REVIEW

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NEUROENDOCRINE PEPTIDES IN THE PATHOGENESIS OF COLORECTAL CARCINOMA

Colorectal carcinoma (CRC) is the third most frequent neoplasm worldwide and the second leading cause of mortality. Neuroendocrine peptides such as glucagon, bombesin, somatostatin, cholecystokinin, and gastrin as well as growth factors such as platelet-derived growth factor, epidermal growth factor, insulin-like growth factor, and fibroblast growth factor have been postulated as being involved in carcinogenesis. The fact that these neuroendocrine peptides are involved in the development of CRC through the activation of growth factors that stimulate a series of molecular pathways that activate oncogenic signaling mechanisms is emphasized in this review. Peptides such as CCK1, serotonin, and bombesin have been found to be over-expressed in human tumor tissues. Meanwhile, the expression of peptides such as GLP2 has been seen mainly in murine models. The information contained in this review provides a better understanding of the role these peptides play in the pathogenesis of CRC for basic and clinical science studies.

Keywords: carcinoma, colon, neuroendocrine peptides, GLP2, bombesin, cholecystokinin.

Colorectal carcinoma (CRC) is a neoplasm that is commonly seen worldwide. In 2020, it ranked third with an incidence of 1,931,590 (10%) cases and second in mortality with 935,173 (9.4%) cases [1]. Several risk factors such as inflammatory bowel disease, a history of CRC in first-degree relatives, an increase in the body mass index, smoking, little physical activity, and eating habits have been associated with CRC [2]. About 70 to 80% of CRCs are sporadic while about 20 to 30% have an inherited component due to rare susceptibility syndromes such as Lynch syndrome and familial adenomatous

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polyposis [3]. Between 1—2% of CRCs arise as a consequence of inflammatory bowel diseases [4].

Initial molecular profiling in CRC showed a progressive multistep pattern where there is a successive accumulation of genetic and epigenetic alterations leading to carcinoma formation. This model indicated that, first, a premalignant lesion is generated which then goes on to acquire a sequence of mutations until it becomes an invasive carcinoma. Although genomic instability is the main alteration, chromosomal instability has also been frequently described [5]. The most frequent driver mutations are in the adenomatous polyposis coli (*APC*) gene, *TP53*, SMAD family member 4 (SMAD4), KRAS, NRAS, BRAF, the catalytic α subunit of PI3K (PI3KCA), all of which confer an adaptive advantage in cell growth and proliferation, angiogenesis, motility, and cell death [5]. APC is a tumor suppressor gene that triggers the formation of nonmalignant adenomas or polyps since it increases proliferation by causing hyperactivation of β-catenin transcriptional activity and blocking p53 activity. Reportedly, 15% of adenomas associated with this mutation become carcinomas over a period of approximately 10 years [5]. However, not all adenomas become carcinomas since the accumulation of specific mutations in a particular order is essential for progression to malignancy, and the time pathway depends on the specific carcinogenesis pathway [6].

Subsequent studies defined three molecular pathways associated with CRC: microsatellite instability (MSI), chromosomal instability (CIN), and CpG island methylated phenotype (CIMP) [7]. The first pathway arises from defects in the DNA mating error repair pathway and the *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes, which code for repair proteins, i.e. these genes are responsible for keeping DNA intact during replication and correcting alterations in nucleotide pairing generated by aberrant DNA cleavage [8]. The second pathway is where the majority of sporadic cases occur, and it is defined as an increase in the rate of gain or loss of chromosomes or fragments of large chromosomes with the resulting generation of aneuploidy. And the third pathway is an epigenetic phenomenon whereby hypermethylation of CpG islands in gene promoters leads to gene silencing [7].

The suggestion has also been made that neuroendocrine cells may have an effect on CRC development through neuroendocrine peptides (bombesin, glucagon, somatostatin, cholecystokinin, and gastrin) or growth factors (platelet-derived growth factor, epidermal growth factor, insulin-like growth factor, and fibroblast growth factor) [9]. The neuroendocrine peptides are defined as hormones and neurotransmitters that act as signal mediators synthesized in neuroendocrine cells and released after receiving signals from the central nervous system [10]. Historically, the term "neuroendocrine" also refers to the suggested relationship between neural/neuroectodermal structures and intestinal cells [11]. This relationship is distributed throughout all organs of the body, but mainly through the gastrointestinal tract, endocrine organs, kidneys, liver, prostate, skin, ovaries, and testes. The physiological mechanisms at the gastrointestinal level include digestive secretion, gastrointestinal motility, visceral blood flow, and tissue growth and proliferation [12]. That is why the goal of the current review is to broaden our understanding of the role the neuroendocrine peptides play and their association with the development of CRC.

Enteroendocrine Cells

The function of enteroendocrine cells (EEC) is to secrete specialized peptides that regulate appetite, participate in digestive responses such as gastrointestinal motility, and interact with the mucosal immune system [13]. These cells arise from the endoderm and come from the same pluripotent stem cells from which enterocytes, goblet cells, and Paneth cells originate [14].

Cell differentiation begins with the proliferation of pluripotent stem cells located at the base of the intestinal epithelium. These cells give rise to transitional proliferative or daughter cells, which differentiate or mature as they migrate towards the upper part of the epithelium, i.e., in both the lower and middle thirds of the epithelium, they are involved in a cellular lineage [14]. Therefore, it is the positioning of cells in the intestinal crypt that dictates cell fate [15]. When these cells contain altered DNA or mutated genes, apoptosis is not induced, and they position themselves in the intestinal crypts to continue proliferating and inducing neoplastic changes [16].

Cells that are involved in the enteroendocrine cell lineage are subdivided into enterochromaffin cells, D cells, L cells, G cells, K cells, and S cells [17].

- Enterochromaffins are the most frequent of them and are found in approximately 75% distributed throughout the gastric antrum, duodenum, jejunum, ileum, colon, and rectum. Their main secretory product is serotonin (5-HT), which is synthesized by the hydroxylation and decarboxylation of tryptophan [14]. Currently, the components that have been evaluated the most are those of the enterochromaffin cells using immunohistochemical markers such as chromogranin-A, synaptofysin-A, neuron-specific enolase, and the protein 9.5 gene product [14].
- D cells are found throughout the gastrointestinal tract but their percentage, between 3% and 5 %, is low, and their secretory product is somatostatin [14].
- L cells are produced from the duodenum to the rectum. Going from proximal to distal, their frequency rises and reaches 14% at the rectum. Their secretory products are GLP1, GLP2, cholecystokinin, and YY peptide [14].
- G cells produce gastrin, the K cells produce gastric inhibitory polypeptide [GIP], and the S cells produce secretins. These cells are very scarce at the intestinal level, and their most frequent anatomical location is the stomach [17].

GLP2 and GLP2-R

GLP2 is defined as a glucagon-like peptide 2, and GLP2-R is defined as a glucagon-like peptide 2 receptor. They come from the proglucagon superfamily of peptide hormones [18]. Proglucagon is synthesized in the L cells in the intestine, that is, where GLP2 and GLP1 are produced [19].

GLP-2R is a G protein-coupled receptor with 7 transmembrane domains. It is encoded by the GLP-2R gene located on chromosome 17p13.3 and is the main target of GLP2 in the gastrointestinal tract [18]. This receptor is expressed in the brainstem, lungs, stomach, small intestine, and colon [20]. GLP2-R at the colon level is located in enteroendocrine L cells and myofibroblasts [18].

The functions of this peptide and its receptor are to stimulate intestinal subepithelial myofibroblasts and cause the release of growth factors involved in the reepithelization and restoration of the colonic mucosa [18]. It also suppresses apoptosis of intestinal cells, increases the blood flow to mesenteric vessels, decreases gastrointestinal motility, and reduces mucosal damage caused by inflammation processes [19]. GLP2-mediated functions have been shown to require multiple factors and hormones such as insulin-like growth factor (IGF), keratinocyte growth factor, fibroblast growth factor 7, nitric oxide synthase 3, TGFB, vascular growth factor A, VIP, and ErbB [20].

Due to reepithelization and restoration processes in which GLP2 and its receptor participate indirectly in the increase in crypt length, this peptide has been associated with the development of dysplasia and colon neoplasms mainly because of the intestinal myofibroblasts that express GLP-2R, IGF1, and IGF2 [21]. The insulin growth factor (IGF1 and IGF2) has key mitogenic and metabolic functions in the growth, differentiation, and survival of numerous cells and tissue. This factor acts systemically as a hormone and locally as an autocrine/paracrine factor [22].

Polypeptide growth factors such as IGF-I and IGF2 are also responsible for regulating the different stages of CRC progression [21]. IGF action is based on a series of signaling pathways such as IGF1-R, AKT, mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (P13K), and beta-catenin. They stimulate colorectal tumor cells and tumor stroma cells that are called cancer-associated fibroblasts [23].

It has been found that IGF-I activates the beta-catenin pathway by inhibiting glycogen synthase kinase 3B (GSK-3) resulting in cytoplasmic accumulation and the nuclear translocation of beta-catenin [19]. A study using neonatal pigs demonstrated that the physiological GLP2 concentrations of 50 to 100 pM in enteral-fed animals activated intestinal epithelial cell survival and apoptosis in association with induction of protein kinase B (PKB), inhibition of GSK-3, and expression of BCL-2 while medium to high concentrations (400-1200 pM) caused increased crypt cell proliferation and protein synthesis [24]. Stimulation of GLP2 activates IGF-1, and this is connected to the PI-3K/AKT and beta-catenin signaling pathways. Therefore, it has been postulated that the coupling of IGF-1 and IGF-1R activates the AKT protein, which then phosphorylates GSK-3. This phosphorylation inhibits both GSK-3 activity and beta-catenin degradation, which, in turn, generates its translocation to the nucleus and increases cyclin D1 and C-MYC levels [18]. The above leads to alterations in the control of cell cycle checkpoints, suppression of the immune response, stimulation of angiogenesis, an increase in the secretion of cytokines as well as growth factors that allow tumor cell differentiation, growth, and tissue invasion [18].

In their literature review, Rowland and Brubaker [25] determined that IGF-1 and, to a lesser degree, IGF-2 are required for the tropic effects of GLP2 in both the small intestine and the colon. This supports the hypothesis that the stimulating effect of GLP2 on IGF1 in the intestinal subepithelial myofibroblasts depends on pathways such as PI3K/AKT. GLP2 has also been reported to be associated with the disruption of TGF-β signaling in the colon thereby causing tumor growth through epithelial cell transformation and/or tumor-stromal interactions [26]. Studies in cell culture have also been described where exogenous GLP2 treatment has been shown to increase IGF-1 ligand mRNA transcription levels but not ErbB1/ErbB2. This suggests that the ErbB system is not as central to tumor growth as the IGF-1 pathway [25].

Thulesen et al. [27], in turn, saw neoplasms in the colon in a case-control study with rodents when they were treated with the carcinogen methylating 1,2-dimentylhydralazine (DMH) and later with a GLP2 analog (Gly2-GLP2). In this study, DMH was administered to mice and, subsequently, one group of mice was treated with a GLP2 analog (3-33), another group with a Gly2-GLP2 analog, and the other was not treated. Treatment days and intervals of treatment-free months varied among the groups. In the end, all the groups of mice presented non-malignant tubular adenomas. Colon neoplasms were present in the group with a Gly2-GLP2 treatment, and a greater increase in cell proliferation was detected in both the small intestine and the colon. At the same time, long-term treatment with GLP2 (3-33) only induced increased small intestinal proliferation.

In another study by Lakoubov et al. [28], GLP2-induced intestinal growth and the effects of GLP2 in combination with a carcinogenic substance were evaluated. In order to evaluate the proliferation of bowel cells, different groups of mice were given: a GLP2 analog (GLP2 (1-33)) for one group, GLP2 antagonists (GLP2 (3-33)) for another, and untreated mice were evaluated as a control group. To identify the effects of GLP2 in combination with a carcinogen, they used azoxymethane (AOM) and divided them into groups. One group received AOM (a carcinogen) and a GLP2 analog, another group received AOM

and a GLP2 antagonist, and the other was the control group that received AOM and PBS. With respect to the evaluation of intestinal growth, the results showed that mice treated with the GLP2 analog had an increase in intestinal weight and an increase in cell proliferation as evaluated by Ki67 compared to those treated with the antagonist. The GLP2 group (3-33) also had a weight decrease compared to the control group. There was no difference between the groups in the absolute weight of the colon. As for the results of GLP2 in combination with a carcinogenic substance, the presence of aberrant crypts was detected in the group of mice treated with AOM and PBS. There was also a marked increase in the development of dysplasia in the group given AOM and the GLP2 analog, and some mice developed adenocarcinomas. The number of aberrant crypts was very low in the group treated with AOM and the GLP2 antagonist compared to the control group and the group treated with the GLP2 agonist. In another study by Trivedy et al. [29], inflammation was induced in the colonic mucosa of a group of mice by feeding them a 2-amino-1-methyl-6-phenylimidazone pyridic carcinogen plus a fat-rich diet in order to induce mild intestinal inflammation. Another group of mice was fed dextran sodium sulfate (DSS) to induce chronic colitis, and they were also given the carcinogenic substance AOM. Subsequently, the groups were subdivided further by administering GLP2 analog (hGly2-GLP2), GLP2 antagonist (hGLP2), or nothing. In models of mice fed the GLP2 agonist, there was an increase in the number of aberrant crypt foci. In addition, mice treated with DSS and OMA had a 56% incidence of high-grade dysplasia compared to 64% of those treated with the GLP2 analog, and the incidence was 46% for the group receiving the GLP2 antagonist. The studies presented above support the hypothesis that GLP2 is involved in colon carcinogenesis.

In studies with humans, such as the one done by Körner et al. [30], in which GLP-2R expression in tumor tissues was examined using *in vitro* autoradiography (a method that allows the binding site of the protein of interest to be seen in tissue by radioligands), an increased expression of GLP2 receptors was found mainly in GIST while there was little to no expression at all in other tumors. In the same study, the GLP-2R gene mRNA expression was confirmed in 15 of 22 GIST, 4 of 4 ileal carcinomas, and 2 of 7 colon adenocarcinomas using RT-PCR. Compared to other methods for GLP2 receptor identification such as immunohistochemistry and expression using RT-PCR, receptor autoradiography is of limited sensitivity in tissues where there are single cells or groups of very small cells expressing a small number of receptors [30]. In another study by Bengi et al. [31], tissue samples from 30 patients with an endoscopic and pathological diagnosis of colon cancer and from 20 patients with a diagnosis of colon polyps were evaluated and compared to normal appearing mucosa from the same patients (control). Histological and immunohistochemical studies with GLP-2R antibodies were done on the samples. The results showed that all control and case samples had GLP-2R expression in enteroendocrine cells. In the adenoma group, none of the cases showed GLP-2R staining and in the colon adenocarcinoma group, GLP-2R only showed expression in 6 patients (20%) and the other 24 patients (80%) were negative for GLP-2R based on immunohistochemistry.

In a systematic review that analyzed teduglutide (a synthetic GLP2 analog resistant to GLy2-GLP2 degradation), currently approved as a drug for patients with short bowel syndrome [20], two studies were found dealing with the drug. The first study had 83 patients with 24 weeks of treatment using teduglutide 0.5 mg/kg/day, another group received teduglutide 0.10 mg/kg/day, and the other a placebo. Only 77 patients underwent colonoscopy with biopsies of the colon and small intestine, which showed no evidence of dysplasia [32]. In another study of

65 patients, there was only one case of metastatic adenocarcinoma after 24 to 30 months of treatment with teduglutide 0.05 mg/kg/day. It happened in the liver from an occulted cancer 11 months after the treatment. This established the fact that patients without pre-existing cancer did not develop neoplasms [33]. The conclusion of the systematic review was that treatment with teduglutide does not increase the risk of intestinal neoplasms in patients with no pre-existing cancer. However, the treatment is contraindicated for patients with previous gastrointestinal and hepatopancreatic-biliary cancer, and a colonoscopy with removal of the adenomas is recommended before and during treatment with this drug [34].

GLP1 and GLP-1R

They are defined as a glucagon-like peptide 1 (GLP1) and a glucagon-like peptide 1 receptor (GLP-1R). They come from the proglucagon superfamily of peptide hormones.

GLP1 is a peptide hormone produced in the gastrointestinal tract by endocrine L cells. Luminal nutrients trigger GLP1 secretion immediately (within 15 to 30 min in both humans and rodents) after food ingestion [35]. This peptide is multifaceted in that it stimulates insulin secretion from pancreatic β-cells, which causes glucose absorbed through the intestinal epithelium to be taken up into peripheral tissues through the insulin action [35]. This function is termed the incretin effect. It predominates in the small intestine rather than in the colon since GLP1 expression in colon cells is hypothesized to function as an energy sensor to slow intestinal transit and allow more time for nutrient collection in the small intestine [36]. Another GLP1 function is the proliferative and protective action on pancreatic β-cells, which increases satiety, delays gastric emptying, increases natriuresis and diuresis, has cardioprotective and neuroprotective effects, and reduce inflammation and apoptosis [35, 37].

The GLP-1R receptor is located in the pancreas and is widely expressed in pancreatic β-cells. It is also found in the stomach, intestine, colon, kidneys, lungs, cardiac myocytes, telencephalon, and medulla [37]. This receptor at the pancreatic level has cross-reactivity with glucagon, which explains the incretin effect [37]. The association of GLP1 with colon carcinoma is controversial, but there is evidence that both obesity and type 2 diabetes increase the incidence rates of some cancers such as colon cancer [38]. Type 2 diabetes, in turn, is due to GLP-1R activation, which stimulates insulin secretion in pancreatic β-cells, and these high insulin levels activate IGF-associated pathways, which promote carcinogenesis [39].

Koehler et al. [38] carried out a study on human and murine cell lines, where the murine colon cancer cell line CT26 was found to express endogenous functional GLP1 receptors, but adenocarcinoma cell lines (DLD-1, SW480, CaCo2 or HT29) and carcinoma cell line T84 did not express them. Since DPP4 inhibitors inhibit the cleavage of both GLP1 and GLP2, they may create an additional intestinal signaling network that could increase the risk of intestinal tumors [39].

YY Peptide (PYY)

The YY peptide is defined as the tyrosine-tyrosine peptide, which is part of the pancreatic peptide family, consists of 36 amino acid residues, and acts as a hormone, neurotransmitter and/or neuromodulator [40, 41]. It is found in the enteroendocrine L cells located in the ileum, colon, and rectum [40]. Its content is the highest in the rectum, followed by the ileum, and finally the colon [41]. Recent studies have shown that this peptide is also secreted by neurons within the spinal cord and by pancreatic alpha, PP, and delta cells [42].

The YY peptide is involved in the stimulation of the immune and antitrophic function of the pancreas and at the same time it inhibits the release of cytokines and amylase. It has also been associated with proliferative and protective ef-

fects on pancreatic B cells [43] and regulation of intestinal motility, secretion, and absorption as well as visceral sensitivity by modulating serotonin release [40].

This peptide has a neuropod mode of action and a synapse-like function: it mediates rather specific cell-to-cell signaling than paracrine mechanisms [43]. Its receptors are Y1, Y2, and Y5. However, it is Y1 that has been shown to participate in the regulation of colonic epithelial growth [42]. This substance has been found in some gastrointestinal neuroendocrine tumors and in peptide YY-producing tumors [43].

Zygulska et al. [43] evaluated plasma levels of peptide YY, cholecystokinin, and other peptides in 80 patients with gastrointestinal malignancies (20 with gastric cancer and 60 with CRC) as compared to a control group of 30 healthy patients. Low levels of PPY were found in patients with colorectal neoplasms compared to controls (54.6 ng/ml *vs.* 79.3 ng/ml). These results support the hypothesis that PPY inhibits tumor cell proliferation in neoplasms of the colonic epithelium and prevents malnutrition in these patients.

Cholecystokinin (CCK)

CCK is a member of the regulatory peptide family that shares the same sequence as gastrin with a C-terminal pentapeptide amide [44]. This peptide is synthesized in the brain, cardiomyocytes, pancreas, and gastrointestinal tract [45]. In the small intestine, the CCK peptides are synthesized in endocrine I cells [44]. These cells are most dense in the duodenum and proximal jejunum followed by the ileum and colon [46]. The function of this peptide is to stimulate pancreatic enzyme secretion and gallbladder contraction [43]. It also participates in the maintenance of gastric mucosa, pancreatic islet integrity, and neurogenesis [47].

The CKK receptors are CCKR1 and CCKR2 both of which are G protein-coupled. CCKR1 is involved in hepatic bile secretion, gallbladder contraction, sphincter of Oddi relaxation, pancreatic enzyme secretion and growth, inhibition of gastric acid secretion through somatostatin cells, and inhibition of gastric emptying. It is also involved in satiety through vagal afferent fibers and intestinal motility [45]. CCKR2 is expressed in the brain, stomach, and the pancreatic islets [45].

Regarding the relationship between this peptide and CRCs, it is said that there have been no studies on humans to date where it has been expressed as a peptide [45]. In contrast, both CCKR1 and CCKR2 receptors have been shown to be expressed by tumor cells through autocrine and paracrine processes [43]. It has been postulated that gastrin (GR) stimulates the focal adhesion kinase (FAK) pathway, which leads to the positive regulation of CCKR2 and, consequently, the progression of colonic malignancies [43]. That is, CCKR2/GR exerts a trophic effect on the normal intestinal mucosa and may also act in an autocrine, endocrine, or paracrine mode to regulate the growth of some cancers of the gastrointestinal tract such as colon carcinomas [48]. In addition, CCKR2 stimulation has also been associated with the induction of cyclooxygenase-2 and prostaglandin E2 production, which also favors oncogenic pathways [49].

Huang et al. [50] evaluated 97 CRC samples and detected the presence of CCKR1 in 91 samples (92.9%) and CCKR2 in 82 samples (83.7%). Chang et al. [51] found that most of the cell lines of CRC patients presented membrane staining due to CCKR2 immunohistochemistry, and 8/19 (42.1%) of the mucinous adenocarcinomas were positive for CCKR2. Another study by Chang et al. [52] showed that CCKR2 is a target of mucinous adenocarcinomas of the colon since more than 50% of patients with this histological type of neoplasm expressed CCKR2.

Serotonin(5-HT)

5-HT is a monoamine neurotransmitter. Its chemical name is 5-hydroxytryptamine. It is produced by hydroxylation and decarboxylation of

tryptophan. The largest concentration is found in enterochromaffin cells of the gastrointestinal tract with small amounts found in the central nervous system and platelets [53].

5-HT is one of the most potent neuronal, peripheral, and gastrointestinal signaling molecules. It acts as a paracrine, endocrine, or exocrine messenger for a variety of cell types including enteroendocrine cells [54]. It requires a local mediator to mediate motility in the gastrointestinal tract and to function as a vasoactive agent in the blood [55]. The paracrine effects of 5-HT within the gastrointestinal tract are determined by the distribution and location of several of its receptors. 5-HT1, 5-HT2, 5-HT3, 5-HT4, and 5-HT7 have been identified at the level of the epithelium in enteroendocrine cells and in the smooth muscle of the intestine [56].

With respect to this peptide and CRC, there are studies where serotonin, *in vitro*, exhibits a growth-stimulating effect in several types of human tumor cell lines such as prostate, bladder, lung, colorectal, biliary tract, breast, and liver carcinomas, gliomas, and carcinoid tumors [55]. Recent findings confirmed that the 5-HT synthesis pathway promotes colitis and cell proliferation in tumors related to colonic inflammations, but may also act protectively against early carcinogenic events in the colon. However, the same process supports the progression of CRC when there is DNA damage at the enterocyte level [54]. Colon adenocarcinoma samples overexpressed 5-HTR compared to normal colon tissue, specifically 5-HT1D, 5-HTR3C, and 5-HTR4 receptors [56].

In conclusion, elevated serotonin levels activate lymphocytes that lead to the release of cytokines mimicking inflammatory bowel disease in humans. Thus, a serotonin-mediated proinflammatory microenvironment may be responsible for colorectal tumorigenesis with 5-HT being responsible for cell proliferation, angiogenesis, invasion, migration, and metastasis [57]. High plasma serotonin levels are associated with lymph node metastasis, disease recurrence, increased risk of mortality, and decreased recurrence-free time [58]. CRC is also associated with higher plasma levels of serotonin.

Somatostatin (SST)

SST is a cyclic polypeptide of the paracrine hormone family, which has inhibitory and regulatory functions [59]. It is produced by endocrine cells and neural cells of the gastrointestinal tract and is the most important natural antiproliferative hormone [60]. SST is stored in the digestive tract, mainly in the intestine and pancreas. It is responsible for inhibiting the secretion of growth hormone, prolactin, thyrotropin, CKK, gastric inhibitory peptide, gastrin, neurotensin, motilin, secretin, glucagon, insulin, and pancreatic polypeptide. It also inhibits amylase and the absorption of glucose, fats, and amino acids [59]. Other functions include suppressing intestinal motility, and gallbladder contraction, inhibiting intestinal exocrine secretion and decreasing epithelial proliferation. At the intestinal level, it participates in stimulating the secretion of proinflammatory cytokines thereby causing this hormone to be associated with inflammatory bowel disease [61, 62].

The presence of SST has been identified in a variety of tumors, mainly neuroendocrine tumors (pituitary tumors, medullary thyroid carcinomas, paraganglioma, small cell lung cancer, pancreatic tumors, endocrine tumors, and carcinoids) but also in meningiomas, astrocytomas, neuroblastomas, and some breast cancers [63]. This has not been clearly described in CRC, but there are studies in which SST through octreotide analogs stimulates the expression of MUC2 in enterocytes, thus increasing mucus secretion by a direct effect on goblet cells that could increase the thickness of the intestinal wall [64].

Leiszter et al. [62] analyzed 81 biopsy samples from 41 healthy patients and 34 patients

with CRC and found that the proportion of SST-producing cells is less than 1% in histologically normal epithelium and is significantly reduced in tumor samples. This suggests that low or absent SST contributes to accelerated and dysregulated cell proliferation in CRC. A study by Kasprzak [65] based on immunohistochemical assays showed that in the normal colonic mucosa, SST labeling exists in enteroendocrine cells that are scattered and individualized among epithelial cells. At the same time, CRC tissues showed a granular cytoplasmic pattern marking in the apical portion of all tumor cells. Therefore, it is inconclusive for the use of SST as a CRC marker [65].

Bombesin (BBS)

BBS is a 14 amino acid neurohormone polypeptide, initially derived from amphibians with a wide range of physiological effects in the brain, lungs, and gastrointestinal tract [66]. It has three types of G protein-coupled receptors: 1) neuromedin B receptors (NMBR) or bombesin 1 receptors, 2) gastrin-releasing peptide receptor (GRPR), also known as bombesin

Table 1. **Neuroendocrine peptides and their tumorigenic action in colorectal carcinoma**

Peptides	Theories on tumor mechanisms of action
GLP2	Stimulates IGF, which, in turn, activates different signaling pathways such as IGF1R, AKT, MAPK, and β-catenin. β-catenin translocates into the nucleus and increases cyclin D1 and C-MYC levels. This reduces protein checkpoints in the cell cycle, encourages the suppression of the immune response, stimulates angiogenesis, and secretes cytokines and growth factors that allow tumor cells differentiation, growth, and tissue invasion
GLP1	This is due to the GLP-1R activation, which stimulates insulin secretion in pancreatic β-cells, and the high insulin levels activate IGF-associated pathways, which inhibit apoptosis and encourage carcinogenesis
Peptide YY	Its Y1 receptor is involved in regulating the growth of the colonic epithelium
Cholecystokinin	This is due to the gastrin stimulation of the focal adhesion kinase pathway, which leads to the upregulation of CCKR2 and, consequently, the progression of colon malignancies. CCKR2 stimulation is also associated with induction of cyclooxygenase-2 and prostaglandin E2 production favoring oncogenic pathways as well
Serotonin	Chemical exposure stimulates two pathways at the colonic level: a normal repair pathway where tryptophan hydrolase (TPH-2) enteric neurons stimulate serotonin and serotonin binds to its receptor HTR4. The other pathway is that of colitis where neuroendocrine cells activate tryptophan hydrolase (TPH-1), which activates serotonin and binds to its receptor HTR7. The last mechanism is the cause of colorectal tumorigenesis associated with colitis since elevated serotonin in serum plus an intense inflammatory response generates DNA damage and leads to tumor development
Somatostatin	This has not been clearly described in colorectal carcinomas, but there are studies where somatostatin stimulates the expression of MUC2 in colonocytes through octreotide analogs, thus increasing mucus secretion by a direct effect on goblet cells, which may increase the thickness of the intestinal wall
Bombesin	The activation of GRPR by bombesin activates NK lymphocytes and regulates the heterochromatin protein 1Hsβ thus stimulating the growth of colorectal cancer cells. Likewise, stimulation with bombesin, GRP, neuromedin B, and neuromedin C contributes to the proliferation of HT-29 cells, which are carcinogenic as well

2 receptor, and 3) orphan receptor or bombesin receptor 3 [66].

BBS has multiple functions such as regulating the release of gastrointestinal hormones and gastrointestinal motility. GRPR serves further physiological functions such as stimulating gastric acid secretion, stimulating the release of hormones such as gastrin, somatostatin, CCK, and exocrine secretion of the pancreas. It also promotes smooth muscle contraction, repairs wounds, and contributes to the growth of intestinal villi [67].

There are reviews evaluating the role of BBS in tumor growth, cell proliferation, and inflammation. Normal human intestinal epithelium does not express endogenous GRPR or other bombesin receptor subtypes. However, a subset of human CRCs expresses GRPR and its GRP ligand, i.e., there is a hypothesis that the activation of GRPR by BBS stimulates the growth of colorectal cancer cells [67].

In RCC, GRPR has been observed in 76 to 100% and NMBR — in 63%. CRC tumor cells express GRP/GRPR to a large extent. This expression is said to be associated with improved survival, late recurrence, and less metastasis in lymph nodes. In addition, the expression of this receptor and its polypeptide is found mainly in well-differentiated tumors that are associated with enhanced binding to the extracellular matrix, which enhances cancer cytolysis by activation of NK lymphocytes and upregulates heterochromatin 1Hsβ protein. Therefore, it acts primarily as a morphogen rather than as a growth factor [68].

Cassano et al. [69] found that HT-29 cells proliferate after BBS, GRP, neuromedin B, and neuromedin C stimulation. GRPR and GRP ligand mRNA were found in these cells. In addition, BBS inhibitors also stimulated the proliferation of HT-29 cells. Therefore, BBS induced their proliferation due to interaction with GRPR. A study by Liu et al. [70] shows the existence of a novel GB-6 peptide that targets GRPR and is a promising candidate for clinical translation of molecular imaging for CRC.

Conclusion

Various studies have found that neuroendocrine peptides are involved in the development of CRC through the activation of growth factors, which, in turn, stimulates signaling mechanisms that lead to tumor development. Their supposed mechanisms are summarized in the Table. Peptides such as CCK1, serotonin, and bombesin have been found to be expressed in human tumor tissues. Meanwhile, the expression of peptides such as GLP2 has been seen mainly in murine models. Therefore, further experimental studies are needed to determine the molecular pathways involving these peptides and possible therapeutic targets.

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Disclosure of Interest

The authors have no conflicts of interest to declare.

Data Availability Statement

All data and material relevant to the study are available from the authors upon request.

Author Contributions

Conceptualization: AR, GM, LD, RPM; methodology: AR, GM, LD, RPM; validation: AR, GM, LD, RPM; investigation: AR, GM, LD, RPM; writing — original draft preparation: AR, GM, LD, RPM; writing — review and editing: AR, GM, LD, RPM.

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НЕЙРОЕНДОКРИННІ ПЕПТИДИ В ПАТОГЕНЕЗІ КОЛОРЕКТАЛЬНОГО РАКУ

Колоректальний рак (КРР) є третім за частотою новоутворенням у світі та другою основною причиною смертності. Вважається, що нейроендокринні пептиди, такі як глюкагон, бомбезин, соматостатин, холецистокінін і гастрин, а також фактори росту, такі як тромбоцитарний фактор росту, епідермальний фактор росту, інсуліноподібний фактор росту та фактор росту фібробластів, беруть участь у канцерогенезі. У цьому огляді підкреслюється той факт, що зазначені нейроендокринні пептиди беруть участь у розвитку КРР через активацію факторів росту, які стимулюють низку молекулярних шляхів, що активують онкогенні сигнальні механізми. Встановлено високі рівні експресії таких пептидів, як ССК1, серотонін і бомбезин у тканинах новоутворень. Експресію GLP2 визначали переважно на мишачих моделях. Інформація, висвітлена в цьому огляді, забезпечує краще розуміння ролі цих пептидів у патогенезі КРР, що актуально для сучасних фундаментальних і клінічних наукових досліджень.

Ключові слова: карцинома, товста кишка, нейроендокринні пептиди, GLP2, бомбезин, холецистокінін.