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Epigenetic control of cancer by neuropeptides (Review)

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Abstract. Neuropeptides act as neurohormones, neurotransmitters and/or neuromodulators. Neuropeptides maintain physiological homeostasis and are paramount in molecular mechanisms of disease progression and regulation, including in cancer. Neuropeptides, by their definition, originate and are secreted from the neuronal cells, they are able to signal to neighboring cells or are released into the blood flow, if they act as neurohormones. The majority of neuropeptides exert their functions through G protein-coupled receptors, with certain exceptions. Although previous studies indicate that neuropeptides function in supporting proliferation of malignant cells in many types of solid tumor, the antitumorigenic action of the neuropeptides and their receptors, for example, in gastric cancers and chondrosarcoma, were also reported. It is known that epigenetically modified chromatin regulates molecular mechanisms involved in gene expression and malignant progression. The epigenetic modifications are genetically heritable, although they do not cause changes in DNA sequence. DNA methylation, histone modifications and miRNA expression are subject to those modifications. While there is substantial data on epigenetic regulation of neuropeptides, the epigenetic control of cancer by neuropeptides is considered to be uncharted territory. The aim of the current review is to describe the involvement of neuropeptides in the epigenetic machinery of cancer based on data obtained from our laboratory and from other authors.

Contents

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1. Introduction

Neuropeptides are an important class of messenger molecules that carry information between neurons; they can act as neurohormones, neurotransmitters, and/or neuromodulators, maintain physiological homeostasis and are involved in regulation of malignant disease progression. Notably, peptide hormones and neuropeptides are synthesized by the same route and enzymes from common precursor cleavage, resulting in the production of bioactive peptides. The majority of neuropeptides exert their functions through G protein-coupled receptors, with certain exceptions (1). The predominant notion was that neuropeptides possess protumorigenic functions demonstrated via paracrine and autocrine loops of regulation, which were reported in different types of solid tumors (2-6); however, antitumorigenic action of the neuropeptides and their receptors has been reported for gastric cancers (6), chondrosarcoma (7-9) and triple negative breast cancer (10). The epigenetic modifications are crucial in regulating gene expression and control the progression of cancer. The epigenetic modifications are genetically heritable, but do not cause changes in DNA sequence. DNA methylation, histone modifications and miRNA expression are subject to those modifications. While there is substantial data regarding epigenetic regulation of neuropeptides (11), the epigenetic control of cancer by neuropeptides is considered to be a particularly promising discipline and requires close attention and further development.

The current review aims to present the involvement of certain neuropeptides in the epigenetic machinery of cancer (12-19) based upon data obtained from our laboratory and from other authors.

2. Neuropeptides involved in epigenetic control of cancer

Proline-rich polypeptide-1 (PRP-1; galarmin). PRP-1 is a cytokine hypothalamic neuropeptide produced by neurosecretory granules of neurohypophysis, in *Nucleus supraopticus* and *Nucleus paraventricularis*, the same neurons from which vasopressin and oxytocin originate. PRP-1 is derived from its precursor, neurophysin-vasopressin-associated glycoprotein precursor (20). In addition, large quantities of PRP-1 were detected in bone marrow granulocytes (21). The antimicrobial, antitumorigenic and antineurodegenerative properties for this immunomodulatory cytokine were previously reported (22) and the quantification of hypothalamic PRP-1 in the blood was recently documented (23). Furthermore, our prevous studies described that PRP-1, mammalian target of rapamycin

complex 1 inhibitor, exerts antiproliferative cytostatic effects in chondrosarcoma (7-9,24) and breast cancer cells (10).

Chondrosarcoma is a type of cartilage cancer, which does not respond to chemotherapy or radiation, and eventually metastasizes rendering surgery as the only treatment option; thus, the search for novel therapeutic strategies is considered to be relevant and urgent (25).

Although PRP-1 is a neuropeptide, our preliminary results (not yet published) did not indicate that PRP-1 exerts its actions via the G protein-coupled receptor. Cytostatic PRP-1 manifests its antiproliferative effect via cell cycle regulation in cancer (10), as well as by its unique ability to upregulate tumor suppressor proteins (26) and micro RNA (miR) tumor suppressors (miR20a, miR125b and miR192) while causing downregulation of onco-miRs (miR509-3p, miR589, miR490-3p and miR 550) in the human chondrosarcoma cell line, JJ012 (27), demonstrating the possibility for future therapeutic interventions.

PRP-1 epigenetically regulates embryonic stem cell marker, miRNA 302c (miR302C) and its targets. miR302C, a component of the miR302 367 cluster, was significantly downregulated by PRP-1. Notably, this cluster is not expressed in adult mesenchymal stem cells and normal tissue (28), although it is particularly characteristic, with a significant role in tumors and human embryonic stem cells, where it regulates renewal of stem cells and the process of differentiation (29). This may explain the strong tumor growth inhibitory role of PRP-1 in certain tumors, particularly in chondrosarcomas and multipotent adult stem cells (marrow-isolated adult multilineage inducible cells) of embryonic primitive type (28,30). Our collaborative study of glioblastoma demonstrated that PRP-1 did not exert inhibitory action on the growth of this type of tumor, as in glioblastoma this cluster suppresses stemness (28,29). This fact served as the basis for the paradigm that the antiproliferative action of PRP-1 is defined by the presence of miR302C and its stemness-inducing potential in particular types of tumor.

The stemness markers, targets of the miR302C polycomb protein, BMI-1, NANOG (28) and c-Myc (8,24,28), were markedly downregulated by PRP-1 (28). Interestingly, PRP-1 demonstrated the inhibition of giant cell tumors of the bone and, conversely, supported the growth of human normal bone marrow stromal cells (31). Epigenetic regulation of miR302C expression (32) is defined by positive regulatory activity of JMJD2, H3K9me2 demethylase and NANOG in the promoter regions (28). Our previous data indicated that PRP-1 inhibited H3K9 demethylase activity (JMJD1 and JMJD2) leading to the conclusion that miR302C activity suppression by this neuropeptide is epigenetically regulated (28).

Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating polypeptide (PACAP). VIP is produced by various cells, however, its primary location is within neurons; this peptide is expressed in the peripheral and central nervous systems, as well as in certain tumors (3,33-36). In a previous study, VIP receptor antagonists facilitated chemotherapeutic agents to cause apoptosis in certain cancer cell lines (33); VIP is cell context-dependent and is known to contribute to leukemogenesis (34). There is reported similarity of VIP with pituitary adenylate cyclase, which belongs to the secretin family. PACAP binds to the G protein-coupled receptor and belongs to the secretin glucagon VIP peptide group (35).

VIP shares 68% homology with PACAP, and is considered to be a rational target against inflammatory disease (35). Notable data on transcriptional modulation of genes involved in production of inflammatory products, such as inducible nitric oxide synthases, revealed the inhibitory effect of VIP on gene transcription, which may possess marked therapeutic potential preventing production of inflammatory molecules (37).

PACAP is significantly involved in regulating the immune response, and is found in neurons and the immune system. PACAP is comprised of three known receptors, PAC-1, VPAC1 (3) and VPAC2, and is involved in signal transduction pathways and, depending on the tumor type, either directly suppresses or promotes tumor growth (36). In cervical cancer, PACAP is considered as a methylation biomarker for cervical cancer early detection (38,39). In a previous study, a low expression of PACAP was demonstrated in cervical cancer, which was due to hypermethylation in its promoter and was correlated with tumor development. Treatment with 5'-Aza-2', a methyltransferase inhibitor, or with histone deacetylase inhibitor (HDACi), trichostatin reactivated PACAP gene expression (38). PACAP in humans is encoded by adenylate cyclase-activating polypeptide 1 (ADCYAP1). Another study reported that the methylation of ADCYAP1 may be highly associated with the development of cervical cancer and that gene promoter hypermethylation suppressed gene expression (40).

Gastrin. Gastrin-releasing peptide (GRP) is a human neuropeptide that controls gastrin release and regulates gastric acid production. Gastrin is released from G cells as a result of vagus nerve postganglionic fiber innervation of stomach G cells. GRP is engaged in stress regulation of the biological circadian rhythm sending signals to the hypothalamic suprachiasmatic nuclei (41,42). GRP and neuromedin C are important in various types of cancer (42). It was established that pro-GRP is produced in small lung cancer cells and is considered to be a biomarker (43). The peptide is utilized for therapeutic purposes, measuring the efficacy of chemo- and radiation therapies. In normal conditions GRP is expressed in the bronchial epithelium and promotes lung development at the fetal stage. When it is associated with bombesin (BB)-like peptide receptors (44), such as GRP receptor (GRPR), it predominantely (although with certain exceptions) acts as a growth promoter for small cell lung cancer. Conversely, epithelial cells of the adult colon under normal conditions are deprived of GRP receptor expression. Notably, GRP/GRPR expression in tumors was identified to correlate with improved patient survival rates and reduced metastatic spread. However, the mechanisms involved in these manifestations require further investigation (45,46). Previous findings provide evidence that a GRPR antagonist stimulates the growth of cancer cells, and that the stimulatory effects were prevented by the HDACi, suggesting that GRPR may interact with epigenetic mechanisms in regulating neuroblastoma cell growth. However, 100 nM GRPR stimulated proliferation of Neuro-2a murine neuroblastoma cells *in vitro*; the stimulatory effects were prevented by the HDACi (47). Involvement of BB in the acetylation of the androgen receptor and activation of

Table I. Epigenetic regulation of neuropeptides in cancer.

Author, year	Description	Refs.
Misawa *et al*, 2014 Misawa *et al*, 2016	CpG hypermethylation was reported as the silencing mechanism for the neuropeptide, GAL and its receptor, GALR1/2 gene, leading to inactivation of their tumor suppressing properties in HNSCC resulting in tumorigenesis. Therefore, the gene's methylation status was proposed as an important biomarker for clinical outcome	(61,62)
Misawa *et al*, 2015	CpG hypermethylation was attributed as a possible mechanism for SST and SSTR1 methylation profiles for HNSCC tumorigenesis	(63)
David *et al*, 2009	TAC1 is the precursor protein for neuroendocrine peptides, including substance P, and is centrally involved in gastric secretion, motility, mucosal immunity and cell proliferation. The authors indicated the aberrant silencing of TAC1 in GC by promoter hypermethylation	(64)
Misawa *et al*, 2013	The specific mechanisms, elucidated by the authors, of TAC1 and TACR1 gene inactivation via frequent promoter hypermethylation methylation led to tumorigenesis	(65)
Mori *et al*, 2006	Gene silencing via promoter hypermethylation of SST and TAC1 and 5, leading to colon cancer tumorigenesis was highlighted in this study	(66)
Kamimae *et al*, 2015	NTSR1 methylation was associated with lateral and non-invasive growth of colorectal tumors, while low levels of methylation contributed to the malignant potential via activation of NTSR1 and the clinical implications were documented	(67)
Zhong *et al*, 2007	In this study, oxytocin receptor was dominantly regulated by histone deacetylation and demonstrated to be frequently downregulated in lung tumors	(68)

CpG, cytosine-guanine dinucleotide; GAL, galanin; HNSCC, head and neck squamous cell carcinoma; SST, somatostatin; SSTR1, somatostatin receptor type 1; TAC1, tachykinin-1; GC, gastric cancer; TACR1, tachykinin receptor type 1; NTSR1, neurotensin receptor 1.

androgen-associated genes in prostate cancer cells via activation of p300 histone acetyltransferase activity was reported in another study (48). The effects of a BB/GRP receptor antagonist, PD176252, and HDACi, MS-275, were investigated in human lung cancer cell lines and the results indicated the ability of GRPR antagonists to potentiate the action of HDACi on lung cancer cellular proliferation by increasing the expression of tumor suppressor genes (49).

Gastrin regulates heterochromatin protein 1 (HP1) expression in cancer and HP1 is directly involved in epigenetic control of gene transcription. The methylation of histone H3 at lysine 9 along with HP1 recruitment secures chromatin assembly to epigenetically control the genome (50). Experimental evidence indicates that blocking GRP signaling results in the down-regulation of $HP1^{Hs\beta}$ expression, resulting in colon cancer cell invasiveness (45). ChIP-seq revealed the targets of HP1β due to BB/GRPR activation, which were as follows: Interleukin-1 receptor accessory protein like 2, family with sequence similarity 13 member A, 1,4-α-glucan branching enzyme 1, polo like kinase 3, and solute carrier organic anion transporter family member 1B3 (51). In addition, gastrin induced the overexpression of miR222 that led to cytoplasmic mislocalisation of p27kip1, causing cell migration. Data indicated a novel mechanism that involves gastrin, which is associated with tumor development. Notably, miR222 may serve as a promising biomarker for observing gastrin-induced premalignant changes (52). The role of GRPR is reported to be tumorigenic. Therefore, the silencing of GRPR suppresses tumorigenesis and the metastatic potential of neuroblastoma (53). Overexpression of miR-335 and miR-363 decreased tumorigenicity as measured by clonogenicity, anchorage-independent growth, and metastasis determined by cell invasion assay and liver metastasis *in vivo*. Thus, miR-335 and miR-363 functioned as tumor suppressors in GRPR-silenced neuroblastoma (54). Novel therapeutic strategies against aggressive neuroblastoma may be derived from upregulation of miR-335 and miR-363, which are capable of reversing tumorigenicity and blocking cell transformation. Initiation of antral gastric cancer was associated with epigenetic silencing of trefoil factor 1 (TFF1) tumor suppressor gene silencing By contrast, inhibition of gastric carcinogenesis by the hormone gastrin was mediated by suppression of TFF1 epigenetic silencing (6).

Somatostatin (SST) is a gut peptide that is able to inhibit the growth of tumor cells in gastric cancer, inhibit gastrin release, gastric acid production, and is regarded as a novel cancer repressive polypeptide. SST promoter methylation is a common occurrence in human gastric cancer, and is connected with a decrease in SST protein and RNA levels, as well as being associated with gastric carcinogens. A significant increase in SST promoter was identified in tumor samples when compared with healthy samples. Thus, the promoter DNA methylation was defined as an epigenetic mechanism of SST expression regulation. SST is therefore a potential biomarker for gastric cancers (55).

Neurotensin (NTS). NTS is a neuropeptide that is involved in the regulation of luteinizing hormone and it is connected to the dopaminergic system. It is highly present in the hypothalamic nucleus accumbens and amygdala, inducing multiple effects, such as hypothermal and increased locomotor activity, and smooth muscle contruction in the small intestine (56). NTS is considered to be a cancer promoting mitogen in colon cancer (57). A notable connection between its neurotensin receptor 1 (NTR1) and induction of inflammation, and

tumor growth mediated by upregulated expression of certain miRNAs (such as miR21 and miR155) has been reported (58). Their upregulation in human colon cancer, also caused down-regulation of major tumor suppressors, including phosphatase and tensin homolog and suppressor of cytokine signaling proteins (58).

NTS and its receptor are implicated in cancer progression. The upregulation of miR-29b-1 and miR-129-3p expression led to impaired proliferation of glioma cells. NTS signaling upregulated c-Myc production and inhibited the above-mentioned miRNAs. These results indicate that the NTS/NTSR1/c-Myc/miRNA axis is important in the pathogenesis of glioblastoma and may be considered as a potential therapeutic target (59).

3. Conclusion

Epigenetics in cancer research is a rapidly developing field. An important lesson is obvious; that the inactivation of tumor suppression pathways in cancer presents potential therapeutic opportunities for epigenetic therapy intervention (60). To better understand the mechanism of derailed epigenetic regulation in malignancies, the insight into epigenetic control in normal and embryonic tissues is of utmost importance. Thus, epigenetic regulation of cancer by neuropeptides is an exciting and novel direction; however, it is in its infancy, although there is substantial data on epigenetic regulation of neuropeptides, some examples are shown in Table I (61-68). Certain neuropeptides, being natural compounds by their origin, possess powerful antitumorigenic, tumor suppressor and immunomodulatory properties, providing added benefit for future potential therapeutic strategies. Whether they are cytotoxic or cytostatic by nature, they are promising in the battle against cancer.

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