Tachykinin and Calcitonin/Calcitonin Gene-Related Peptide Families in Cancer

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The structure and dynamics of the neurokinin (NK)-2, NK-3, and calcitonin gene-related peptide (CGRP) receptors are studied together with the intracellular signaling pathways in which they are involved. These peptides play an important role in many cancers, such as breast cancer, colorectal cancer, glioma, lung cancer, neuroblastoma, oral squamous cell carcinoma, phaeochromocytoma, leukemia, bladder cancer, endometrial cancer, Ewing sarcoma, gastric cancer, liver cancer, melanoma, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, renal carcinoma, and thyroid cancer. These peptides are involved in tumor cell proliferation, migration, metastasis, angiogenesis, and lymphangiogenesis.

Keywords: neurokinin ; cancer ; tachykinin

1. Introduction

To attain a better quality of life, with higher cure rates and fewer sequelae in cancer patients, new molecular targets and compounds that specifically destroy tumor cells must be urgently investigated. One of these promising targets could be peptidergic systems, i.e., peptides and their receptors, which play a crucial role in cell communication. Peptidergic systems have opened up new research lines and possibilities to improve cancer diagnosis and explore new antitumor strategies [1][2][3][4]. The involvement of peptidergic systems in cancer has attracted increasing interest in the last few years. Peptides such as substance P, neurotensin, orexin, angiotensin II, neuropeptide Y, vasoactive intestinal peptide, calcitonin gene-related peptide, adrenomedullin, adrenomedullin 2 or intermedin, and amylin contribute to cancer development [1][2][5]. These peptides promote the mitogenesis/migration of tumor cells, exert an antiapoptotic action, and stimulate the growth of blood vessels and lymphangiogenesis. However, some peptides such as neuropeptide Y, orexin, and vasoactive intestinal peptide also exert an anticancer effect [6]. Furthermore, tumor cells release peptides acting through autocrine, paracrine, and endocrine (tumor mass) mechanisms [1][2][3][5][7][8][9][10][11]. While some peptides (e.g., the heptapeptide angiotensin (1-7)) exert an anticancer effect, others (e.g., galanin) promote both proliferative and antiproliferative actions on tumor cells [3].

Tumor cells also overexpress peptide receptors, allowing for a specific treatment against cancer cells with peptide antagonists. In addition, the overexpression of these receptors can be used as a prognostic biomarker [1]. The overexpression of peptidergic systems has been associated with higher tumor aggressiveness, tumor size, poor prognosis, worse sensitivity to chemotherapy agents, and increased relapse risk [1][7]. Peptide antagonists promote apoptosis in tumor cells, block the migration of cancer cells, and inhibit angiogenesis. In combination therapy with chemotherapy, peptide antagonists decrease the side-effects promoted by cytostatics and exert a synergic effect [1][4]. Because peptide receptors are potential new targets in cancer treatment, peptide antagonists are promising antitumor drugs.

2. Tachykinin and Calcitonin Peptide Families

2.1. Tachykinin Peptide Family

The tachykinin family of peptides includes kassinin, ranakinin, eledoisin, neuropeptide K, hemokinin-1, substance P (SP), neurokinin B (NKB), and neurokinin A (NKA) [12]. Activated metabotropic neurokinin receptors (neurokinin-1 receptor (NK-1R), NK-2R, and NK-3R), widely distributed by the central and peripheral nervous systems, exert many physiological actions and determine many pathophysiological [13][14][15]. NKA and NKB mediate many physiological effects and are involved in several pathologies [14][16][17][18][19][20].

2.1.1. Genes and Products of Human Tachykinins

Tachykinin is the general name for a large family of peptides (hundreds) found in all bilaterians (from insects to amphibians and humans) [21][22]. In humans, three principal tachykinins, SP, NKA, and NKB, participate in cellular mechanisms responsible for physiological and pathological outcomes. Three human genes named *TAC1*, *TAC3*, and *TAC4* encode the peptides mentioned above, plus hemokinin1 (HK-1) and endokinins [15][23][24][25]. Tachykinin genes transcribe into splice variants [26][27][28]. Gene *TAC1* with seven exons is located on chromosome 7 (7q21.3). It gives rise to four different splice mRNA variants, α, β, γ, and δ, that encode four protachykinin peptide isoforms of various sizes, α (111 residues), β (129 residues), γ (114 residues), and δ (96 residues). Exon 3 of TAC1 appears transcribed in all four mRNA variants. It encodes the sequence of the undecapeptide SP. The exon 6 sequence transcript is only present in the β and γ splice variants and encodes the decapeptide NKA. Gene *TAC3*, with seven exons, is on chromosome 12 (12q13.3) and generates two alternative coding transcript variants, isoforms 1 and 2. Isoform 1 translates into a peptide precursor of 121 residues, and isoform 2 translates into a peptide precursor of 103 amino acids. Exon 5 of both mRNAs encodes the decapeptide NKB. Gene *TAC4* sits on chromosome17 (17q21.33) and encodes five splice variants, α, α-2, β, γ, and δ, translating into five peptide precursors that provide functional HK-1 and endokinins after post-translational processing.

Tachykinin peptide precursors undergo post-translational modifications, generating functional peptides [29]. Endopeptidase processing at a specific pair of basic residues liberates the N-terminal ends of SP, NKA, and NKB from their respective precursors. SP occupies amino-acid positions 58–68 in all precursor peptide variants encoded by TAC1. NKA corresponds to amino-acid positions 98–107 in the precursor variants β and γ. Lastly, precursor peptides 1 and 2 encoded by the *TAC3* gene contain NKB (amino-acid positions 81–90). Splitting the C-terminal ends of the three neurokinins from their protachykinins follows a shared mechanism required for functional activity, consisting of a PAM (peptidyl glycine α-amidating monooxygenase, EC 1.14.17.3)-catalyzed reaction cleaving the N–Cα bond between methionine and neighboring glycine [30][31].

2.1.2. Structure of NK-2R and NK-3R

Three mammalian neurokinin receptors convey the activity of tachykinins. NK-1R binds with high-affinity SP and HK-1, NK-2R preferentially binds NKA, and NKB is the natural agonist of NK-3R. All three neurokinins exhibit full agonist capacity in all three receptors, albeit with different rank order potency [32]. Sequence homology between NK-2R and NK-3R is 57%. NK-2R has a sequence homology of 54% with NK-1R; NK-3R shares a sequence homology of 61% with NK-1R (according to the SIM alignment tool [33]). The tertiary structure of the NK-2R and NK-3R is very similar when predicted with Alpha-Fold. However, specific residue positions and transmembrane segment displacements make interactions with agonists and antagonists different. Neurokinin receptors belong to class A of the large family of G-protein-coupled receptors (GPCR), membrane-bound proteins sharing a 3D structure arranged in seven transmembrane domains linked with extra and intracellular loops [34][35]. Structural and functional studies of these membrane proteins have provided broad information on the structure–activity relationships that explain their role in cell function and their relevance in drug discovery with therapeutic applications [35][36][37][38][39].

The Structure of NK-2R

NK-2R is a monomeric integral membrane protein (UNIPROT, P-21452) [23] made of 398 amino-acids that expand through the plasma membrane lipid bilayers with seven domains. The human gene *TACR1* (Gene ID 6865 from the Entrez Gene database, National Library of Medicine [40]) has five exons with chromosomal localization 10q22.1 and encodes the protein NK-2R [41]. Post-translational modifications of NK-2R include glycosylation of asparagines 11 and 19 (N-terminal region), a disulfide bridge between cysteines 106 (in TM3) and 181 (in ECL2), and the palmitoylation of Cys324 (intracellular C-terminal domain). The preferred endogenous ligand of NK-2R is NKA.

Early pharmacological studies in isolated organs revealed the functional importance of the NKA sequence from amino acids 4–10. This sequence retained the activity of full NKA (1-10) [42]. Additionally, the substitution of Gly8 for Ala8 increased the selectivity and potency of the short form of NKA [43] Radioligand binding and functional experiments in human specimens showed the importance of amino acids Asp4, Phe6, Val7, Leu9, and Met10 for binding selectivity [44]. The position of Phe6 within the C-terminal pentapeptide determines the binding of NKA to all neurokinin receptors [45]. It makes important contact with the protein through aromatic (π–π) and amino–aromatic (N–π) interactions [42]. Site-directed mutagenesis bestowed crucial amino-acid positions in transmembrane helices 3, 5, and 7 as part of the binding site for NKA and different interactions with SP and NKB agonists, and with NK-2R antagonist SR-48968 [46]. Homology modeling analysis implemented indirect data to attain forms of minimal energy to understand the coupling of agonists, antagonists, and cellular signaling proteins. Molecular modeling and docking of the NKA within NK-2R, using rhodopsin as a structural template and the three-dimensional NKA structure determined with NMR [47] resulted in the definition of the site where NKA contacts the receptor protein. Within a distance of less than 3 Å, predicted hydrogen bonds (residues His1, Lys2,

Thr3, Asp4, Gly8, Leu9, and Met10) stabilize the agonist and receptor interaction. Furthermore, residues Phe6, Leu9, and Met10 are relevant in biological activity.

NK-2R may adopt different active conformations where NKA adapts to generate different intracellular responses (biased agonism). Different receptor conformations linked to cellular responses facilitate the design of allosteric modulators that may help to control specific signaling by affecting the affinity of NKA to the receptor's conformations [48]. Binding selectivity depends on the C-terminal end and the interactions of amino acids of the rest of the molecule with the receptor.

Further stabilization of M10 occurs with I114 in TM3 through hydrophobic interaction. Additionally, the N-terminus of NKA contacts the ECL2 region of NK-2R (D175 forms a salt bridge with Lys2 carbonyl oxygen), and Phe6 further contacts Met28 in the N-terminal part of NK-2R and I285 in TM7.

The Structure of NK-3R

NK-3R is a monomeric membrane protein made (UNIPROT P29371) [23] of 465 amino acids that expand through the plasma membrane lipid bilayers with seven domains. The human gene *TACR3* (Gene ID 6870), [40] has five exons with chromosomal localization 4q24 and encodes the protein NK-3R [49]. Main post-translational modifications of the receptor include the glycosylation of asparagines 23, 50, and 73 (in the N-terminal region), a disulfide bridge between cysteines 158 (in TM3) and 233 (in ECL2), and the palmitoylation of cysteine at position 374 in the intracellular C-terminal domain. The preferred endogenous ligand of NK-3R is NKB.

Molecular modeling studies using the structure of rhodopsin receptors and manual docking of NKB (PDB ID 1P9F [50] within the NK-3R model resulted in the definition of the site where the NKB C-terminal region contacts the receptor protein [51]. According to the refined model, the C-terminal region of NKB lodges three pharmacophores (Phe6, Leu9, and Met10) that stabilize closely interacting with three hydrophobic holes in the NK-3R. The aromatic ring of Phe6 favors contacts with residues S130, P165, I166, A168, V169, F170, and W312. Interactions π–π between the phenyl group of F6 and the aromatic rings of F170 and W312 orientate the peptide in an optimal position within the receptor cleft. The isobutyl l chain of L9 contacts with residues C311, W312, P314, L344, A345, M346, and S347. The binding pocket for Met10 includes residues F123, V169, S172, M176, V304, F308, C311, S347, S348, and M350.

Docking analysis performed in a model of NK-3R based on the 3D structure of bovine rhodopsin reported different binding sites for the NKB in TM domains 2, 6, and 7, as well as ECL2. Additionally, the antagonists metaltenant and osatenant occupied different positions within the receptor, indicating that the binding site for the antagonists greatly coincided but did not entirely overlap [52].

Further refined structural analysis will unravel the atomic setting accommodating agonists, antagonists, and receptor modulators. The structure dynamics analysis will contribute essential information supporting the physiological and pathological contribution of NK-3R and their collaboration with other NK receptors responding to the three agonists, NKA, SP, and NKB.

2.1.3. Intracellular Signaling of NK-2R and NK-3R

NKA and NKB favorably bind and activate NK-2R and NK-3R, respectively, but they can also bind and activate NK-1R. Consequently, when studying the intracellular signaling of NK-2R and NK-3R, one should consider the possible activation of NK-1R by both neurokinins. The presence, absence, and abundance of the three neurokinin receptors and their endogenous agonists result in a possible explanation for the multiple outcomes and physiological and pathological consequences in various tissues and organs. Redundance of tachykinin receptors may be a compensatory mechanism [53]. It, however, may also serve excessive stimulation leading to malfunction. For example, NKA commits NK-1R, not NK-2R, in mouse macrophages to activate cellular events dependent on transcription factor NF-κB [53]. Basic information on neurokinin signaling comes from experimental analysis in cell lines and cell expression systems where a total determination of intracellular second messengers points to the activation of specific biochemical cascades. However, the study of signaling endosomes and compartmentalized intracellular signals should also be considered [15].

Activation of adenylyl cyclase generates cAMP, which triggers protein kinase A (PKA) [54][55]. The nucleotide cAMP, independently of PKA, also activates Epac (guanosine exchange proteins directly activated by cAMP) and nonselective cation channels [56]. Numerous substrates of PKA include phosphorylase kinase, GSK3 (glycogen synthase kinase), CaMKII (calcium–calmodulin kinase), and the transcription factor CREB (cAMP-responsive element binding protein), to mention a few [55]. The aberrant function of the signaling axis cAMP/PKA/CREB and the abnormal behavior of other PKA substrates may cause altered cell metabolism and gene expression affecting cell growth, proliferation, migration, and cell adhesion, driving the development of tumors in different tissues [57].

The PLC/IP3/intracellular calcium axis activates PKC (protein kinase C) and other calcium-dependent kinases: CaMKII or PI3K (phosphatidylinositol 3-kinase). PKC is a serine–threonine kinase with copious potential substrates, including, for example, GSK3, histones, integrins, dynamins, the apoptosis regulator Bcl2 (B-cell lymphoma), Bad (Bcl-associated death protein), and the proto-oncogene transcription factor cMyc [58]. PKC, therefore, is a crucial enzyme with a regulatory role associated with many aspects of cell survival and proliferation.

Heterotrimeric Gα12/13 proteins regulate signaling pathways that modulate cell functioning through several targets. One primary target, through Rho GTPase, is the protein kinase ROCK (Rho-associated coiled-coil kinase) [59]. ROCK modulates cytoskeleton organization and assembly by controlling the activity of LIMK (LIM protein domains kinase) and MLC (myosin light chain) phosphatase. In endothelial cells, ROCK regulates angiogenesis by activating transcription factors, such as c-Fos, c-Jun, or HIF-1α (hypoxia-inducible factor) [60]. ROCK proteins also maintain cell proliferation by directing cell-cycle cyclins (cyclin A) and cyclin-dependent kinases (CDK1) [61].
The activation of NK receptors by neurokinins depends on several factors, from receptor number, activated states, receptor occupancy, recruited effectors, and allosteric regulators to neurokinin concentrations and their competitivity for the three receptors NK-1R, NK-2R, and NK-3R. The intricacy of signaling pathways and their fine-tuned regulation protect the cell by employing redundant reactions and controls. Cancer development requires the malfunction of several biochemical mechanisms that make it difficult for the cell to overcome. Not only can all activate signaling pathways triggered by tachykinins crosstalk, but also those dependent on the activity of agonists acting on other co-existing GPCR receptors [62].

2.1.4. The Expression of NK-2R and NK-3R

The NK receptors appear in the central and peripheral nervous system, endothelial cells, smooth muscle, or blood cells (lymphocytes, neutrophils, and macrophages), where they control multiple biochemical mechanisms attending endocrine, inflammation, or smooth muscle activity regulation [63][64].

According to the human protein atlas [65], the expression of NK-2R, measured as mRNA, distributes in different tissues, but the higher presence appears in the gastrointestinal tract, kidney, urinary bladder, muscle tissues (smooth, heart, and skeletal), monocytes, and female and male tissues. Its detection in the brain and other tissues is scarce. The mRNA coding for the NK-3R is detected in the brain, eye, kidney, and urinary bladder with a weak signal in other tissues (lung, pancreas, or gastrointestinal tract). The mRNA coding for the NK-2R increased in human cancer samples from the gastrointestinal tract, testis, breast, endometrial, cervical, and urothelial tissues. The upregulation of mRNA coding for the NK-3R was higher in human lung, breast, urothelial, endometrium, testis, and ovarian cancer than in normal tissues [15][66][67].

2.2. Calcitonin/Calcitonin Gene-Related Peptide Family

The peptides of this family (adrenomedullin, adrenomedullin 2, amylin, and calcitonin gene-related peptide) regulate the secretion of hormones and are widely distributed by the body [68][69]. Many tumor types have reported AM expression and secretion [70]. AM exerts an antiapoptotic effect in endothelial cells, and cancer cells promote angiogenesis, regulate the permeability of endothelial cells, and contribute to the differentiation of bone marrow-derived mononuclear cells into endothelial progenitor cells. It is also involved in several pathologies [70][71][72][73][74][75][76][77][78][79][80][81]. Amylin, an islet amyloid polypeptide, regulates insulin secretion/glucose homeostasis and is a crucial constituent of the amyloid in insulinomas [82][83][84][85].

2.2.1. Genes and Products of Human Calcitonin

The human calcitonin family of peptides includes calcitonin (CT), α and β forms of CGRP, amylin (AMY or islet amyloid polypeptide (IAPP)), AM, and AM2 or intermedin. Their amino-acid sequence length varies from 32 in CT to 52 for ADM [86]. Although the amino-acid sequence among the six peptides is variable, they share common architectural traits essential for functionality, including a coil structure, a central area showing a helical or disordered structure, and an amidated C-terminal amino acid [87][88][89]. These peptides activate a family of receptors belonging to class B GPCR to serve numerous and diversified functions, such as plasma calcium reduction (CT), food intake modulation (AMY), and vasodilatation and inflammation (CGRPs) in different tissues [88][89][90].

2.2.2. Structure and Dynamics of the CGRP Receptor: A Three-Component Complex

The structural states of CGRP receptors (CGRPR), in both their apo and their ligand-bound forms, are essential to understand how structural dynamics direct the recruitment of intracellular proteins responsible for signaling mechanisms leading to molecular changes and cellular adaptations [91]. Defining the functional architecture of protein receptors

requires fine studies at the atomic level that unveil how ligands (agonists and antagonists) interact with the protein. Combining CLR (calcitonin receptor-like receptor) and RAMPs homologous (receptor activity modifying protein 1) 1, 2, and 3 generates different receptors with variable affinities for endogenous ligands. The CGRPR (calcitonin-gene-related peptide receptor) is a heterodimer formed by CLR and RAMP1 exhibiting a high affinity for CGRP. CLR-RAMP2 (AM-1-receptor) and CLR-RAMP3 (AM-2-receptor) bind with higher affinity to AM, and CTR (calcitonin receptor) associated with RAMP1 is the AMY-1-receptor [92][93]. CLR belongs to class B1 (secretin), subfamily CT-like [94] of GPCR (G-protein-coupled receptors). The human CLR protein (UNIPROT Q16602) comprises 461 amino acids and exhibits post-translational modifications affecting the amino- and carboxy-terminal ends.

2.2.3. Mechanisms of Signaling of the CGRP Receptor

The heterodimer CLR-RAMP1 shapes the fully functional CGRPR. RAMP1 serves several functions, from determining, together with CLR, the peptide binding site to helping the glycosylation of the N-terminal segment of CLR and the intracellular trafficking of the receptor [95][96]. However, the high-affinity state of the receptor requires the recruitment of RCP, a peripheral membrane protein, acting as an allosteric modulator that augments the effective functioning of the receptor complex but does not modify agonist binding [97]. In cell cultures, eliminating RCP by knockout significantly reduced cAMP production by stimulating CGRP receptors [97]. Interestingly, this protein does not favor the recruitment of Gq protein, does not participate in Gq-conveyed events [98], and may contribute to CGRPR bias signaling. The precise mechanism explaining the influence of RCP on CGRP receptor signaling is not fully understood [96].

Like many other GPCRs, the CGRP receptor signals through several kinase cascades, which amplify the signal to modulate many intracellular components, from metabolic enzymes to transcription factors [35][62]. As CGRP may signal through CGRP receptors, AM, and AMY receptors, delimiting the activity of CGRP only through CGRP receptors may be difficult [96]. However, signaling profiles depend on the selectivity of the agonist-receptor binding, the availability of signal transducers, and intracellular kinase targets.

3. Involvement of the Tachykinin and Calcitonin/Calcitonin Gene-Related Peptide Families in Cancer

3.1. Tachykinin Peptide Family

3.1.1. Breast Cancer

NKA exerts a proliferative action on breast carcinoma tumor cells expressing NK-2R [99]. Compared to non-metastatic breast cancer cells, overexpression of NK-2R/NK-1R was reported in metastatic breast cancer cell lines [100]. Malignant breast biopsies and breast cancer cells lines showed an increased expression of both NK-1R and pre-protachykinin A compared with benign breast biopsies and normal mammary epithelial cells; the level of NK-2R was high in both malignant and normal cells [101]. NK-2R and NK-1R antagonists blocked the proliferation of breast cancer cells, and this suggests that an autocrine stimulation of these cells occurs via pre-protachykinin A peptides (NKA, SP) [101]. Importantly, NK-2R mediated the proliferation of breast cancer cells but not that of normal cells [101].

NKA and SP increased the aggressiveness of a metastatic breast cancer cell line by increasing its ability to migrate and invade tissues [102]. Both peptides augmented the expression of NK-2R and NK-1R on the metastatic breast cancer cell line and, in addition, promoted the release from these cells of the high-molecular-weight kininogen molecule (bradykinin precursor) which exerted tumorigenic and pro-nociceptive actions [102].

3.1.2. Colorectal Cancer

A high expression of the *NK-2R* gene has been related to poor survival in patients with colorectal cancer; this expression was increased by interferon-α/β in a Janus kinase 1/2-dependent manner [103]. NK-2R rs4644560 GC polymorphism alone or in combination with NK-1R rs10198644 GC is a prognostic marker for lymph node metastasis in patients with colorectal cancer [104]. Patients with NK-2R rs4644560 CC showed lesser positive lymph nodes than those with rs4644560 GC, and the number of positive lymph nodes was increased in NK-2R rs4644560 GC/NK-1R rs10198644 GG patients compared to NK-2R rs4644560 GG/NK-1R rs10198644 GG individuals.

3.1.3. Glioma

NKA promoted the proliferation and release of interleukin-6 from glioma cells expressing NK-1R; these actions mediated by NKA were entirely blocked with a specific NK-1R antagonist (MEN-11467) [105]. The above means that NKA exerted its actions not only via NK-2R but also through NK-1R.

SP binding sites but not NKA binding sites have been reported in an astrocytoma cell line (U 373) [106]. NKA and NKB promoted taurine release from astrocytoma cells. NKA induced a greater release than NKB; however, SP promoted the most significant release of taurine from these cells [107].

3.1.4. Insulinoma

RIN5mF cells (rat insulinoma cells) express the *pre-protachykinin A* gene and release NKA and SP [108][109]. No change in the concentration of NKA/SP was observed in the small intestine and stomach of insulinoma rats [110].

3.1.5. Lung Cancer

Pulmonary carcinoid tumors express mRNA pre-protachykinin A; in some, NKA/SP has been reported [111]. NKA and NKB inhibited the growth of small-cell lung cancer cells [18].

3.1.6. Medullary Thyroid Carcinoma

NKA has not been detected in medullary thyroid carcinoma [112].

3.1.7. Midgut Carcinoid Tumor

Pre-pro-tachykinin A mRNA expression and the presence of NKA/SP have been reported in midgut carcinoid tumors and in the plasma of patients with midgut carcinoids [111][113]. These tumors show an unpredictable clinical behavior; hence, specific biomarkers are needed to detect the disease early [114]. Plasma NKA level is an excellent biomarker of prognosis; patients with a high NKA level showed worse survival than those with a decreased or stabilized level [114].

3.1.8. Neuroblastoma

NKB but not NKA/SP has been located in neuroblastoma [115]. NK-2R and NK-1R mediate the proliferation exerted by pre-protachykinin A peptides on neuroblastoma cells [116]. The murine neuroblastoma C1300 cell line expresses mRNA NK-2R/NK-3R, but not mRNA NK-1R and NKA; NK-3R increased its cytosolic Ca^{++} concentration, which was inhibited with the NK-2R antagonist SR-48968 [117][118]. NK-2R and NK-3R are activated independently by NKA; the activation of both receptors promoted not only a Ca^{++} increase but also the formation of inositol trisphosphate, whereas both mechanisms were blocked with phospholipase C inhibitors [117].

3.1.9. Oral Squamous Cell Carcinoma

NK-3R expression was very high in oral squamous tumor cells, whereas, in normal epithelial cells, NK-3R was not observed [19]. Moreover, those squamous cells that invaded the mandible bone matrix showed a higher expression of NK-3R and using the selective NK-3R antagonist SB-222,200 significantly inhibited tumorigenesis and the osteolytic lesion [19][119]. Cancer cells did not express NKB, but this peptide was observed in sensory nerves in the mandible. This discovery suggests that the release of NKB from these nerves could regulate the proliferation of tumor cells.

3.1.10. Phaeochromocytoma

NKB has only been detected in one of the 10 phaeochromocytomas studied; in the same study, NKB was not detected in carcinoid tumors [120]. Moreover, in a human phaeochromocytoma extract, NKA/SP was detected [29].

3.1.11. Schwannoma-Derived Cells

NKA and SP were located in the cytoplasm of malignant schwannoma-derived cells [121]. Both peptides seem to play a role in the tumor microenvironment; however, future studies must elucidate this.

3.1.12. Small Bowel Neuroendocrine Tumors

Small bowel neuroendocrine tumors are difficult to diagnose; thus, it is important to determine specific biomarkers associated with the disease. NKA is a specific blood biomarker because high plasma NKA levels (≥50 ng/L) have been associated with poor prognosis in patients with these tumors. Monitoring such levels could be useful in selecting patients with a poor prognosis; hence, a high NKA level means that an urgent therapeutic intervention is needed [122][123][124][125][126].

Compared with healthy individuals, a rise in circulating NKA/SP has been reported in patients suffering from ileal metastatic carcinoid tumors showing cutaneous flushing; the release of both peptides from carcinoid tumors was partially blocked after the administration of a somatostatin analog [127]. The presence of NKA, NKA_{3-10}, and NKA_{4-10} has been detected in ileal metastatic carcinoid tumors [128].

3.1.13. Uterine Leiomyomata

Leiomyoma, a benign smooth muscle tumor, showed an upregulation of NK-2R mRNA compared with normal myometrium; however, the levels of NK-2R protein were similar in both tumor and normal cells [129]. Moreover, leiomyomas express NKB and NK-3R, which were significantly more highly expressed in this benign tumor than in normal myometrium [130]. NKB was observed in the nuclei of smooth muscle cells in normal myometrium, whereas leiomyoma cells showed a predominant cytoplasmic expression of the peptide [130].

3.2. Calcitonin/Calcitonin Gene-Related Peptide Family

Extensive data have shown the involvement of this peptide family in cancer. For example, adrenomedullin (AM) is released from choroid plexus carcinoma [131]; AM released from tumor cells drives both tumor and lymph node lymphangiogenesis, and AM gene dosage has been related to both mechanisms [132]. Tumor cells express/overexpress AM (e.g., ovary, prostate, kidney, skin, endometrial, liver, pancreatic, brain, and breast cancer), and the level of AM has been correlated with cancer severity [79][133].

AM acts as a mitogenic agent on tumor cells and favors a more aggressive tumor phenotype. Under hypoxic conditions that occur in the proximity of solid tumors, the peptide is upregulated via an HIF 1-dependent pathway in normal and tumor cells, promoting angiogenesis [134][135][136][137]. AM also prevents apoptosis, suppresses the immune system, and is involved in bone metastasis [138]. Adrenomedullin 2 (AM2/intermedin) and CGRP act as tumor survival/growth factors promoting lymphangiogenesis and angiogenesis [133]. The implication of AM, AM2, AMY, and CGRP in 29 tumors is summarized in **Table 1**.

Table 1. Participation of adrenomedullin (AM), adrenomedullin 2 (AM2), amylin (AMY), and calcitonin gene-related peptide (CGRP) in cancer.

Tumor	AM/AM2/AMY/CGRP	References
Acute myeloid leukemia	**AM, CLR, RAMP 2/3 expression.** **A high AM level is associated with low overall survival/disease-free survival.** **AM/$AM_{22–52}$ regulates cell growth.** **AM expression associated with genes related to immunosuppression resistance.** **AM correlates with adverse outcomes.** **Targeting calcitonin receptor-like receptors prevents relapse.** ***Calcitonin* gene methylation pattern: independent prognostic factor.** **High calcitonin receptor expression: poor prognosis and correlates with chemotherapy resistance.** **Olcegepant decreases leukemic burden/stem cell characteristics.** **MK0974 promotes apoptosis.**	**[139][140][141][142][143][144]**
Adrenocortical tumor	**AM is synthesized/released from adrenocortical tumors and phaeochromocytomas.** **Phaeochromocytomas: higher AM/receptor mRNA expression.** **Phaeochromocytomas and adenomas: AM2 expression.** **AM blocks phaeochromocytoma cell proliferation.** **AM level as a biomarker.** **Adrenal tumors: AM2, CLR, RAMP1/RAMP2/RAMP3 mRNA expression.** **Phaeochromocytomas: high CGRP tissue level.**	**[145][146][147][148][149][150]**
Bladder cancer	**High AM level.** **AM knockdown promotes apoptosis.** **AM knockdown/cisplatin combination decreases tumor growth.**	**[151]**
Breast cancer	**AM expression associated with axillary lymph node metastasis.** **RAMP3: involved in metastasis.** **Tumor cells overexpressing AM: potential angiogenic increase/less apoptotic mechanisms.** **Tumor cells expressing/releasing AM: favor cell proliferation, breast cancer bone metastasis, and angiogenesis.** **AM is a tumor survival factor.** **Triple-negative breast cancer samples: AM expression decreased; this low expression is related to poor prognosis and increased risk of recurrence/metastasis.** **$AM_{22–52}$ disrupts tumor vasculature, decreases tumor cell proliferation, and induces apoptosis.** **Plasma AM2 level associated with poor patient outcomes.** **AM2 expression increased: correlated with Ki67 expression/lymph node metastasis.** **AM2 promotes cancer cells' growth, migration, and invasion; these actions were blocked with anti-AM2 antibodies. CGRP expression increased.** **CGRP is involved in metastasis.**	**[74][152][153][154][155][156][157][158][159]**

Tumor	AM/AM2/AMY/CGRP	References
Choriocarcinoma	AM mRNA expression.	[160]
Colon cancer	CLR and RAMP2/3 expressions. High levels of AM, CLR, and RAMP2/3 are correlated with lymph nodes and distant metastasis. High AM level is related to low disease-free survival. Higher AM level and AM mRNA expression. AM promotes tumor cell proliferation/invasion and antiapoptotic effect. AM level associated with clinical survival rate/cancer stage. Knockdown AM promotes apoptosis/blocks angiogenesis. AM expression is associated with vascular endothelial growth factor and hypoxia-inducible factor-1α. AM positive modulator (145425) decreases the number of tumors. Higher mRNA pre-proAM, pre-proAM2, CLR, RAMP2/3, MMP-9, and VEGF-A expression. Positive correlation between *MMP-9* gene expression and pre-proAM, but not pre-proAM2.	[137][161][162][163] [164][165][166]
Cutaneous nerve neuromas	Saphenous nerve neuromas: CGRP release from nerve fibers.	[167]
Endometrial cancer	AM favors angiogenesis/tumor growth and blocks tumor cell death. AM level increases from normal, simple, or complex hyperplasia with or without atypia to grade 1 adenocarcinoma.	[76][168][169][170]
Ewing sarcoma	CGRP expression. CGRP promotes the proliferation of cancer cells.	[171]
Gastric cancer	Tumor-derived AM promotes mast cell degranulation, as well as favors tumor cell proliferation, and the apoptosis blockade in cancer cells.	[172]
Glioma	AM favors mitogenesis in tumor cells and exerts angiogenic/antiapoptotic effects. AM mRNA is associated with tumor type and grade. c-Jun/JNK pathway is involved in the growth regulatory activity mediated by AM. AM expression is upregulated in temozolomide-resistant glioma samples: miR-1297 targets AM, blocks its expression, and sensitizes tumor cells to temozolomide treatment. AM2 expression is increased and correlated with higher-grade gliomas. AM2 increases the invasive capacity of tumor cells and improves tumor blood. AMY promotes the release of inflammatory cytokines from tumor cells. The signal transducer and STAT-3 in astroglioma control AM expression. AM promotes the migration of astroglioma cells.	[173][174][175][176] [177][178][179][180] [181]
Head and neck squamous cell carcinoma	Peripheral nerve terminals release CGRP, which exerts a paracrine action on tumor cells. CGRP links perineural invasion and lymph node metastasis. Pre-operative plasma CGRP level: lymph node metastasis predictor.	[182][183]
Liver cancer	CLR and RAMP2/3 expression. High AM level is related to increased intrahepatic metastasis. Higher AM mRNA levels in tumor tissues than in adjacent nontumor tissues. AM mediates the epithelial–mesenchymal transition and promotes tumor cell growth. Knockdown AM expression promotes apoptotic mechanisms and, combined with cisplatin, decreases tumor growth. Microvessel density and mRNA AM/erythropoietin receptor levels are higher in hepatocellular carcinoma than in nontumor tissues: both levels are correlated with tumor metastasis, pathological differentiation, and capsule invasion. AM is associated with N-cadherin intensity, vascular invasion, and poor prognosis. AM level as a prognostic factor. High AM2 mRNA expression even in early stages. AM2 increases tumor cell proliferation and survival, and is involved in angiogenesis: $AM2_{17–47}$ blocked this proliferation. AMY binding site expression.	[184][185][186][187] [188][189][190][191] [192]
Lung cancer	AM expression does not correlate with survival, cancer stage, or tumor differentiation. AM contributes to the carcinogenicity of tobacco-activated aryl hydrocarbon receptor products. *CGRP* gene expression.	[193][194][195][196]

Tumor	AM/AM2/AMY/CGRP	References
Melanoma	Tumor-associated macrophages, through AM, favor melanoma growth and angiogenesis. The number of tumor-associated macrophages (express/release AM) in the tumor microenvironment is correlated with poor prognosis. Tumor-associated macrophages favor the migration of endothelial cells and increase tumor cell growth.	[197]
Nasopharyngeal carcinoma	AM level as a biomarker for predicting prognosis.	[198]
Neuroblastoma	AM receptor expression. AM mRNA expression is associated with tumor differentiation.	[199][200]
Neuroendocrine tumors	High plasma and tissue AM expression: predictive factors for tumor progression and worsened prognosis.	[201]
Oropharyngeal squamous cell carcinoma	Jumonji domain-containing 1A, H3K9me1/2, and AM expression: predictor markers for progression and prognosis. *JMJD1A* gene target AM favors tumorigenesis/cell growth.	[202]
Osteosarcoma	AM expression is associated with metastasis degree/malignancy. AM overexpression. AM exerts an antiapoptotic effect.	[203][204]
Ovarian cancer	High AM level is related to tumor stage. *AM* gene is correlated with histological grade, lymph node metastasis, and prognosis but not with disease stage, histological subtype, residual tumor mass after initial surgery, and patient's age at diagnosis. Tumor cells express AM mRNA for both ligand/receptor. AM is involved in tumor progression/cell migration. *AM* gene silencing blocks cell proliferation and increases tumor cell chemosensitivity. Cancer patients with high AM expression show larger residual size of tumors, shorter disease-free/overall survival time, and higher metastasis incidence. AM as biomarker to evaluate prognosis/malignant potential. AM is correlated with expressions of HIF-1α, VEGF, or microvessel density. AM favors angiogenesis.	[205][206][207][208] [209][210]
Pancreatic cancer	High AM levels are associated with disease-free survival decrease. Higher AM plasma level. AM level is higher in cancer patients with diabetes than those without diabetes. Insulinoma: circulating AM increased. AM and its receptor are expressed. AM is involved in tumor cell proliferation, migration, invasion, metastasis, and angiogenesis. AM mRNA/protein expressions are increased. AM as a tumor marker. AM receptor silencing blocks AM-induced cell growth and invasion. AM antagonists decrease tumor cell growth/blood vessel diameter. Selective RAMP2 activation/RAMP3 inhibition: tumor metastasis suppression. AM2 as tumor angiogenic factor. AM2 level: poorer survival predictor. AM2 is a biomarker predicting survival. Insulinomas express AMY. Plasma AMY levels are increased in nondiabetic patients with cancer; this level is low in patients with diabetes. CALCA (αCGRP) and CALCB (βCGRP) methylation increases.	[211][212][213][214] [215][216][217][218] [219][220][221][222]
Pituitary adenoma	AM expression is decreased in anterior pituitary tumors.	[223]

Tumor	AM/AM2/AMY/CGRP	References
Prostate cancer	AM is expressed in prostate carcinomas. A high AM level is associated with a high Gleason score. Plasma AM2 level is associated with Gleason's score, tumor node metastasis, and 5 year metastasis. AM overexpression inhibits tumor cell growth and dysregulates genes involved in apoptosis, cell cycle, extracellular matrix, cell adhesion, and cytoskeleton. AM promotes human prostate growth via the AM2 receptor (CLR/RAMP3) subtype. AM blocks apoptosis in specific tumor cells. AM, upon androgen ablation, is involved in hormone-independent tumor growth, lymphangiogenesis, and neoangiogenesis. AM promotes cancer cell migration and invasion. AM2 is involved in cancer cell migration/angiogenesis. Higher plasma AM2 level in patients with prostate cancer. Patients with a Gleason score ≥7, unconfined organ, seminal vesicle invasion, tumor node metastasis stage T2, positive lymph node, or extra-prostatic extension show high AM2. AM2 as a prognostic, predictive biomarker for 5 year metastasis and 5 year progression. CGRP increases the invasive/migratory capacity of tumor cells. CGRP serum level correlates with cancer progression. Higher serum CGRP level is associated with higher histological grade/clinical stages. CGRP receptor mediates metastasis. CGRP promotes tumor growth which is blocked with CGRP antagonists.	[138][224][225][226][227][228][229][230][231][232][233]
Renal carcinoma	AM, CLR, and RAMP2/3 expression. High CLR level is associated with high tumor grade. AM and AM mRNA expression. AM mRNA expression is correlated with VEGF-A mRNA. AM, via CLR/RAMP2 and CLR/RAMP3 receptors, promotes cell proliferation, migration, and invasion. High AM mRNA level is related to increased risk of relapse.	[234][235][236]
Thymic lymphomas	Pramlintide promotes tumor regression. AMY blocks glycolysis, promotes reactive oxygen species formation, and induces apoptosis.	[237]
Thyroid cancer	AM2 expression is increased in obese patients with thyroid cancer, showing locoregional recurrence, a high prevalence of lymph node metastasis, and larger tumor size. High circulating AM2/tumor cell AM2 expression levels are associated with aggressive pathological parameters. AM2 as a biomarker for predicting thyroid tumor progression. Medullary thyroid carcinoma: high AMY levels. Plasma AMY/insulin levels are correlated in medullary thyroid carcinoma. *CGRP* gene expression. Plasma CGRP level marker for medullary thyroid carcinoma.	[195][238][239][240][241]
Uterine cervical carcinoma	High AM and AM mRNA expression. AM is involved in promoting malignant progression and in selecting carcinoma cells resistant to apoptosis.	[242][243]

4. Antitumor Therapeutic Strategies Based on the Modulation of Peptidergic Systems

4.1. Tachykinin Peptide Family

No NK-2R or NK-3R antagonist has been approved for clinical practice [12], although several NK-2R or NK-3R antagonists have been tested in clinical trials [14]. Unfortunately, although NK-2R/NK-3R antagonists were safe, these trials were abandoned due to the lack of efficacy. The ineffective results could also have been due to a non-appropriate selection of patients and endpoints in clinical trials and a lack of knowledge regarding the molecular interaction between tachykinin ligands and NK receptors [15]. Moreover, the ineffective effects could also be due to a non-appropriate selection of patients and endpoints in clinical trials and to a lack of knowledge regarding the molecular interaction between tachykinin ligands and NK receptors [15]. NK-2R antagonists (e.g., nepadutant (MEN-11,420) blocked tumor cell proliferation promoted by NKA in breast carcinoma [99]. Metastatic and non-metastatic breast cancer cell proliferation was blocked by inhibiting the action of SP, at NK-2R, with NK-2R antagonists (GR-159,897); however, this action was less prominent than that observed with NK-1R antagonists (RP-67,580) [100]. This finding suggests that breast cancer cells respond differently to NK-2R and NK-1R antagonists. Moreover, these cells reacted differently to NK-2R and NK-1R agonists (e.g., SP) [100].

4.2. Calcitonin/Calcitonin Gene-Related Peptide Family

4.2.1. Adrenomedullin

AM ligand/receptor overexpression occurs in colonic cancers, and antibodies directed against both targets decreased tumor growth [162][163][164][244][245][246][247]. The peptide fragment $AM_{22–52}$ [212], polyclonal antibodies against AM [175][248] or its receptor [247], monoclonal antibodies [249], and small interfering RNAs [215] regulate AM expression and actions [166]. Small molecules (e.g., 16311, a negative AM modulator; 145425, a positive AM modulator) also regulate the effects mediated by AM. For example, 145425 reduced tumor burden, colon weight/length ratio, and tumor growth in mice [166]. AM promotes cell proliferation and survival, alters the cell phenotype more aggressively, and increases vascularization [250]. Tumors are, in general, the main source of excessive AM production since AM levels returned to normal levels when the tumor was removed after surgery [251]. The blockade of AM receptors or lowering AM amounts are antitumor strategies to decrease the tumor mass [133]. Many preclinical studies have shown reduced tumor cell proliferation, metastasis, and angiogenesis after applying AM receptor antagonists, AM receptor interference, or AM-neutralizing antibodies [250]. Thus, a cocktail of antibodies directed against CLR and RAMP2/3 exerted an antitumor effect against glioblastoma, mesothelioma, and lung and colon cancer, and peptide antagonists such as $AM_{22–52}$ also showed an antitumor action against melanoma, mesothelioma, and renal, ovarian, breast and pancreatic cancer [175][247][252].

Tumor development is highly dependent on the formation of both lymphatic (lymphangiogenesis) and blood (angiogenesis) vessels from pre-existing ones; these mechanisms are regulated by AM and VEGF, which are released from cancer and tumor stroma cells (e.g., endothelial cells, pericytes, fibroblasts, and macrophages) [250]. Thus, the inhibition of both angiogenesis and lymphangiogenesis mechanisms is a sound antitumor strategy. The AM/RAMP2 system controls vascular integrity. It has been reported that the deletion of RAMP2 favored vascular permeability and the formation of pre-metastatic niches in distant organs by altering the vascular structure and promoting inflammation [253]. As a result, the AM/RAMP2 system regulates vascular integrity, and this system could be a promising antitumor therapeutic target to block metastasis. AM plays an essential role as a crosstalk agent integrating mast and tumor cell communication [254]. AM favors the release of beta-hexosaminidase or histamine from human mast cells, which are also involved in angiogenesis; this was inhibited with anti-AM monoclonal antibodies [254].

The AM/RAMP2 system is involved in tumor angiogenesis; liver metastasis (PAN02 pancreatic cancer cells were administered into the spleen) increased in vascular endothelial cell-specific RAMP2 knockout mice, and liver metastasis was suppressed in $RAMP3^{-/-}$ animals in which the number of podoplanin-positive cancer-associated fibroblasts decreased in the periphery of tumors at metastatic sites [216]. RAMP3 deficiency cancer-associated fibroblasts inhibited cell proliferation/migration and metastasis, and the activation of RAMP2 in $RAMP3^{-/-}$ mice blocked tumor growth and metastasis [216]. Moreover, podoplanin upregulation in $RAMP2^{-/-}$ animals augmented malignancy, and podoplanin downregulation in $RAMP3^{-/-}$ mice decreased malignancy [216]. The observation means that RAMP2 activation and RAMP3 inhibition can suppress metastasis, and that deficiency of the AM/RAMP3 system inhibited metastasis via the modification of cancer-associated fibroblasts. Acylated truncated AM/AM2 analogs of 27–31 residues showed a potent antagonistic action toward CLR/RAMP1, and non-acylated analogs showed minimal activity [255].

4.2.2. Adrenomedullin 2

AM2 is involved in vascular remodeling processes and angiogenesis; hence, the peptide is an important target for developing angiogenesis-based antitumor strategies [256]. AM2 increases tumor blood perfusion and promotes quiescent endothelial cells to proliferate by restraining endothelial cell response to VEGF; hence, the excessive vessel sprouting is blocked, and the vascular lumen is increased [257]. AM2 also favors the formation of a signaling complex containing CLR/β-arrestin1/Src in endothelial cells and promotes its internalization into the cytoplasm via a clathrin-dependent manner to activate downstream ERK1/2 pathway; this action was not inhibited by endothelial cell contact [257].

AM2 blockade with neutralizing antibodies/antagonist peptides inhibited the growth of tumor cells by promoting apoptosis, Bcl2/Gli1 downregulation, and caspase-8 cleavage [189]. Significantly, administering anti-AM2 monoclonal antibodies not only inhibited tumor growth but also increased the antitumor activity of temozolomide [180]. By using anti-AM2 antibodies, ERK1/2 phosphorylation was inhibited in endothelial cells and, in the same cells, a decreased expression of vascular endothelial cadherin and dissociation of vascular endothelial cadherin/vascular endothelial growth factor receptor 2/phosphoinositide 3-kinase complex occurred, leading to the internalization and phosphorylation of vascular endothelial growth factor receptor 2 and the blockade of the PI3K/Akt pathway [256].

4.2.3. Amylin

The p53 family promotes tumor suppression, and deletion of the ΔN isoforms of p63 or p73 led to metabolic reprogramming and regression of p53-deficient tumors via upregulation of the *AMY* gene [237]. AMY is involved in tumor regression and, via the CT receptor/receptor activity modifying protein 3, promotes apoptosis, induces reactive oxygen species, and blocks glycolysis [237]. Pramlintide, a synthetic analog of AMY, stimulated tumor regression in p53-deficient thymic lymphomas, representing a novel strategy to target p53-deficient cancers [237]. Pramlintide also exerted an antiproliferative action against colorectal cancer cells, and its coadministration with classic chemotherapeutics increased cytotoxicity [258].

4.2.4. Calcitonin Gene-Related Peptide

CGRP signaling, through the CT receptor, increased chemotherapy resistance and stem cell properties in acute myeloid leukemia, and olcegepant, a CGRP antagonist, decreased key stem cell properties and leukemic burden [140]. The CGRP/CT receptor system could be an antitumor target against acute myeloid leukemia. Moreover, the CGRP8-37 peptide antagonist exerted an antitumor action against prostate cancer [259].

CGRP augmented cytotoxic $CD8^+$ T cell exhaustion, limiting their capacity to eliminate melanoma cells [260]. CGRP antagonism of the receptor RAMP1 or pharmacological silencing of nociceptors decreased tumor-infiltrating leukocyte exhaustion and B16F10 melanoma cell growth [260]. Thus, reducing CGRP release from tumor-innervating nociceptors is a valuable strategy to improve antitumor immunity via eliminating the immunomodulatory actions exerted by CGRP on these cytotoxic T cells [260].

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