
39. Terry NA, Walp ER, Lee RA, Kaestner KH, May CL. Impaired enteroendocrine development in intestinal-specific Islet1 mouse mutants causes impaired glucose homeostasis. *Am J Physiol Gastrointest Liver Physiol* 2014; **307**(10): G979-991.
40. Larsson LI, Madsen OD, Serup P, Jonsson J, Edlund H. Pancreatic-duodenal homeobox 1 -role in gastric endocrine patterning. *Mech Dev* 1996; **60**(2): 175-184.
41. Miller CP, McGehee RE, Jr., Habener JF. IDX-1: a new homeodomain transcription factor expressed in rat pancreatic islets and duodenum that transactivates the somatostatin gene. *The EMBO journal* 1994; **13**(5): 1145-1156.

42. Offield MF, Jetton TL, Labosky PA, Ray M, Stein RW, Magnuson MA *et al.* PDX-1 is required for pancreatic outgrowth and differentiation of the rostral duodenum. *Development* 1996; **122**(3): 983-995.
43. Lee E, Ryu GR, Moon SD, Ko SH, Ahn YB, Song KH. Reprogramming of enteroendocrine K cells to pancreatic beta-cells through the combined expression of Nkx6.1 and Neurogenin3, and reaggregation in suspension culture. *Biochem Biophys Res Commun* 2014; **443**(3): 1021-1027.
44. Desai S, Loomis Z, Pugh-Bernard A, Schrunk J, Doyle MJ, Minic A *et al.* Nkx2.2 regulates cell fate choice in the enteroendocrine cell lineages of the intestine. *Developmental Biology* 2008; **313**(1): 58-66.
45. Gross S, Balderes D, Liu J, Asfaha S, Gu G, Wang TC *et al.* Nkx2.2 is expressed in a subset of enteroendocrine cells with expanded lineage potential. *Am J Physiol Gastrointest Liver Physiol* 2015; **309**(12): G975-987.
46. Middendorp S, Schneeberger K, Wiegerinck CL, Mokry M, Akkerman RD, van Wijngaarden S *et al.* Adult stem cells in the small intestine are intrinsically programmed with their location-specific function. *Stem Cells* 2014; **32**(5): 1083-1091.
47. Fang R, Olds LC, Sibley E. Spatio-temporal patterns of intestine-specific transcription factor expression during postnatal mouse gut development. *Gene expression patterns : GEP* 2006; **6**(4): 426-432.
48. Grainger S, Savory JG, Lohnes D. Cdx2 regulates patterning of the intestinal epithelium. *Dev Biol* 2010; **339**(1): 155-165.
49. Mutoh H, Sakamoto H, Hayakawa H, Arao Y, Satoh K, Nokubi M *et al.* The intestine-specific homeobox gene Cdx2 induces expression of the basic helix-loop-helix transcription factor Math1. *Differentiation* 2006; **74**(6): 313-321.
50. Beuling E, Baffour-Awuah NY, Stapleton KA, Aronson BE, Noah TK, Shroyer NF *et al.* GATA factors regulate proliferation, differentiation, and gene expression in small intestine of mature mice. *Gastroenterology* 2011; **140**(4): 1219-1229.e1211-1212.
51. Bosse T, Piaseckyj CM, Burghard E, Fialkovich JJ, Rajagopal S, Pu WT *et al.* Gata4 is essential for the maintenance of Jejunal-Ileal identities in the adult mouse small intestine. *Molecular and Cellular Biology* 2006; **26**(23): 9060-9070.
52. Dimaline R, Campbell BJ, Watson F, Sandvik AK, Struthers J, Noble PJ. Regulated expression of GATA-6 transcription factor in gastric endocrine cells. *Gastroenterology* 1997; **112**(5): 1559-1567.

53. Dusing MR, Wiginton DA. Epithelial lineages of the small intestine have unique patterns of GATA expression. *J Mol Histol* 2005; **36**(1): 15-24.
54. Gao XP, Sedgwick T, Shi YB, Evans T. Distinct functions are implicated for the GATA-4, -5, and -6 transcription factors in the regulation of intestine epithelial cell differentiation. *Molecular and Cellular Biology* 1998; **18**(5): 2901-2911.
55. Lussier CR, Brial F, Roy SA, Langlois MJ, Verdu EF, Rivard N *et al.* Loss of hepatocyte-nuclear-factor-1alpha impacts on adult mouse intestinal epithelial cell growth and cell lineages differentiation. *PLoS One* 2010; **5**(8): e12378.
56. D'Angelo A, Bluteau O, Garcia-Gonzalez MA, Gresh L, Doyen A, Garbay S *et al.* Hepatocyte nuclear factor 1alpha and beta control terminal differentiation and cell fate commitment in the gut epithelium. *Development* 2010; **137**(9): 1573-1582.
57. Boudreau F, Rings EH, Swain GP, Sinclair AM, Suh ER, Silberg DG *et al.* A novel colonic repressor element regulates intestinal gene expression by interacting with Cux/CDP. *Mol Cell Biol* 2002; **22**(15): 5467-5478.
58. Amcheslavsky A, Song W, Li Q, Nie Y, Bragatto I, Ferrandon D *et al.* Enteroendocrine cells support intestinal stem-cell-mediated homeostasis in *Drosophila*. *Cell reports* 2014; **9**(1): 32-39.
59. Radford IR, Lobachevsky PN. An enteroendocrine cell-based model for a quiescent intestinal stem cell niche. *Cell Prolif* 2006; **39**(5): 403-414.
60. Jung P, Sommer C, Barriga FM, Buczacki SJ, Hernando-Momblona X, Sevillano M *et al.* Isolation of Human Colon Stem Cells Using Surface Expression of PTK7. *Stem cell reports* 2015; **5**(6): 979-987.
61. Buczacki SJ, Zecchini HI, Nicholson AM, Russell R, Vermeulen L, Kemp R *et al.* Intestinal label-retaining cells are secretory precursors expressing Lgr5. *Nature* 2013; **495**(7439): 65-69.
62. Sykaras AG, Demenis C, Case RM, McLaughlin JT, Smith CP. Duodenal enteroendocrine I-cells contain mRNA transcripts encoding key endocannabinoid and fatty acid receptors. *PLoS One* 2012; **7**(8): e42373.
63. Egerod KL, Engelstoft MS, Grunddal KV, Nohr MK, Secher A, Sakata I *et al.* A major lineage of enteroendocrine cells coexpress CCK, secretin, GIP, GLP-1, PYY, and neurotensin but not somatostatin. *Endocrinology* 2012; **153**(12): 5782-5795.

64. Habib AM, Richards P, Cairns LS, Rogers GJ, Bannon CA, Parker HE *et al.* Overlap of endocrine hormone expression in the mouse intestine revealed by transcriptional profiling and flow cytometry. *Endocrinology* 2012; **153**(7): 3054-3065.
65. Grunddal KV, Ratner CF, Svendsen B, Sommer F, Engelstoft MS, Madsen AN *et al.* Neurotensin Is Coexpressed, Coreleased, and Acts Together With GLP-1 and PYY in Enteroendocrine Control of Metabolism. *Endocrinology* 2016; **157**(1): 176-194.
66. Svendsen B, Pedersen J, Albrechtsen NJ, Hartmann B, Torang S, Rehfeld JF *et al.* An analysis of cosecretion and coexpression of gut hormones from male rat proximal and distal small intestine. *Endocrinology* 2015; **156**(3): 847-857.
67. Svendsen B, Pais R, Engelstoft MS, Milev NB, Richards P, Christiansen CB *et al.* GLP1- and GIP-producing cells rarely overlap and differ by bombesin receptor-2 expression and responsiveness. *The Journal of endocrinology* 2016; **228**(1): 39-48.
68. Psichas A, Reimann F, Gribble FM. Gut chemosensing mechanisms. *J Clin Invest* 2015; **125**(3): 908-917.
69. Diakogiannaki E, Pais R, Tolhurst G, Parker HE, Horscroft J, Rauscher B *et al.* Oligopeptides stimulate glucagon-like peptide-1 secretion in mice through proton-coupled uptake and the calcium-sensing receptor. *Diabetologia* 2013; **56**(12): 2688-2696.
70. Gorboulev V, Schurmann A, Vallon V, Kipp H, Jaschke A, Klessen D *et al.* Na(+)-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. *Diabetes* 2012; **61**(1): 187-196.
71. Gribble FM, Diakogiannaki E, Reimann F. Gut Hormone Regulation and Secretion via FFA1 and FFA4. *Handb Exp Pharmacol* 2016.
72. Brighton CA, Rievaj J, Kuhre RE, Glass LL, Schoonjans K, Holst JJ *et al.* Bile Acids Trigger GLP-1 Release Predominantly by Accessing Basolaterally Located G Protein-Coupled Bile Acid Receptors. *Endocrinology* 2015; **156**(11): 3961-3970.
73. Christensen LW, Kuhre RE, Janus C, Svendsen B, Holst JJ. Vascular, but not luminal, activation of FFAR1 (GPR40) stimulates GLP-1 secretion from isolated perfused rat small intestine. *Physiological reports* 2015; **3**(9): e12551.
74. Bogunovic M, Dave SH, Tilstra JS, Chang DTW, Harpaz N, Xiong HB *et al.* Enteroendocrine cells express functional Toll-like receptors. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 2007; **292**(6): G1770-G1783.

75. Chimerel C, Emery E, Summers DK, Keyser U, Gribble FM, Reimann F. Bacterial metabolite indole modulates incretin secretion from intestinal enteroendocrine L cells. *Cell reports* 2014; **9**(4): 1202-1208.
76. Nguyen AT, Mandard S, Dray C, Deckert V, Valet P, Besnard P *et al.* Lipopolysaccharides-mediated increase in glucose-stimulated insulin secretion: involvement of the GLP-1 pathway. *Diabetes* 2014; **63**(2): 471-482.
77. Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK *et al.* Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci U S A* 2008; **105**(43): 16767-16772.
78. Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E *et al.* Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* 2012; **61**(2): 364-371.
79. Psichas A, Sleeth ML, Murphy KG, Brooks L, Bewick GA, Hanyaloglu AC *et al.* The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. *International journal of obesity (2005)* 2015; **39**(3): 424-429.
80. Gabellec MM, Griffais R, Fillion G, Haour F. Expression of interleukin 1 alpha, interleukin 1 beta and interleukin 1 receptor antagonist mRNA in mouse brain: regulation by bacterial lipopolysaccharide (LPS) treatment. *Molecular Brain Research* 1995; **31**(1-2): 122-130.
81. Saffouri B, Weir G, Bitar K, Makhoul G. Stimulation of gastrin secretion from the perfused rat stomach by somatostatin antiserum. *Life Sci* 1979; **25**(20): 1749-1753.
82. Engelstoft MS, Park WM, Sakata I, Kristensen LV, Husted AS, Osborne-Lawrence S *et al.* Seven transmembrane G protein-coupled receptor repertoire of gastric ghrelin cells. *Molecular metabolism* 2013; **2**(4): 376-392.
83. Houlden A, Hayes KS, Bancroft AJ, Worthington JJ, Wang P, Grencis RK *et al.* Chronic *Trichuris muris* Infection in C57BL/6 Mice Causes Significant Changes in Host Microbiota and Metabolome: Effects Reversed by Pathogen Clearance. *PLoS One* 2015; **10**(5): e0125945.
84. Karaki S, Mitsui R, Hayashi H, Kato I, Sugiyama H, Iwanaga T *et al.* Short-chain fatty acid receptor, GPR43, is expressed by enteroendocrine cells and mucosal mast cells in rat intestine. *Cell Tissue Res* 2006; **324**(3): 353-360.
85. Zeng MY, Inohara N, Nunez G. Mechanisms of inflammation-driven bacterial dysbiosis in the gut. *Mucosal Immunol* 2017; **10**(1): 18-26.

86. Wesemann DR, Nagler CR. The Microbiome, Timing, and Barrier Function in the Context of Allergic Disease. *Immunity* 2016; **44**(4): 728-738.
87. Nohr MK, Pedersen MH, Gille A, Egerod KL, Engelstoft MS, Husted AS *et al.* GPR41/FFAR3 and GPR43/FFAR2 as cosensors for short-chain fatty acids in enteroendocrine cells vs FFAR3 in enteric neurons and FFAR2 in enteric leukocytes. *Endocrinology* 2013; **154**(10): 3552-3564.
88. Cani PD, Dewever C, Delzenne NM. Inulin-type fructans modulate gastrointestinal peptides involved in appetite regulation (glucagon-like peptide-1 and ghrelin) in rats. *The British journal of nutrition* 2004; **92**(3): 521-526.
89. Delzenne NM, Cani PD, Daubioul C, Neyrinck AM. Impact of inulin and oligofructose on gastrointestinal peptides. *The British journal of nutrition* 2005; **93** **Suppl 1**: S157-161.
90. Cani PD, Knauf C, Iglesias MA, Drucker DJ, Delzenne NM, Burcelin R. Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. *Diabetes* 2006; **55**(5): 1484-1490.
91. Ropert A, Cherbut C, Roze C, Le Quellec A, Holst JJ, Fu-Cheng X *et al.* Colonic fermentation and proximal gastric tone in humans. *Gastroenterology* 1996; **111**(2): 289-296.
92. Cani PD, Lecourt E, Dewulf EM, Sohet FM, Pachikian BD, Naslain D *et al.* Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. *The American journal of clinical nutrition* 2009; **90**(5): 1236-1243.
93. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. *The American journal of clinical nutrition* 2009; **89**(6): 1751-1759.
94. Breton J, Tennoune N, Lucas N, Francois M, Legrand R, Jacquemot J *et al.* Gut Commensal E. coli Proteins Activate Host Satiety Pathways following Nutrient-Induced Bacterial Growth. *Cell Metab* 2016; **23**(2): 324-334.
95. Cani PD, Everard A, Duparc T. Gut microbiota, enteroendocrine functions and metabolism. *Curr Opin Pharmacol* 2013; **13**(6): 935-940.
96. Cani PD, Knauf C. How gut microbes talk to organs: The role of endocrine and nervous routes. *Molecular metabolism* 2016; **5**(9): 743-752.

97. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O *et al.* Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 2009; **58**(8): 1091-1103.
98. Everard A, Lazarevic V, Derrien M, Girard M, Muccioli GG, Neyrinck AM *et al.* Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes* 2011; **60**(11): 2775-2786.
99. Plaisancie P, Dumoulin V, Chayvialle JA, Cuber JC. Luminal glucagon-like peptide-1(7-36) amide-releasing factors in the isolated vascularly perfused rat colon. *The Journal of endocrinology* 1995; **145**(3): 521-526.
100. Lin HV, Frassetto A, Kowalik EJ, Jr., Nawrocki AR, Lu MM, Kosinski JR *et al.* Butyrate and propionate protect against diet-induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. *PLoS One* 2012; **7**(4): e35240.
101. Cani PD, Neyrinck AM, Fava F, Knauf C, Burcelin RG, Tuohy KM *et al.* Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia* 2007; **50**(11): 2374-2383.
102. Lee SJ, Lee J, Li KK, Holland D, Maughan H, Guttman DS *et al.* Disruption of the murine Glp2r impairs Paneth cell function and increases susceptibility to small bowel enteritis. *Endocrinology* 2012; **153**(3): 1141-1151.
103. Harrison E, Lal S, McLaughlin JT. Enteroendocrine cells in gastrointestinal pathophysiology. *Curr Opin Pharmacol* 2013; **13**(6): 941-945.
104. Rioux JD, Xavier RJ, Taylor KD, Silverberg MS, Goyette P, Huett A *et al.* Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. *Nat Genet* 2007; **39**(5): 596-604.
105. Sakiyama T, Fujita H, Tsubouchi H. Autoantibodies against ubiquitination factor E4A (UBE4A) are associated with severity of Crohn's disease. *Inflamm Bowel Dis* 2008; **14**(3): 310-317.
106. Moran GW, Pennock J, McLaughlin JT. Enteroendocrine cells in terminal ileal Crohn's disease. *J Crohns Colitis* 2012; **6**(9): 871-880.
107. Rindi G, Leiter AB, Kopin AS, Bordi C, Solcia E. The "normal" endocrine cell of the gut: changing concepts and new evidences. *Annals of the New York Academy of Sciences* 2004; **1014**: 1-12.
108. Zissimopoulos A, Vradelis S, Konialis M, Chadolias D, Bampali A, Constantinidis T *et al.* Chromogranin A as a biomarker of disease activity and biologic therapy in inflammatory

- bowel disease: a prospective observational study. *Scand J Gastroenterol* 2014; **49**(8): 942-949.
109. Sciola V, Massironi S, Conte D, Caprioli F, Ferrero S, Ciafardini C *et al.* Plasma chromogranin a in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2009; **15**(6): 867-871.
  110. Strid H, Simren M, Lasson A, Isaksson S, Stridsberg M, Ohman L. Fecal chromogranins and secretogranins are increased in patients with ulcerative colitis but are not associated with disease activity. *J Crohns Colitis* 2013; **7**(12): e615-622.
  111. Wagner M, Stridsberg M, Peterson CG, Sangfelt P, Lampinen M, Carlson M. Increased fecal levels of chromogranin A, chromogranin B, and secretoneurin in collagenous colitis. *Inflammation* 2013; **36**(4): 855-861.
  112. Tari A, Teshima H, Sumii K, Haruma K, Ohgoshi H, Yoshihara M *et al.* Peptide YY abnormalities in patients with ulcerative colitis. *Japanese journal of medicine* 1988; **27**(1): 49-55.
  113. Adrian TE, Savage AP, Bacarese-Hamilton AJ, Wolfe K, Besterman HS, Bloom SR. Peptide YY abnormalities in gastrointestinal diseases. *Gastroenterology* 1986; **90**(2): 379-384.
  114. Koch TR, Roddy DR, Go VL. Abnormalities of fasting serum concentrations of peptide YY in the idiopathic inflammatory bowel diseases. *The American journal of gastroenterology* 1987; **82**(4): 321-326.
  115. Moran GW, Leslie FC, McLaughlin JT. Crohn's disease affecting the small bowel is associated with reduced appetite and elevated levels of circulating gut peptides. *Clinical nutrition (Edinburgh, Scotland)* 2013; **32**(3): 404-411.
  116. Payer J, Huorka M, Duris I, Mikulecky M, Kratochvilova H, Ondrejka P *et al.* Plasma somatostatin levels in ulcerative colitis. *Hepato-gastroenterology* 1994; **41**(6): 552-553.
  117. Binimelis J, Webb SM, Mones J, Serrano J, Casamitjana R, Elena M *et al.* Circulating immunoreactive somatostatin in gastrointestinal diseases. Decrease after vagotomy and enhancement in active ulcerative colitis, irritable bowel syndrome, and duodenal ulcer. *Scand J Gastroenterol* 1987; **22**(8): 931-937.
  118. Karmiris K, Koutroubakis IE, Xidakis C, Polychronaki M, Voudouri T, Kouroumalis EA. Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. *Inflamm Bowel Dis* 2006; **12**(2): 100-105.
  119. Peracchi M, Bardella MT, Caprioli F, Massironi S, Conte D, Valenti L *et al.* Circulating ghrelin levels in patients with inflammatory bowel disease. *Gut* 2006; **55**(3): 432-433.



120. Ates Y, Degertekin B, Erdil A, Yaman H, Dagalp K. Serum ghrelin levels in inflammatory bowel disease with relation to disease activity and nutritional status. *Dig Dis Sci* 2008; **53**(8): 2215-2221.
121. Cekic C, Arabul M, Alper E, Pakoz ZB, Saritas E, Yuksel *et al.* Evaluation of the relationship between serum ghrelin, C-reactive protein and interleukin-6 levels, and disease activity in inflammatory bowel diseases. *Hepato-gastroenterology* 2014; **61**(133): 1196-1200.
122. Nishi Y, Isomoto H, Ueno H, Ohnita K, Wen CY, Takeshima F *et al.* Plasma leptin and ghrelin concentrations in patients with Crohn's disease. *World J Gastroenterol* 2005; **11**(46): 7314-7317.
123. Triantafillidis JK, Tzourmakliotis D, Peros G, Merikas E, Barbatzas C, Cheracakis P *et al.* Serum gastrin levels in patients with inflammatory bowel disease. *Hepato-gastroenterology* 2003; **50 Suppl 2**: cccxv-cccxvii.
124. Essop AR, Segal I, Ming R. High serum gastrin in ulcerative colitis. *N Engl J Med* 1982; **307**(3): 192.
125. Hopman WP, de Jong DJ, Naber AH, Jansen JB. Tumour necrosis factor alpha antibody affects gastrin release in Crohn disease. *Scand J Gastroenterol* 2003; **38**(5): 522-525.
126. Bendet N, Scapa E, Cohen O, Bloch O, Aharoni D, Ramot Y *et al.* Enhanced glucose-dependent glucagon-like peptide-1 and insulin secretion in Crohn patients with terminal ileum disease is unrelated to disease activity or ileal resection. *Scand J Gastroenterol* 2004; **39**(7): 650-656.
127. Vu MK, Gielkens HA, van Hogezaand RA, van Oostayen JA, Lamers CB, Masclee AA. Gallbladder motility in Crohn disease: influence of disease localization and bowel resection. *Scand J Gastroenterol* 2000; **35**(11): 1157-1162.
128. Keller J, Beglinger C, Holst JJ, Andresen V, Layer P. Mechanisms of gastric emptying disturbances in chronic and acute inflammation of the distal gastrointestinal tract. *Am J Physiol Gastrointest Liver Physiol* 2009; **297**(5): G861-868.
129. Keller J, Binnewies U, Rosch M, Juul Holst J, Beglinger C, Andresen V *et al.* Gastric emptying and disease activity in inflammatory bowel disease. *Eur J Clin Invest* 2015; **45**(12): 1234-1242.
130. Dawson J, Bryant MG, Bloom SR, Peters TJ. Gastrointestinal regulatory peptide storage granule abnormalities in jejunal mucosal diseases. *Gut* 1984; **25**(6): 636-643.

131. Yokoyama I, Kozuka S, Takagi H. Gastrin producing cells in the regenerating mucosa of the small intestine. *The Japanese journal of surgery* 1988; **18**(1): 54-60.
132. El-Salhy M, Danielsson A, Stenling R, Grimelius L. Colonic endocrine cells in inflammatory bowel disease. *Journal of internal medicine* 1997; **242**(5): 413-419.
133. Schmidt PT, Ljung T, Hartmann B, Hare KJ, Holst JJ, Hellstrom PM. Tissue levels and post-prandial secretion of the intestinal growth factor, glucagon-like peptide-2, in controls and inflammatory bowel disease: comparison with peptide YY. *Eur J Gastroenterol Hepatol* 2005; **17**(2): 207-212.
134. Magro F, Vieira-Coelho MA, Fraga S, Serrao MP, Veloso FT, Ribeiro T *et al.* Impaired synthesis or cellular storage of norepinephrine, dopamine, and 5-hydroxytryptamine in human inflammatory bowel disease. *Dig Dis Sci* 2002; **47**(1): 216-224.
135. El-Salhy M, Gundersen D, Hatlebakk JG, Hausken T. High densities of serotonin and peptide YY cells in the colon of patients with lymphocytic colitis. *World J Gastroenterol* 2012; **18**(42): 6070-6075.
136. Watanabe T, Kubota Y, Sawada T, Muto T. Distribution and quantification of somatostatin in inflammatory disease. *Diseases of the colon and rectum* 1992; **35**(5): 488-494.
137. Xiao Q, Boushey RP, Cino M, Drucker DJ, Brubaker PL. Circulating levels of glucagon-like peptide-2 in human subjects with inflammatory bowel disease. *American journal of physiology Regulatory, integrative and comparative physiology* 2000; **278**(4): R1057-1063.
138. Tanaka M, Saito H, Kusumi T, Fukuda S, Shimoyama T, Sasaki Y *et al.* Spatial distribution and histogenesis of colorectal Paneth cell metaplasia in idiopathic inflammatory bowel disease. *Journal of gastroenterology and hepatology* 2001; **16**(12): 1353-1359.
139. Ardesjo B, Portela-Gomes GM, Rorsman F, Gerdin E, Loof L, Grimelius L *et al.* Immunoreactivity against Goblet cells in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2008; **14**(5): 652-661.
140. Koehler JA, Baggio LL, Yusta B, Longuet C, Rowland KJ, Cao X *et al.* GLP-1R agonists promote normal and neoplastic intestinal growth through mechanisms requiring Fgf7. *Cell Metab* 2015; **21**(3): 379-391.
141. Dube PE, Forse CL, Bahrami J, Brubaker PL. The essential role of insulin-like growth factor-1 in the intestinal tropic effects of glucagon-like peptide-2 in mice. *Gastroenterology* 2006; **131**(2): 589-605.

142. Ivory CP, Wallace LE, McCafferty DM, Sigalet DL. Interleukin-10-independent anti-inflammatory actions of glucagon-like peptide 2. *Am J Physiol Gastrointest Liver Physiol* 2008; **295**(6): G1202-1210.
143. Kochar B, Long MD, Shelton E, Young L, Farraye FA, Yajnik V *et al.* Safety and Efficacy of Teduglutide (Gattex) in Patients With Crohn's Disease and Need for Parenteral Support Due to Short Bowel Syndrome-associated Intestinal Failure. *Journal of clinical gastroenterology* 2016.
144. Hirotani Y, Mikajiri K, Ikeda K, Myotoku M, Kurokawa N. Changes of the peptide YY levels in the intestinal tissue of rats with experimental colitis following oral administration of mesalazine and prednisolone. *Yakugaku zasshi : Journal of the Pharmaceutical Society of Japan* 2008; **128**(9): 1347-1353.
145. Zlatkina AR, Bezzubik KV, Peeters TL, Kuznetsova OG. [Plasma motilin and diarrhea in ulcerative colitis]. *Sovetskaia meditsina* 1990; **53**(10): 14-18.
146. Annese V, Piepoli A, Andriulli A, Napolitano G, Bisceglia L, Zelante L *et al.* Polymorphism of motilin gene in patients with Crohn's disease. *Dig Dis Sci* 1998; **43**(4): 715-719.
147. McHugh K, Castonguay TW, Collins SM, Weingarten HP. Characterization of suppression of food intake following acute colon inflammation in the rat. *The American journal of physiology* 1993; **265**(5 Pt 2): R1001-1005.
148. El-Salhy M, Hatlebakk JG. Changes in enteroendocrine and immune cells following colitis induction by TNBS in rats. *Molecular medicine reports* 2016; **14**(6): 4967-4974.
149. O'Hara JR, Lomax AE, Mawe GM, Sharkey KA. Ileitis alters neuronal and enteroendocrine signalling in guinea pig distal colon. *Gut* 2007; **56**(2): 186-194.
150. Schmidt PT, Hartmann B, Bregenholt S, Hoist JJ, Claesson MH. Deficiency of the intestinal growth factor, glucagon-like peptide 2, in the colon of SCID mice with inflammatory bowel disease induced by transplantation of CD4+ T cells. *Scand J Gastroenterol* 2000; **35**(5): 522-527.
151. Bang-Berthelsen CH, Holm TL, Pyke C, Simonsen L, Sokilde R, Pociot F *et al.* GLP-1 Induces Barrier Protective Expression in Brunner's Glands and Regulates Colonic Inflammation. *Inflamm Bowel Dis* 2016; **22**(9): 2078-2097.
152. Rubin DC, Zhang HY, Qian PQ, Lorenz RG, Hutton K, Peters MG. Altered enteroendocrine cell expression in T cell receptor alpha chain knock-out mice. *Microscopy Research and Technique* 2000; **51**(2): 112-120.

153. Qian BF, El-Salhy M, Melgar S, Hammarstrom ML, Danielsson A. Neuroendocrine changes in colon of mice with a disrupted IL-2 gene. *Clin Exp Immunol* 2000; **120**(3): 424-433.
154. Al Moutaery A. Proglumide attenuates experimental colitis in rats. *Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie* 2005; **56**(4-5): 327-332.
155. Barbier M, Attoub S, Joubert M, Bado A, Laboisie C, Cherbut C *et al.* Proinflammatory role of leptin in experimental colitis in rats benefit of cholecystokinin-B antagonist and beta3-agonist. *Life Sci* 2001; **69**(5): 567-580.
156. Oehlers SH, Flores MV, Hall CJ, Wang L, Ko DC, Crosier KE *et al.* A whole animal chemical screen approach to identify modifiers of intestinal neutrophilic inflammation. *The FEBS journal* 2016.
157. Palasz A, Krzystanek M, Worthington J, Czajkowska B, Kostro K, Wiaderkiewicz R *et al.* Nesfatin-1, a unique regulatory neuropeptide of the brain. *Neuropeptides* 2012; **46**(3): 105-112.
158. Ozturk CC, Oktay S, Yuksel M, Akakin D, Yarat A, Kasimay Cakir O. Anti-inflammatory effects of nesfatin-1 in rats with acetic acid - induced colitis and underlying mechanisms. *J Physiol Pharmacol* 2015; **66**(5): 741-750.
159. Eliakim R, Karmeli F, Okon E, Rachmilewitz D. Octreotide effectively decreases mucosal damage in experimental colitis. *Gut* 1993; **34**(2): 264-269.
160. Li X, Wang Q, Xu H, Tao L, Lu J, Cai L *et al.* Somatostatin regulates tight junction proteins expression in colitis mice. *International journal of clinical and experimental pathology* 2014; **7**(5): 2153-2162.
161. Li X, Cai L, Xu H, Geng C, Lu J, Tao L *et al.* Somatostatin regulates NHE8 protein expression via the ERK1/2 MAPK pathway in DSS-induced colitis mice. *Am J Physiol Gastrointest Liver Physiol* 2016; **311**(5): G954-g963.
162. Brun P, Mastrotto C, Beggiao E, Stefani A, Barzon L, Sturniolo GC *et al.* Neuropeptide neurotensin stimulates intestinal wound healing following chronic intestinal inflammation. *Am J Physiol Gastrointest Liver Physiol* 2005; **288**(4): G621-629.
163. Drucker DJ, Yusta B, Boushey RP, DeForest L, Brubaker PL. Human [Gly2]GLP-2 reduces the severity of colonic injury in a murine model of experimental colitis. *The American journal of physiology* 1999; **276**(1 Pt 1): G79-91.

164. Boushey RP, Yusta B, Drucker DJ. Glucagon-like peptide 2 decreases mortality and reduces the severity of indomethacin-induced murine enteritis. *The American journal of physiology* 1999; **277**(5 Pt 1): E937-947.
165. Alavi K, Schwartz MZ, Palazzo JP, Prasad R. Treatment of inflammatory bowel disease in a rodent model with the intestinal growth factor glucagon-like peptide-2. *J Pediatr Surg* 2000; **35**(6): 847-851.
166. Halaclar B, Agac Ay A, Akcan AC, Ay A, Oz B, Arslan E. Effects of glucagon-like peptide-2 on bacterial translocation in rat models of colitis. *The Turkish journal of gastroenterology : the official journal of Turkish Society of Gastroenterology* 2012; **23**(6): 691-698.
167. Anbazhagan AN, Thaqi M, Priyamvada S, Jayawardena D, Kumar A, Gujral T *et al.* GLP-1 nanomedicine alleviates gut inflammation. *Nanomedicine : nanotechnology, biology, and medicine* 2016; **13**(2): 659-665.
168. Moran GW, Leslie FC, Levison SE, McLaughlin JT. Enteroendocrine cells: Neglected players in gastrointestinal disorders? *Therapeutic Advances in Gastroenterology* 2008; **1**(1): 51-60.
169. Kiesler P, Fuss IJ, Strober W. Experimental Models of Inflammatory Bowel Diseases. *Cellular and molecular gastroenterology and hepatology* 2015; **1**(2): 154-170.
170. Matsumoto S, Okabe Y, Setoyama H, Takayama K, Ohtsuka J, Funahashi H *et al.* Inflammatory bowel disease-like enteritis and caecitis in a senescence accelerated mouse P1/Yit strain. *Gut* 1998; **43**(1): 71-78.
171. el-Salhy M. The nature and implication of intestinal endocrine cell changes in coeliac disease. *Histol Histopathol* 1998; **13**(4): 1069-1075.
172. Domschke S, Bloom SR, Adrian TE, Lux G, Bryant MG, Domschke W. Coeliac sprue: abnormalities of the hormone profile of gastroduodenal mucosa. *Scandinavian journal of gastroenterology Supplement* 1989; **167**: 86-89.
173. Papastamataki M, Papassotiriou I, Bartzeliotou A, Vazeou A, Roma E, Chrousos GP *et al.* Incretins, amylin and other gut-brain axis hormones in children with coeliac disease. *Eur J Clin Invest* 2014; **44**(1): 74-82.
174. Di Sabatino A, Giuffrida P, Vanoli A, Luinetti O, Manca R, Biancheri P *et al.* Increase in neuroendocrine cells in the duodenal mucosa of patients with refractory celiac disease. *The American journal of gastroenterology* 2014; **109**(2): 258-269.
175. Jarocka-Cyrta E, Kasacka I, Kaczmarek M. The ghrelin-positive cells number is increased in duodenum in children with celiac disease. *J Endocrinol Invest* 2010; **33**(3): 165-170.

176. Rocco A, Sarnelli G, Compare D, de Colibus P, Micheli P, Somma P *et al.* Tissue ghrelin level and gastric emptying rate in adult patients with celiac disease. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society* 2008; **20**(8): 884-890.
177. Fraquelli M, Bardella MT, Peracchi M, Cesana BM, Bianchi PA, Conte D. Gallbladder emptying and somatostatin and cholecystokinin plasma levels in celiac disease. *The American journal of gastroenterology* 1999; **94**(7): 1866-1870.
178. Caddy GR, Ardill JE, Fillmore D, Caldwell CM, McKibben BM, Gardiner KR *et al.* Plasma concentrations of glucagon-like peptide-2 in adult patients with treated and untreated coeliac disease. *Eur J Gastroenterol Hepatol* 2006; **18**(2): 195-202.
179. Le Quellec A, Kervran A, Blache P, Ciurana AJ, Bataille D. [Oxyntomodulin, a new hormonal marker of intestinal malabsorption syndromes]. *La Revue de medecine interne* 1993; **14**(10): 982.
180. Bardella MT, Fraquelli M, Peracchi M, Cesana BM, Bianchi PA, Conte D. Gastric emptying and plasma neurotensin levels in untreated celiac patients. *Scand J Gastroenterol* 2000; **35**(3): 269-273.
181. Sjolund K, Ekman R. Plasma motilin in untreated celiac disease. *Peptides* 2003; **24**(3): 483-486.
182. Minderhoud IM, Oldenburg B, Schipper ME, ter Linde JJ, Samsom M. Serotonin synthesis and uptake in symptomatic patients with Crohn's disease in remission. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2007; **5**(6): 714-720.
183. Keszthelyi D, Troost FJ, Jonkers DM, Helyes Z, Hamer HM, Ludidi S *et al.* Alterations in mucosal neuropeptides in patients with irritable bowel syndrome and ulcerative colitis in remission: a role in pain symptom generation? *European journal of pain (London, England)* 2013; **17**(9): 1299-1306.
184. Serna H, Porras M, Vergara P. Mast cell stabilizer ketotifen 4-(1-methyl-4-piperidylidene)-4H-benzo 4,5 cyclohepta 1,2-b thiophen-10(9H)-one fumarate prevents mucosal mast cell hyperplasia and intestinal dysmotility in experimental *Trichinella spiralis* inflammation in the rat. *Journal of Pharmacology and Experimental Therapeutics* 2006; **319**(3): 1104-1111.
185. Torrents D, Vergara P. In vivo changes in the intestinal reflexes and the response to CCK in the inflamed small intestine of the rat. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 2000; **279**(3): G543-G551.

186. Aerssens J, Hillsley K, Peeters PJ, De Hoogt R, Stanis A, Lin JH *et al.* Alterations in the brain-gut axis underlying visceral chemosensitivity in *Nippostrongylus brasiliensis*-infected mice. *Gastroenterology* 2007; **132**(4): 1375-1387.
187. Kalia N, Hardcastle J, Keating C, Pelegrin P, Grundy D, Grasa L *et al.* Intestinal secretory and absorptive function in *Trichinella spiralis* mouse model of postinfective gut dysfunction: role of bile acids. *Gut* 2008; **57**(1): 41-48.
188. Dlugosz A, Tornblom H, Mohammadian G, Morgan G, Veress B, Edvinsson B *et al.* Chlamydia trachomatis antigens in enteroendocrine cells and macrophages of the small bowel in patients with severe irritable bowel syndrome. *BMC gastroenterology* 2010; **10**: 19.
189. Dynes RA, Poppi DP, Barrell GK, Sykes AR. Elevation of feed intake in parasite-infected lambs by central administration of a cholecystokinin receptor antagonist. *British Journal of Nutrition* 1998; **79**(1): 47-54.
190. Yang S, Gaafar SM, Bottoms GD. Effects of Multiple Dose Infections with *Ascaris-Suum* on Blood Gastrointestinal Hormone Levels in Pigs. *Veterinary Parasitology* 1990; **37**(1): 31-44.
191. Forbes AB, Warren M, Upjohn M, Jackson B, Jones J, Charlier J *et al.* Associations between blood gastrin, ghrelin, leptin, pepsinogen and *Ostertagia ostertagi* antibody concentrations and voluntary feed intake in calves exposed to a trickle infection with *O. ostertagi*. *Vet Parasitol* 2009; **162**(3-4): 295-305.
192. Scott I, Hodgkinson SM, Lawton DEB, Khalaf S, Reynolds GW, Pomroy WE *et al.* Infection of sheep with adult and larval *Ostertagia circumcincta*: gastrin. *International Journal for Parasitology* 1998; **28**(9): 1393-1401.
193. Bosi G, Shinn AP, Giari L, Simoni E, Pironi F, Dezfuli BS. Changes in the neuromodulators of the diffuse endocrine system of the alimentary canal of farmed rainbow trout, *Oncorhynchus mykiss* (Walbaum), naturally infected with *Eubothrium crassum* (Cestoda). *J Fish Dis* 2005; **28**(12): 703-711.
194. Dezfuli BS, Pironi F, Shinn AP, Manera M, Giari L. Histopathology and ultrastructure of *Platichthys flesus* naturally infected with *Anisakis simplex* s.l. larvae (Nematoda : anisakidae). *Journal of Parasitology* 2007; **93**(6): 1416-1423.
195. Worthington JJ, Samuelson LC, Grecis RK, McLaughlin JT. Adaptive immunity alters distinct host feeding pathways during nematode induced inflammation, a novel mechanism in parasite expulsion. *PLoS Pathog* 2013; **9**(1): e1003122.
196. McDermott JR, Leslie FC, D'Amato M, Thompson DG, Grecis RK, McLaughlin JT. Immune control of food intake: enteroendocrine cells are regulated by CD4(+) T lymphocytes during small intestinal inflammation. *Gut* 2006; **55**(4): 492-497.

197. Ovington KS, Bacaresehamilton AJ, Bloom SR. Nippostrongylus-Brasiliensis - Changes in Plasma-Levels of Gastrointestinal Hormones in the Infected-Rat. *Experimental Parasitology* 1985; **60**(3): 276-284.
198. Castro GA, Copeland EM, Dudrick SJ, Johnson LR. Serum and antral gastrin levels in rats infected with intestinal parasites. *The American journal of tropical medicine and hygiene* 1976; **25**(6): 848-853.
199. De Jonge F, Van Nassauw L, De Man JG, De Winter BY, Van Meir F, Depoortere I *et al.* Effects of Schistosoma mansoni infection on somatostatin and somatostatin receptor 2A expression in mouse ileum. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society* 2003; **15**(2): 149-159.
200. Leslie FC, Thompson DG, McLaughlin JT, Varro A, Dockray GJ, Mandal BK. Plasma cholecystokinin concentrations are elevated in acute upper gastrointestinal infections. *QJM-An Int J Med* 2003; **96**(11): 870-871.
201. Roma SM, Alonso EE, Fodor ME, Nacio CD, Perez FA, Bassan ND *et al.* [Enteroendocrine cells modifications in Helicobacter pylori gastritis]. *Acta gastroenterologica Latinoamericana* 2001; **31**(5): 377-381.
202. Jeffery PL, McGuckin MA, Linden SK. Endocrine impact of Helicobacter pylori: focus on ghrelin and ghrelin o-acyltransferase. *World J Gastroenterol* 2011; **17**(10): 1249-1260.
203. Choi YJ, Kim N, Yoon H, Shin CM, Park YS, Park JH *et al.* Increase in plasma acyl ghrelin levels is associated with abatement of dyspepsia following Helicobacter pylori eradication. *J Gastroenterol* 2016; **51**(6): 548-559.
204. Khosravi Y, Bunte RM, Chiow KH, Tan TL, Wong WY, Poh QH *et al.* Helicobacter pylori and gut microbiota modulate energy homeostasis prior to inducing histopathological changes in mice. *Gut microbes* 2016; **7**(1): 48-53.
205. van Marle G, Sharkey KA, Gill MJ, Church DL. Gastrointestinal viral load and enteroendocrine cell number are associated with altered survival in HIV-1 infected individuals. *PLoS One* 2013; **8**(10): e75967.
206. Dlugosz A, Muschiol S, Zakikhany K, Assadi G, D'Amato M, Lindberg G. Human enteroendocrine cell responses to infection with Chlamydia trachomatis: a microarray study. *Gut pathogens* 2014; **6**: 24.
207. Gledhill A, Hall PA, Cruse JP, Pollock DJ. Enteroendocrine cell hyperplasia, carcinoid tumours and adenocarcinoma in long-standing ulcerative colitis. *Histopathology* 1986; **10**(5): 501-508.



208. Jezkova J, Williams JS, Pinto F, Sammut SJ, Williams GT, Gollins S *et al*. Brachyury identifies a class of enteroendocrine cells in normal human intestinal crypts and colorectal cancer. *Oncotarget* 2016; **7**(10): 11478-11486.
209. Banck MS, Kanwar R, Kulkarni AA, Boora GK, Metge F, Kipp BR *et al*. The genomic landscape of small intestine neuroendocrine tumors. *J Clin Invest* 2013; **123**(6): 2502-2508.
210. Leedham SJ. MAP(K)ing the Path to Stem Cell Quiescence and the Elusive Enteroendocrine Cell. *Cell stem cell* 2017; **20**(2): 153-154.
211. Kunz PL. Carcinoid and neuroendocrine tumors: building on success. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33**(16): 1855-1863.
212. Gulubova M, Vlaykova T. Chromogranin A-, serotonin-, synaptophysin- and vascular endothelial growth factor-positive endocrine cells and the prognosis of colorectal cancer: an immunohistochemical and ultrastructural study. *Journal of gastroenterology and hepatology* 2008; **23**(10): 1574-1585.
213. Swatek J, Chibowski D. Endocrine cells in colorectal carcinomas. Immunohistochemical study. *Polish journal of pathology : official journal of the Polish Society of Pathologists* 2000; **51**(3): 127-136.
214. Smith DM, Jr., Haggitt RC. The prevalence and prognostic significance of argyrophil cells in colorectal carcinomas. *The American journal of surgical pathology* 1984; **8**(2): 123-128.
215. Cho YB, Yang SS, Lee WY, Song SY, Kim SH, Shin HJ *et al*. The clinical significance of neuroendocrine differentiation in T3-T4 node-negative colorectal cancer. *International journal of surgical pathology* 2010; **18**(3): 201-206.
216. Kleist B, Poetsch M. Neuroendocrine differentiation: The mysterious fellow of colorectal cancer. *World J Gastroenterol* 2015; **21**(41): 11740-11747.
217. La Rosa S, Chiaravalli AM, Capella C, Uccella S, Sessa F. Immunohistochemical localization of acidic fibroblast growth factor in normal human enterochromaffin cells and related gastrointestinal tumours. *Virchows Archiv : an international journal of pathology* 1997; **430**(2): 117-124.
218. Okines A, Cunningham D. Current perspective: bevacizumab in colorectal cancer--a time for reappraisal? *European journal of cancer (Oxford, England : 1990)* 2009; **45**(14): 2452-2461.

219. Kohne CH, Lenz HJ. Chemotherapy with targeted agents for the treatment of metastatic colorectal cancer. *The oncologist* 2009; **14**(5): 478-488.
220. Ciunci CA, Perini RF, Avadhani AN, Kang HC, Sun W, Redlinger M *et al.* Phase 1 and pharmacodynamic trial of everolimus in combination with cetuximab in patients with advanced cancer. *Cancer* 2014; **120**(1): 77-85.
221. McRee AJ, Davies JM, Sanoff HG, Goldberg RM, Bernard S, Dees EC *et al.* A phase I trial of everolimus in combination with 5-FU/LV, mFOLFOX6 and mFOLFOX6 plus panitumumab in patients with refractory solid tumors. *Cancer chemotherapy and pharmacology* 2014; **74**(1): 117-123.
222. Drucker DJ. Evolving Concepts and Translational Relevance of Enteroendocrine Cell Biology. *J Clin Endocrinol Metab* 2016; **101**(3): 778-786.
223. El-Salhy M, Umezawa K. Effects of AP1 and NFkappaB inhibitors on colonic endocrine cells in rats with TNBSinduced colitis. *Molecular medicine reports* 2016; **14**(2): 1515-1522.
224. Zhang WJ, Duan JZ, Lei N, Xing H, Shao Y, Yang GB. Cellular bases for interactions between immunocytes and enteroendocrine cells in the intestinal mucosal barrier of rhesus macaques. *Cell Tissue Res* 2012; **350**(1): 135-141.
225. O'Hara JR, Skinn AC, MacNaughton WK, Sherman PM, Sharkey KA. Consequences of *Citrobacter rodentium* infection on enteroendocrine cells and the enteric nervous system in the mouse colon. *Cellular Microbiology* 2006; **8**(4): 646-660.
226. Motomura Y, Verma-Gandhu M, El-Sharkawy RT, McLaughlin J, Grecis RK, Khan WI. Colonic 5-HT and muscle responses to the same infectious agent differ in Th1 and Th2 dominant environments. *Gastroenterology* 2004; **126**(4): A216-A216.
227. Wang HQ, Steeds J, Motomura Y, Deng YK, Verma-Gandhu M, El-Sharkawy RT *et al.* CD4(+) T cell-mediated immunological control of enterochromaffin cell hyperplasia and 5-hydroxytryptamine production in enteric infection. *Gut* 2007; **56**(7): 949-957.
228. Motomura Y, Ghia JE, Wang H, Akiho H, El-Sharkawy RT, Collins M *et al.* Enterochromaffin cell and 5-hydroxytryptamine responses to the same infectious agent differ in Th1 and Th2 dominant environments. *Gut* 2008; **57**(4): 475-481.
229. Hernandez-Trejo JA, Suarez-Perez D, Gutierrez-Martinez IZ, Fernandez-Vargas OE, Serrano C, Candelario-Martinez AA *et al.* The pro-inflammatory cytokines IFNgamma/TNFalpha increase chromogranin A-positive neuroendocrine cells in the colonic epithelium. *The Biochemical journal* 2016; **473**(21): 3805-3818.

230. O'Hara JR, Sharkey KA. Proliferative capacity of enterochromaffin cells in guinea-pigs with experimental ileitis. *Cell and Tissue Research* 2007; **329**(3): 433-441.
231. Mahapatro M, Foersch S, Hefe M, He GW, Giner-Ventura E, McHedlidze T *et al.* Programming of Intestinal Epithelial Differentiation by IL-33 Derived from Pericryptal Fibroblasts in Response to Systemic Infection. *Cell reports* 2016; **15**(8): 1743-1756.
232. Tsukahara T, Watanabe K, Watanabe T, Yamagami H, Sogawa M, Tanigawa T *et al.* Tumor necrosis factor alpha decreases glucagon-like peptide-2 expression by up-regulating G-protein-coupled receptor 120 in Crohn disease. *Am J Pathol* 2015; **185**(1): 185-196.
233. Ellingsgaard H, Hauselmann I, Schuler B, Habib AM, Baggio LL, Meier DT *et al.* Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. *Nat Med* 2011; **17**(11): 1481-1489.
234. Kidd M, Gustafsson BI, Drozdov I, Modlin IM. IL1beta- and LPS-induced serotonin secretion is increased in EC cells derived from Crohn's disease. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society* 2009; **21**(4): 439-450.
235. Wang A, Huen SC, Luan HH, Yu S, Zhang C, Gallezot JD *et al.* Opposing Effects of Fasting Metabolism on Tissue Tolerance in Bacterial and Viral Inflammation. *Cell* 2016; **166**(6): 1512-1525.e1512.
236. Howitt MR, Lavoie S, Michaud M, Blum AM, Tran SV, Weinstock JV *et al.* Tuft cells, taste-chemosensory cells, orchestrate parasite type 2 immunity in the gut. *Science* 2016; **351**(6279): 1329-1333.
237. von Moltke J, Ji M, Liang HE, Locksley RM. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. *Nature* 2016; **529**(7585): 221-225.
238. Grencis RK, Worthington JJ. Tuft Cells: A New Flavor in Innate Epithelial Immunity. *Trends in parasitology* 2016; **32**(8): 583-585.
239. Selleri S, Palazzo M, Deola S, Wang E, Balsari A, Marincola FM *et al.* Induction of pro-inflammatory programs in enteroendocrine cells by the Toll-like receptor agonists flagellin and bacterial LPS. *Int Immunol* 2008; **20**(8): 961-970.
240. Friedrich M, Diegelmann J, Schaubert J, Auernhammer CJ, Brand S. Intestinal neuroendocrine cells and goblet cells are mediators of IL-17A-amplified epithelial IL-17C production in human inflammatory bowel disease. *Mucosal Immunol* 2014.
241. Hougaard DM, Larsson LI. Carboxypeptidase E in rat antropyloric mucosa: distribution in progenitor and mature endocrine cell types. *Histochem Cell Biol* 2004; **121**(1): 55-61.

242. Jeon TI, Seo YK, Osborne TF. Gut bitter taste receptor signalling induces ABCB1 through a mechanism involving CCK. *The Biochemical journal* 2011; **438**(1): 33-37.
243. Higgins GA, Kilpatrick GJ, Bunce KT, Jones BJ, Tyers MB. 5-HT<sub>3</sub> receptor antagonists injected into the area postrema inhibit cisplatin-induced emesis in the ferret. *Br J Pharmacol* 1989; **97**(1): 247-255.
244. Hagbom M, Istrate C, Engblom D, Karlsson T, Rodriguez-Diaz J, Buesa J *et al.* Rotavirus stimulates release of serotonin (5-HT) from human enterochromaffin cells and activates brain structures involved in nausea and vomiting. *PLoS Pathog* 2011; **7**(7): e1002115.
245. Sukhdeo MV, Sukhdeo SC. Gastrointestinal hormones: environmental cues for *Fasciola hepatica*? *Parasitology* 1989; **98 Pt 2**: 239-243.
246. Delgado M, Anderson P, Garcia-Salcedo JA, Caro M, Gonzalez-Rey E. Neuropeptides kill African trypanosomes by targeting intracellular compartments and inducing autophagic-like cell death. *Cell Death Differ* 2009; **16**(3): 406-416.
247. Chorny A, Anderson P, Gonzalez-Rey E, Delgado M. Ghrelin protects against experimental sepsis by inhibiting high-mobility group box 1 release and by killing bacteria. *J Immunol* 2008; **180**(12): 8369-8377.
248. Beebe K, Park D, Taghert PH, Micchelli CA. The Drosophila Prosecretory Transcription Factor dimmed Is Dynamically Regulated in Adult Enteroendocrine Cells and Protects Against Gram-Negative Infection. *G3 (Bethesda, Md)* 2015; **5**(7): 1517-1524.
249. Dong CX, Zhao W, Solomon C, Rowland KJ, Ackerley C, Robine S *et al.* The intestinal epithelial insulin-like growth factor-1 receptor links glucagon-like peptide-2 action to gut barrier function. *Endocrinology* 2014; **155**(2): 370-379.
250. Moran GW, O'Neill C, McLaughlin JT. GLP-2 enhances barrier formation and attenuates TNF $\alpha$ -induced changes in a Caco-2 cell model of the intestinal barrier. *Regul Pept* 2012; **178**(1-3): 95-101.
251. Orskov C, Hartmann B, Poulsen SS, Thulesen J, Hare KJ, Holst JJ. GLP-2 stimulates colonic growth via KGF, released by subepithelial myofibroblasts with GLP-2 receptors. *Regul Pept* 2005; **124**(1-3): 105-112.
252. Yusta B, Holland D, Koehler JA, Maziarz M, Estall JL, Higgins R *et al.* ErbB signaling is required for the proliferative actions of GLP-2 in the murine gut. *Gastroenterology* 2009; **137**(3): 986-996.

253. Genton L, Kudsk KA. Interactions between the enteric nervous system and the immune system: role of neuropeptides and nutrition. *American Journal of Surgery* 2003; **186**(3): 253-258.
254. Shajib MS, Khan WI. The role of serotonin and its receptors in activation of immune responses and inflammation. *Acta physiologica (Oxford, England)* 2015; **213**(3): 561-574.
255. Abella V, Scotece M, Conde J, Pino J, Gonzalez-Gay MA, Gomez-Reino JJ *et al.* Leptin in the interplay of inflammation, metabolism and immune system disorders. *Nature reviews Rheumatology* 2017; **13**(2): 100-109.
256. O'Mahony L, Akdis M, Akdis CA. Regulation of the immune response and inflammation by histamine and histamine receptors. *The Journal of allergy and clinical immunology* 2011; **128**(6): 1153-1162.
257. Chung Y, Kim H, Im E, Kim P, Yang H. Th 17 Cells and Nesfatin-1 are associated with Spontaneous Abortion in the CBA/j x DBA/2 Mouse Model. *Development & reproduction* 2015; **19**(4): 243-252.
258. Dixit VD, Yang H, Cooper-Jenkins A, Giri BB, Patel K, Taub DD. Reduction of T cell-derived ghrelin enhances proinflammatory cytokine expression: implications for age-associated increases in inflammation. *Blood* 2009; **113**(21): 5202-5205.
259. Xu Y, Li Z, Yin Y, Lan H, Wang J, Zhao J *et al.* Ghrelin inhibits the differentiation of T helper 17 cells through mTOR/STAT3 signaling pathway. *PLoS One* 2015; **10**(2): e0117081.
260. Souza-Moreira L, Delgado-Maroto V, Morell M, O'Valle F, Del Moral RG, Gonzalez-Rey E. Therapeutic effect of ghrelin in experimental autoimmune encephalomyelitis by inhibiting antigen-specific Th1/Th17 responses and inducing regulatory T cells. *Brain, behavior, and immunity* 2013; **30**: 54-60.
261. Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, Palaniappan R *et al.* Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. *J Clin Invest* 2004; **114**(1): 57-66.
262. Zhang JG, Liu JX, Jia XX, Geng J, Yu F, Cong B. Cholecystokinin octapeptide regulates the differentiation and effector cytokine production of CD4(+) T cells in vitro. *Int Immunopharmacol* 2014; **20**(2): 307-315.
263. Hadjiyanni I, Siminovitch KA, Danska JS, Drucker DJ. Glucagon-like peptide-1 receptor signalling selectively regulates murine lymphocyte proliferation and maintenance of peripheral regulatory T cells. *Diabetologia* 2010; **53**(4): 730-740.

264. He L, Wong CK, Cheung KK, Yau HC, Fu A, Zhao HL *et al.* Anti-inflammatory effects of exendin-4, a glucagon-like peptide-1 analog, on human peripheral lymphocytes in patients with type 2 diabetes. *Journal of diabetes investigation* 2013; **4**(4): 382-392.
265. Lee JH, Patel K, Tae HJ, Lustig A, Kim JW, Mattson MP *et al.* Ghrelin augments murine T-cell proliferation by activation of the phosphatidylinositol-3-kinase, extracellular signal-regulated kinase and protein kinase C signaling pathways. *FEBS Lett* 2014; **588**(24): 4708-4719.
266. Pamukcu O, Kumral ZN, Ercan F, Yegen BC, Ertem D. Anti-inflammatory effect of obestatin and ghrelin in dextran sulfate sodium-induced colitis in rats. *Journal of pediatric gastroenterology and nutrition* 2013; **57**(2): 211-218.
267. Hosomi S, Oshitani N, Kamata N, Sogawa M, Yamagami H, Watanabe K *et al.* Phenotypical and functional study of ghrelin and its receptor in the pathogenesis of Crohn's disease. *Inflamm Bowel Dis* 2008; **14**(9): 1205-1213.
268. Tang SC, Braunsteiner H, Wiedermann CJ. Regulation of human T lymphoblast growth by sensory neuropeptides: augmentation of cholecystokinin-induced inhibition of Molt-4 proliferation by somatostatin and vasoactive intestinal peptide in vitro. *Immunol Lett* 1992; **34**(3): 237-242.
269. Yoon WK, Kim HJ, Son HY, Jeong KS, Park SJ, Kim TH *et al.* Somatostatin down-regulates LFA-1 activation by modulating Rap1 expression in CD4+ and CD8+ T cells. *Regul Pept* 2005; **124**(1-3): 151-156.
270. Petrovic-Djergovic DM, Rakin AK, Kustrimovic NZ, Ristovski JS, Dimitrijevic LA, Mileva MV. Somatostatin modulates T cells development in adult rat thymus. *Regul Pept* 2007; **142**(3): 101-110.
271. Yusta B, Baggio LL, Koehler J, Holland D, Cao X, Pinnell LJ *et al.* GLP-1 receptor (GLP-1R) agonists modulate enteric immune responses through the intestinal intraepithelial lymphocyte (IEL) GLP-1R. *Diabetes* 2015.
272. Lynch L, Hogan AE, Duquette D, Lester C, Banks A, LeClair K *et al.* iNKT Cells Induce FGF21 for Thermogenesis and Are Required for Maximal Weight Loss in GLP1 Therapy. *Cell Metab* 2016; **24**(3): 510-519.
273. Hogan AE, Tobin AM, Ahern T, Corrigan MA, Gaoatswe G, Jackson R *et al.* Glucagon-like peptide-1 (GLP-1) and the regulation of human invariant natural killer T cells: lessons from obesity, diabetes and psoriasis. *Diabetologia* 2011; **54**(11): 2745-2754.
274. Agro A, Padol I, Stanis AM. Immunomodulatory activities of the somatostatin analogue BIM 23014c: effects on murine lymphocyte proliferation and natural killer activity. *Regul Pept* 1991; **32**(2): 129-139.

275. van Tol EA, Verspaget HW, Lamers CB. Effects of CCK-8 and CCK-33 on human natural killer cell activity: studies on intestinal lamina propria and peripheral blood mononuclear cells. *Immunopharmacology* 1993; **25**(1): 11-18.
276. Reardon C, Duncan GS, Brustle A, Brenner D, Tusche MW, Olofsson PS *et al.* Lymphocyte-derived ACh regulates local innate but not adaptive immunity. *Proc Natl Acad Sci U S A* 2013; **110**(4): 1410-1415.
277. Zhang JG, Cong B, Li QX, Chen HY, Qin J, Fu LH. Cholecystokinin octapeptide regulates lipopolysaccharide-activated B cells co-stimulatory molecule expression and cytokines production in vitro. *Immunopharmacology and immunotoxicology* 2011; **33**(1): 157-163.
278. Liu L, Tan Q, Hu B, Wu H, Wang C, Liu R *et al.* Somatostatin Improved B Cells Mature in Macaques during Intestinal Ischemia-Reperfusion. *PLoS One* 2015; **10**(7): e0133692.
279. Sung EZ, Da Silva NF, Goodyear SJ, McTernan PG, Arasaradnam RP, Nwokolo CU. Ghrelin promotes nuclear factor kappa-B activation in a human B-lymphocyte cell line. *Molecular biology reports* 2011; **38**(8): 4833-4838.
280. Saada S, Marget P, Fauchais AL, Lise MC, Chemin G, Sindou P *et al.* Differential expression of neurotensin and specific receptors, NTSR1 and NTSR2, in normal and malignant human B lymphocytes. *J Immunol* 2012; **189**(11): 5293-5303.
281. Chen J, Dong JT, Li XJ, Gu Y, Cheng ZJ, Cai YK. Glucagon-like peptide-2 protects impaired intestinal mucosal barriers in obstructive jaundice rats. *World J Gastroenterol* 2015; **21**(2): 484-490.
282. Hanna MK, Zarzaur BL, Fukatsu K, DeWitt RC, Renegar KB, Sherrell C *et al.* Individual neuropeptides regulate gut-associated lymphoid tissue integrity, intestinal immunoglobulin A levels, and respiratory antibacterial immunity. *Journal of Parenteral and Enteral Nutrition* 2000; **24**(5): 261-268.
283. Jia X, Cong B, Zhang J, Li H, Liu W, Chang H *et al.* CCK8 negatively regulates the TLR9-induced activation of human peripheral blood pDCs by targeting TRAF6 signaling. *Eur J Immunol* 2014; **44**(2): 489-499.
284. Kao JY, Pierzchala A, Rathinavelu S, Zavros Y, Tessier A, Merchant JL. Somatostatin inhibits dendritic cell responsiveness to *Helicobacter pylori*. *Regul Pept* 2006; **134**(1): 23-29.
285. da Silva L, Neves BM, Moura L, Cruz MT, Carvalho E. Neurotensin downregulates the pro-inflammatory properties of skin dendritic cells and increases epidermal growth factor expression. *Biochimica et biophysica acta* 2011; **1813**(10): 1863-1871.

286. Li Q, Han D, Cong B, Shan B, Zhang J, Chen H *et al.* Cholecystokinin octapeptide significantly suppresses collagen-induced arthritis in mice by inhibiting Th17 polarization primed by dendritic cells. *Cell Immunol* 2011; **272**(1): 53-60.
287. Dunzendorfer S, Kaser A, Meierhofer C, Tilg H, Wiedermann CJ. Cutting edge: peripheral neuropeptides attract immature and arrest mature blood-derived dendritic cells. *J Immunol* 2001; **166**(4): 2167-2172.
288. Miyamoto S, Shikata K, Miyasaka K, Okada S, Sasaki M, Kodera R *et al.* Cholecystokinin plays a novel protective role in diabetic kidney through anti-inflammatory actions on macrophage: anti-inflammatory effect of cholecystokinin. *Diabetes* 2012; **61**(4): 897-907.
289. Li S, Ni Z, Cong B, Gao W, Xu S, Wang C *et al.* CCK-8 inhibits LPS-induced IL-1 $\beta$  production in pulmonary interstitial macrophages by modulating PKA, p38, and NF- $\kappa$ B pathway. *Shock* 2007; **27**(6): 678-686.
290. De la Fuente M, Campos M, Del Rio M, Hernanz A. Inhibition of murine peritoneal macrophage functions by sulfated cholecystokinin octapeptide. *Regul Pept* 1995; **55**(1): 47-56.
291. Saia RS, Mestriner FL, Bertozi G, Cunha FQ, Carnio EC. Cholecystokinin inhibits inducible nitric oxide synthase expression by lipopolysaccharide-stimulated peritoneal macrophages. *Mediators Inflamm* 2014; **2014**: 896029.
292. Cunningham ME, Shaw-Stiffel TA, Bernstein LH, Tinghitella TJ, Claus RE, Brogan DA *et al.* Cholecystokinin-stimulated monocytes produce inflammatory cytokines and eicosanoids. *The American journal of gastroenterology* 1995; **90**(4): 621-626.
293. Liang CP, Han S, Li G, Tabas I, Tall AR. Impaired MEK signaling and SERCA expression promote ER stress and apoptosis in insulin-resistant macrophages and are reversed by exenatide treatment. *Diabetes* 2012; **61**(10): 2609-2620.
294. Hogan AE, Gaoatswe G, Lynch L, Corrigan MA, Woods C, O'Connell J *et al.* Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus. *Diabetologia* 2014; **57**(4): 781-784.
295. Xie S, Liu B, Fu S, Wang W, Yin Y, Li N *et al.* GLP-2 suppresses LPS-induced inflammation in macrophages by inhibiting ERK phosphorylation and NF- $\kappa$ B activation. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology* 2014; **34**(2): 590-602.
296. Komorowski J, Stepien H. Somatostatin (SRIF) stimulates the release of interleukin-6 (IL-6) from human peripheral blood monocytes (PBM) in vitro. *Neuropeptides* 1995; **29**(2): 77-81.



297. Peluso G, Petillo O, Melone MA, Mazzarella G, Ranieri M, Tajana GF. Modulation of cytokine production in activated human monocytes by somatostatin. *Neuropeptides* 1996; **30**(5): 443-451.
298. Arakawa M, Mita T, Azuma K, Ebato C, Goto H, Nomiyama T *et al.* Inhibition of monocyte adhesion to endothelial cells and attenuation of atherosclerotic lesion by a glucagon-like peptide-1 receptor agonist, exendin-4. *Diabetes* 2010; **59**(4): 1030-1037.
299. Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, Palaniappan R *et al.* Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. *Journal of Clinical Investigation* 2004; **114**(1): 57-66.
300. Kellokoski E, Kunnari A, Jokela M, Makela S, Kesaniemi YA, Horkko S. Ghrelin and obestatin modulate early atherogenic processes on cells: enhancement of monocyte adhesion and oxidized low-density lipoprotein binding. *Metabolism: clinical and experimental* 2009; **58**(11): 1572-1580.
301. Tanaka M, Matsuo Y, Yamakage H, Masuda S, Terada Y, Muranaka K *et al.* Differential effects of GLP-1 receptor agonist on foam cell formation in monocytes between non-obese and obese subjects. *Metabolism: clinical and experimental* 2016; **65**(2): 1-11.
302. Mitchell PD, Salter BM, Oliveria JP, El-Gammal A, Tworek D, Smith SG *et al.* Glucagon-like peptide-1 receptor expression on human eosinophils and its regulation of eosinophil activation. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2017; **47**(3): 331-338.
303. De la Fuente M, Carrasco M, Hernanz A. Modulation of human neutrophil function in vitro by gastrin. *The Journal of endocrinology* 1997; **153**(3): 475-483.
304. Goldman R, Bar-Shavit Z, Romeo D. Neurotensin modulates human neutrophil locomotion and phagocytic capability. *FEBS Lett* 1983; **159**(1-2): 63-67.
305. Carrasco M, Del Rio M, Hernanz A, De la Fuente M. Inhibition of human neutrophil functions by sulfated and nonsulfated cholecystokinin octapeptides. *Peptides* 1997; **18**(3): 415-422.
306. Adeyemi EO, Savage AP, Bloom SR, Hodgson HJ. Somatostatin inhibits neutrophil elastase release in vitro. *Peptides* 1990; **11**(4): 869-871.
307. Robbins RA, Nelson KJ, Gossman GL, Rubinstein I. Neurotensin stimulates neutrophil adherence to bronchial epithelial cells in vitro. *Life Sci* 1995; **56**(16): 1353-1359.

308. Varol C, Zvibel I, Spektor L, Mantelmacher FD, Vugman M, Thurm T *et al.* Long-acting glucose-dependent insulinotropic polypeptide ameliorates obesity-induced adipose tissue inflammation. *J Immunol* 2014; **193**(8): 4002-4009.
309. Fukamachi S, Mori T, Sakabe J, Shiraishi N, Kuroda E, Kobayashi M *et al.* Topical cholecystokinin depresses itch-associated scratching behavior in mice. *The Journal of investigative dermatology* 2011; **131**(4): 956-961.
310. Vergara P, Saavedra Y, Juanola C. Neuroendocrine control of intestinal mucosal mast cells under physiological conditions. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society* 2002; **14**(1): 35-42.
311. Saavedra Y, Vergara P. Somatostatin inhibits intestinal mucosal mast cell degranulation in normal conditions and during mast cell hyperplasia. *Regul Pept* 2003; **111**(1-3): 67-75.
312. Hirayama T, Kawabe T, Matsushima M, Nishimura Y, Kobe Y, Ota Y *et al.* Ghrelin and obestatin promote the allergic action in rat peritoneal mast cells as basic secretagogues. *Peptides* 2010; **31**(11): 2109-2113.
313. Grundemar L, Hakanson R. Neuropeptide Y, peptide YY and C-terminal fragments release histamine from rat peritoneal mast cells. *Br J Pharmacol* 1991; **104**(4): 776-778.
314. Li E, Zhao A, Shea-Donohue T, Singer SM. Mast cell-mediated changes in smooth muscle contractility during mouse giardiasis. *Infect Immun* 2007; **75**(9): 4514-4518.
315. Jenny M, Uhl C, Roche C, Duluc I, Guillermin V, Guillemot F *et al.* Neurogenin3 is differentially required for endocrine cell fate specification in the intestinal and gastric epithelium. *Embo Journal* 2002; **21**(23): 6338-6347.
316. Li HJ, Johnston B, Aiello D, Caffrey DR, Giel-Moloney M, Rindi G *et al.* Distinct cellular origins for serotonin-expressing and enterochromaffin-like cells in the gastric corpus. *Gastroenterology* 2014; **146**(3): 754-764.e753.
317. Lieb K, Fiebich BL, Busse-Grawitz M, Hull M, Berger M, Bauer J. Effects of substance P and selected other neuropeptides on the synthesis of interleukin-1 beta and interleukin-6 in human monocytes: a re-examination. *J Neuroimmunol* 1996; **67**(2): 77-81.
318. Goverse G, Stakenborg M, Matteoli G. The intestinal cholinergic anti-inflammatory pathway. *The Journal of physiology* 2016; **594**(20): 5771-5780.
319. Bohorquez DV, Samsa LA, Roholt A, Medicetty S, Chandra R, Liddle RA. An enteroendocrine cell-enteric glia connection revealed by 3D electron microscopy. *PLoS One* 2014; **9**(2): e89881.

320. Bohorquez DV, Shahid RA, Erdmann A, Kreger AM, Wang Y, Calakos N *et al.* Neuroepithelial circuit formed by innervation of sensory enteroendocrine cells. *J Clin Invest* 2015; **125**(2): 782-786.
321. Davies GA, Bryant AR, Reynolds JD, Jirik FR, Sharkey KA. Prion diseases and the gastrointestinal tract. *Canadian journal of gastroenterology = Journal canadien de gastroenterologie* 2006; **20**(1): 18-24.
322. Drummond CG, Bolock AM, Ma C, Luke CJ, Good M, Coyne CB. Enteroviruses infect human enteroids and induce antiviral signaling in a cell lineage-specific manner. *Proc Natl Acad Sci U S A* 2017; **114**(7): 1672-1677.
323. Luyer MD, Greve JWM, Hadfoune M, Jacobs JA, Dejong CH, Buurman WA. Nutritional stimulation of cholecystokinin receptors inhibits inflammation via the vagus nerve. *Journal of Experimental Medicine* 2005; **202**(8): 1023-1029.
324. Glatzle J, Wang Y, Adelson DW, Kalogeris TJ, Zittel TT, Tso P *et al.* Chylomicron components activate duodenal vagal afferents via a cholecystokinin A receptor-mediated pathway to inhibit gastric motor function in the rat. *The Journal of physiology* 2003; **550**(Pt 2): 657-664.
325. Lubbers T, de Haan JJ, Hadfoune M, Zabeau L, Tavernier J, Zhang Y *et al.* Chylomicron formation and glucagon-like peptide 1 receptor are involved in activation of the nutritional anti-inflammatory pathway. *The Journal of nutritional biochemistry* 2011; **22**(12): 1105-1111.
326. Wu R, Dong W, Ji Y, Zhou M, Marini CP, Ravikumar TS *et al.* Orexigenic hormone ghrelin attenuates local and remote organ injury after intestinal ischemia-reperfusion. *PLoS One* 2008; **3**(4): e2026.
327. Sigalet DL, Wallace LE, Holst JJ, Martin GR, Kaji T, Tanaka H *et al.* Enteric neural pathways mediate the anti-inflammatory actions of glucagon-like peptide 2. *Am J Physiol Gastrointest Liver Physiol* 2007; **293**(1): G211-221.
328. Lubbers T, Luyer MD, de Haan JJ, Hadfoune M, Buurman WA, Greve JW. Lipid-rich enteral nutrition reduces postoperative ileus in rats via activation of cholecystokinin-receptors. *Ann Surg* 2009; **249**(3): 481-487.
329. Eisner F, Martin EM, Kuper MA, Raybould HE, Glatzle J. CCK1-receptor stimulation protects against gut mediator-induced lung damage during endotoxemia. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology* 2013; **32**(6): 1878-1890.

330. Ghia JE, Blennerhassett P, Collins SM. Vagus nerve integrity and experimental colitis. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 2007; **293**(3): G560-G567.
331. Matteoli G, Gomez-Pinilla PJ, Nemethova A, Di Giovangiulio M, Cailotto C, van Bree SH *et al.* A distinct vagal anti-inflammatory pathway modulates intestinal muscularis resident macrophages independent of the spleen. *Gut* 2014; **63**(6): 938-948.
332. de Haan JJ, Hadfoune M, Lubbers T, Hodin C, Lenaerts K, Ito A *et al.* Lipid-rich enteral nutrition regulates mucosal mast cell activation via the vagal anti-inflammatory reflex. *Am J Physiol Gastrointest Liver Physiol* 2013; **305**(5): G383-391.
333. Dalli J, Colas RA, Arnardottir H, Serhan CN. Vagal Regulation of Group 3 Innate Lymphoid Cells and the Immunosolvent PCTRI Controls Infection Resolution. *Immunity* 2017; **46**(1): 92-105.
334. Matteoli G, Boeckstaens GE. The vagal innervation of the gut and immune homeostasis. *Gut* 2013; **62**(8): 1214-1222.
335. Murray MJ, Murray AB. Anorexia of infection as a mechanism of host defense. *The American journal of clinical nutrition* 1979; **32**(3): 593-596.
336. Wing EJ, Young JB. Acute starvation protects mice against *Listeria monocytogenes*. *Infect Immun* 1980; **28**(3): 771-776.
337. Feingold KR, Grunfeld C, Heuer JG, Gupta A, Cramer M, Zhang T *et al.* FGF21 is increased by inflammatory stimuli and protects leptin-deficient ob/ob mice from the toxicity of sepsis. *Endocrinology* 2012; **153**(6): 2689-2700.
338. Ayres JS, Schneider DS. The role of anorexia in resistance and tolerance to infections in *Drosophila*. *PLoS Biol* 2009; **7**(7): e1000150.
339. Castex N, Fioramonti J, Ducos de Lahitte J, Luffau G, More J, Bueno L. Brain Fos expression and intestinal motor alterations during nematode-induced inflammation in the rat. *The American journal of physiology* 1998; **274**(1 Pt 1): G210-216.
340. Gay J, More J, Bueno L, Fioramonti J. CCK-induced Fos expression in brain stem is enhanced after intestinal nematode infection in rats. *Brain Research* 2002; **942**(1-2): 124-127.
341. Procaccini C, Jirillo E, Matarese G. Leptin as an immunomodulator. *Molecular aspects of medicine* 2012; **33**(1): 35-45.

342. Lord GM, Matarese G, Howard LK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* 1998; **394**(6696): 897-901.
343. Batra A, Okur B, Glauben R, Erben U, Ihbe J, Stroh T *et al.* Leptin: A Critical Regulator of CD4(+) T-cell Polarization in Vitro and in Vivo. *Endocrinology* 2009; **151**(1): 56-62.
344. Tu T, Koski KG, Scott ME. Mechanisms underlying reduced expulsion of a murine nematode infection during protein deficiency. *Parasitology* 2008; **135**(1): 81-93.
345. McDermott JR, Bartram RE, Knight PA, Miller HRP, Garrod DR, Grencis RK. Mast cells disrupt epithelial barrier function during enteric nematode infection. *Proceedings of the National Academy of Sciences of the United States of America* 2003; **100**(13): 7761-7766.

**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 proton 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- $\alpha$
<b>Ghrelin</b>	X (NC st) <sup>31</sup>	NE	NE	NE	NC <sup>39</sup>	NE	$\uparrow$ (d, j, i) <sup>44</sup>	$\uparrow$ (d, j, i) <sup>48</sup>	NE	NC <sup>50</sup>	$\uparrow$ (d, j, i) <sup>55</sup>
<b>Histamine</b>	X (NC st) <sup>31</sup>	NE	NE	NE	NE	NE	NE	NE	NE	NC <sup>50</sup>	NE
<b>Gastrin</b>	X <sup>30</sup>	NC	NC <sup>36</sup>	$\downarrow$ <sup>36</sup>	NE	X <sup>40</sup>	$\downarrow$ (d, j, i) <sup>44</sup>	NE	NE	NC <sup>50</sup>	NE
<b>Somatostatin</b>	X <sup>30</sup>	$\downarrow$ (d, i) <sup>35</sup>	X (st) <sup>36</sup>	X (st) <sup>36</sup>	$\downarrow$ (d) <sup>39</sup>	NC <sup>40, 42</sup>	$\downarrow$ (d, j, i) <sup>44</sup>	NE	NE	$\downarrow$ (i) <sup>50</sup>	$\downarrow$ (d, j, i) <sup>55</sup>
<b>5-HT</b>	X (NC st) <sup>31</sup>	$\downarrow$ (d, i) <sup>35</sup>	$\downarrow$ (st d) <sup>36</sup>	NC <sup>36, 38</sup>	$\uparrow$ (d) <sup>39</sup>	$\uparrow$ (st) <sup>40</sup> $\downarrow$ (d) <sup>42</sup>	$\downarrow$ (d, j, i) <sup>44</sup>	NE	NE	NC <sup>50</sup>	NE
<b>CCK</b>	X <sup>30</sup>	X(d, j, i) <sup>34, 35</sup>	$\downarrow$ (d) <sup>36</sup>	X (d) <sup>36</sup>	$\downarrow$ (d) <sup>39</sup>	$\downarrow$ (d) <sup>42</sup>	$\downarrow$ (d, j, i) <sup>44</sup>	NE	$\downarrow$ (d, j) <sup>51</sup>	$\downarrow$ (i) <sup>50</sup>	NE
<b>GIP</b>	X <sup>30</sup>	$\downarrow$ (d, i) <sup>35</sup>	$\downarrow$ (d) <sup>36</sup>	$\downarrow$ (d) <sup>36</sup>	$\downarrow$ (d) <sup>39</sup>	$\downarrow$ (d) <sup>40</sup>	$\downarrow$ (d, j, i) <sup>44</sup>	NE	NE	NC <sup>50</sup>	$\downarrow$ (d, j, i) <sup>55</sup>
<b>Secretin</b>	X <sup>30</sup>	X(d, j, i) <sup>34, 35</sup>	$\downarrow$ (d) <sup>36</sup>	NC <sup>36, 38</sup>	NE	$\downarrow$ (d) <sup>40</sup>	NC <sup>44</sup>	NE	NE	NC <sup>50</sup>	NE
<b>GLP-1</b>	X <sup>30</sup>	$\downarrow$ (d, i) <sup>35</sup>	NC <sup>36</sup>	X <sup>38</sup>	$\downarrow$ (d) <sup>39</sup>	NC <sup>42</sup>	$\downarrow$ (d, j, i) <sup>44</sup>	NE	NE	$\downarrow$ (i) <sup>50</sup>	NC <sup>55</sup>
<b>GLP-2</b>	X <sup>30</sup>	$\downarrow$ (d, i) <sup>35</sup>	NC <sup>36</sup>	X <sup>38</sup>	$\downarrow$ (d) <sup>39</sup>	NE	$\downarrow$ (d, j, i) <sup>44</sup>	NE	NE	$\downarrow$ (i) <sup>50</sup>	NE
<b>PYY</b>	X <sup>30</sup>	$\downarrow$ (d, i) <sup>35</sup>	$\downarrow$ (d) <sup>36</sup>	NC <sup>36, 38</sup>	NE	$\downarrow$ (st) <sup>40</sup>	NC <sup>44</sup>	NE	$\uparrow$ (d, j) <sup>51</sup>	$\downarrow$ (i) <sup>50</sup>	NE
<b>Neurotensin</b>	X <sup>30</sup>	NC <sup>34</sup>	NE	NE	NE	$\downarrow$ (d) <sup>40</sup>	$\downarrow$ (d, j, i) <sup>44</sup>	NE	NE	$\downarrow$ (i) <sup>50</sup>	NE

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



	Chemical		Genetically prone		Immunocompromised
	TNBS	DSS	TCR $\alpha$ -/-	IL-2-/-	T-cell transfer
CgA	↓ <sup>148</sup>				
Somatostatin	↑ <sup>148</sup>	↓ <sup>160</sup>			
5-HT	↑ <sup>148, 149</sup>		↓ <sup>152</sup>	↓ <sup>153</sup>	
Neurotensin		↑ <sup>162</sup>	↓ <sup>152</sup>		
CCK			↓ <sup>152</sup>		
GLP-1					↑ <sup>151</sup>
GLP-2	↑ <sup>149</sup>				↓ <sup>150</sup>
PYY	↓ <sup>148</sup>	↓ <sup>144</sup>		↓ <sup>153</sup>	
Oxyntomodulin	↑ <sup>148</sup>				





