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Antitumor Strategies Targeting Peptidergic Systems

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Definition: Peptidergic systems show promise as targets for fighting tumors. While some peptides encourage the growth and spread of tumor cells and angiogenic mechanisms, others display antitumor properties. As such, peptide ligands and receptor antagonists could be used as antitumor agents alone or in conjunction with chemotherapy or radiotherapy. Peptide receptor antagonists can counteract the oncogenic effects of specific peptides by inducing apoptosis in various types of tumor cells, hindering cancer cell migration and inhibiting angiogenesis. Peptides and peptide receptor antagonists are not currently used in clinical practice as antitumor agents. Still, aprepitant, a neurokinin 1 receptor antagonist, is a promising candidate due to its ability to promote apoptosis in many cancer cells. However, to utilize aprepitant as an anticancer agent, the dosage must be increased and administered for a more extended period. Moving beyond current protocols for aprepitant's use as an antiemetic is essential. Additionally, a common anticancer strategy with aprepitant is possible regardless of cancer cell type. Finally, combining aprepitant with chemotherapy or radiotherapy is encouraged.

Keywords: peptide; peptide receptor; antitumor drug; anticancer; substance P; neurokinin-1 receptor antagonist; aprepitant

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1. Introduction

Many in vitro and in vivo experiments have demonstrated the fundamental roles that peptides and their receptors play in cancer progression [1]. After binding to their respective receptors, peptides promote proliferative and antiproliferative effects in cancer cells: the same peptide (e.g., galanin, orexin) can exert both effects in tumor cells (the reason for this being the G protein type and the subtype of receptor involved, for example, galanin 1, 2, and 3 receptors), whereas other peptides (e.g., substance P, neurotensin) mainly induce a proliferative action (oncogenic effect) in many types of tumor cells [2,3]. Accordingly, peptides and receptor antagonists can be used as potential anticancer drugs, although the latter compounds show a higher therapeutic capacity than peptides [4]. This is because peptides generally show poor bioavailability and a short half-life. However, it is essential to emphasize that some strategies are being developed to increase the therapeutic effects of peptides as well as their stability and delivery (e.g., peptide-loaded nanoparticles, peptide cyclization, conjugation of peptide drugs to natural/synthetic polymers, manipulation of the amino acid sequence, cell-targeting peptides, and cell-penetrating peptides) [5,6]. Some cell-penetrating short peptides show an antitumor action, and, in addition, they can also be used to carry anticancer cargo into tumor cells [7]. Indeed, cell-penetrating peptides–cargo complexes (CPP) are valuable for intracellular drug delivery. Different strategies provide safe, effective, and targeted transport without altering the membrane's physicochemical properties [8].

Unfortunately, although large amounts of data support the previously mentioned promising antitumor strategies, no antitumor drug targeting peptidergic systems is currently available in clinical practice. It is inexplicable that the tremendous clinical potential

of peptide receptor antagonists as antitumor drugs has been entirely forgotten by pharmaceutical companies. In preclinical studies, peptide receptor antagonists (e.g., neurokinin-1 receptor antagonists) have shown anti-inflammatory, antiviral, antipruritic, anticonvulsant, anxiolytic, and analgesic effects. Still, unfortunately, these positive effects have not been reported in clinical trials [9,10]. This could be one of the reasons why pharmaceutical companies have not shown much interest in studying the antitumor capacity of peptide receptor antagonists. However, many convincing data show that the use of these antagonists is an encouraging antitumor strategy and that these compounds can be used as broad antitumor drugs because tumor cells overexpress peptide receptors compared to normal cells [11,12] and because peptide receptor antagonists promote apoptotic mechanisms in many types of cancer cells.

The apoptotic capacity promoted by these antagonists also occurs in normal cells but in a significantly lesser proportion [13]. A crucial challenge is to confirm the antitumor effects mediated by peptide receptor antagonists in clinical trials. Hence, repurposing these compounds as anticancer agents is urgently needed since some peptide receptor antagonists are currently used in clinical practice to fight other pathologies but not as antitumor drugs [11,13]. Thus, the repurposing of peptide receptor antagonists as anticancer agents must be developed and potentiated by researchers and clinicians. The beneficial effects of these antagonists would be enormous since tumor cells overexpress peptide receptors and the same antagonist promotes apoptosis in many types of tumors overexpressing the same peptide receptors. In addition, these antagonists could be administered alone or in combination with chemotherapy or radiotherapy [4].

The primary objective of this paper is to explore the various discoveries that have highlighted the role of peptides in the formation and progression of tumors. Additionally, this article aims to shed light on the vast therapeutic possibilities of peptide receptor antagonists as effective and comprehensive antitumor agents. Specifically, the focus is on antagonists that hinder peptides, such as undecapeptide substance P [10], responsible for promoting cell growth in different types of cancers.

2. Applications and Influences

Are there any shared characteristics among tumor cells? Additionally, can one antitumor therapeutic approach effectively combat a range of tumors? The good news is that both queries can now be answered with confidence. One such shared trait prevalent in cancer cells is the overexpression of peptide receptors, a phenomenon not observed in normal cells. This biomarker could also be utilized for diagnosis purposes.

The same antitumor therapeutic strategy could be applied by administering peptide receptor antagonists, which block the proliferative effects of peptides on tumor cells and promote apoptosis, exhibiting a broad anticancer effect against various tumors [11]. What is most needed in order for this to be applied in clinical practice? Why has this antitumor strategy not been used alone or combined with radiotherapy or chemotherapy in clinical practice? This is not due to the lack of preclinical data; on the contrary, there are numerous and reliable published results supporting this assertion; in addition, a case report has been published regarding a patient who had lung cancer and was successfully treated with both radiotherapy and a peptide receptor antagonist (aprepitant, a non-peptide neurokinin-1 receptor antagonist used as an antiemetic in clinical practice) [14].

Several key findings have confirmed the role of peptides in cancer progression. These include the following: (1) peptides promote the growth of various cancer cells, which can contribute to tumor progression; (2) the same peptides can prevent programmed cell death in different types of cancer cells; (3) peptides facilitate the movement of cancer cells, which can lead to metastasis; (4) peptides encourage the growth of endothelial cells, which can contribute to angiogenesis and tumor development; (5) cancer cells produce and release peptides that promote the actions outlined above; (6) the same peptides released by cancer cells can also be produced and released by different cells within the tumor microenvironment, such as immune cells or nerve terminals; (7) the levels of peptides in

the blood are elevated in patients with cancer compared to those in healthy individuals; and (8) the overexpression of peptidergic systems has been linked to cancer development, tumor size, and poor prognoses [15–20]. The microenvironment of a tumor is of utmost importance in the development of cancer as it is near immune cells, and the peptidergic systems regulate the response of these cells. Additionally, nerve cells release peptides in this microenvironment, creating a communication pathway between cancer cells and the released peptides, as shown in Figure 1.

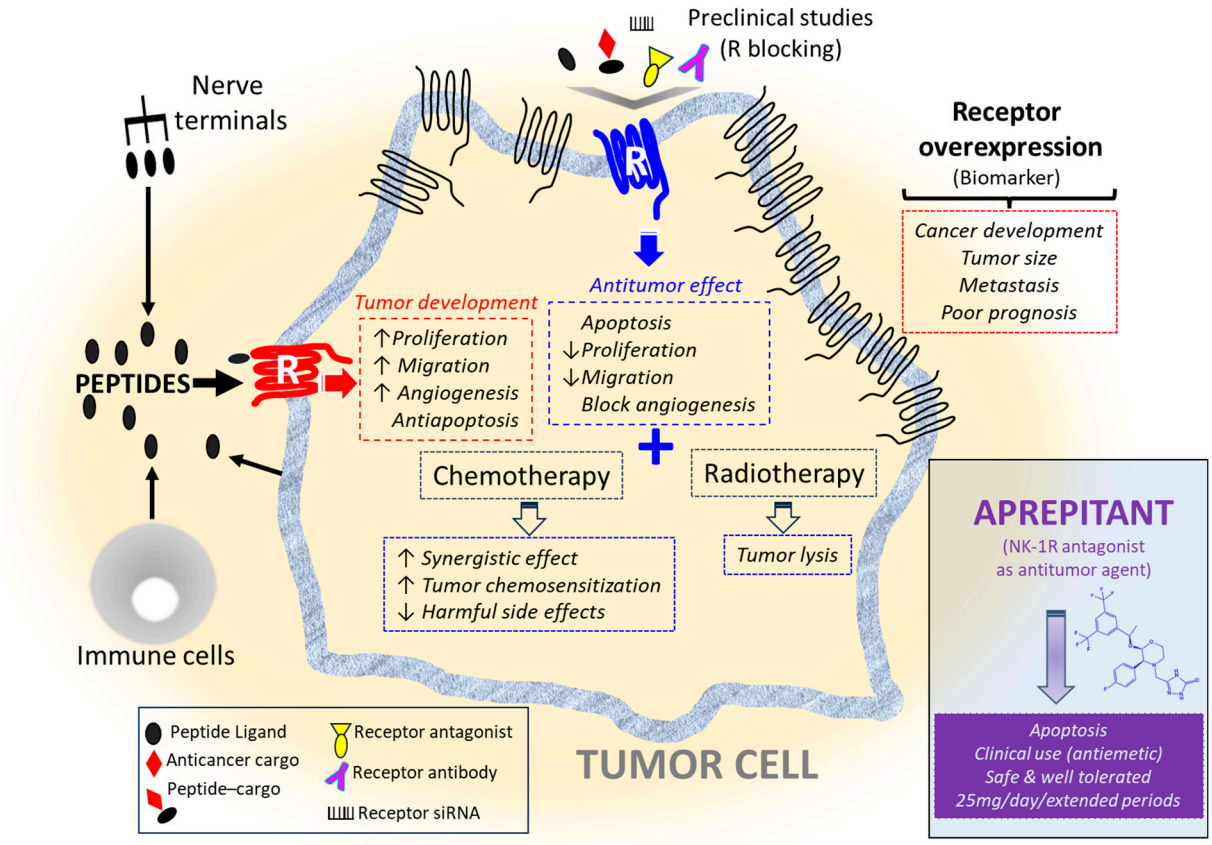

Figure 1. The role of peptidergic signaling in cancer. The overproduction of peptides or the overexpression of peptide receptors can lead to malignant cell transformation and proliferation. To attain favorable results in cancer treatment, receptor-based techniques, including receptor antagonists, receptor siRNA, receptor antibodies, and peptides attached to anticancer agents, can be employed with chemotherapy or radiotherapy. Aprepitant, a neurokinin-1 receptor antagonist, shows promise as a potential candidate for clinical use in combating cell growth and proliferation in various types of cancer.

The foremost vital findings confirming the broad anticancer effect mediated by peptide receptor antagonists are the following [11,13,15,16]: (1) a peptide receptor antagonist blocks the proliferation of different cancer cells mediated by the same peptide as well as the migration of tumor cells and metastasis; (2) the same peptide receptor antagonist favors apoptosis in many different tumor cells showing a ubiquitous antitumor effect; (3) peptide receptor antagonists inhibit angiogenesis, abrogating tumor development; and, (4) in general, these antagonists are safe and well tolerated. In sum, these antagonists generally exert the opposite actions to those carried out by peptides.

Tumor cells overexpress peptide receptors. Why? Because these receptors mediate many beneficial effects for tumor cells (e.g., proliferation, migration, and anti-apoptotic effect) and because, by overexpressing peptide receptors, tumor cells ensure proliferative and anti-apoptotic peptide-mediated signals. Many data confirm this hypothesis: (1) the use of antibodies directed against specific peptides provokes apoptosis in tumor cells; (2) if

cancer cells do not receive the stimulus mediated by peptides, the synthesis of cell cycle proteins appears to be inhibited in these cells; (3) peptide receptor antagonists, after binding to peptide receptors and blocking the signal mediated by peptides, promote apoptosis in tumor cells; (4) the silencing of the expression of peptide receptors in tumor cells favors apoptotic mechanisms in cancer cells, although this does not occur in normal cells; and (5) the blockade of the expression of peptides in cancer cells does not affect the viability of these cells [11,21,22]. The preceding data clearly show crucial findings: cancer cells become a hostage of their peptidergic signals; these receptors are involved in the viability of cancer cells; and the targeting of peptide receptors surfaces as an effective anticancer strategy by using, for example, peptide receptor antagonists. Moreover, profound knowledge of peptide receptors' oligomerization and dimerization and the epigenetic mechanisms regulating the expression and function of peptidergic systems are also two exciting lines of research for the development of new anticancer strategies, since epigenetic mechanisms have been associated with carcinogenesis and the rate of recurrence [23].

Encouraging preclinical findings promote the use of peptide receptor antagonists as antitumor agents alone, but what about combining peptide receptor antagonists and radiotherapy or chemotherapy? Many preclinical data support the beneficial antitumor effects observed after the application of this combined therapy: (1) the administration of peptide receptor antagonists and chemotherapeutic drugs exerts a synergic antitumor effect, decreases the harmful effects mediated by these drugs, and favors tumor chemosensitization [24]; and (2) a combination therapy of radiotherapy and peptide receptor antagonists has also shown beneficial effects [14,24]. Only a clinical case has been published to date regarding the use of peptide receptor antagonists to treat cancer: the patient had lung cancer, and, after the application of radiotherapy alongside peptide receptor antagonist (the NK-1R antagonist aprepitant), the tumor disappeared following several months of treatment. Importantly, although a high dose of aprepitant was administered (1140 mg/day for forty-five days), no severe side effects were observed, and the patient showed good health, including weight increase [14]. The report concluded that the combination therapy of aprepitant and radiotherapy is an excellent therapeutic approach to treat patients where neither pneumonectomy nor chemotherapy is applicable, just as it had been the case for the mentioned patient [14]. The combination of aprepitant and chemotherapy has been suggested to treat rhabdoid tumors [17], and the antitumor effect of aprepitant alone was lower than that observed following the co-administration of chemotherapeutic drugs and aprepitant [25]. Significant findings have been recently reported: the new combination therapy of cisplatin and aprepitant increased the antitumor efficacy of this treatment against triple-negative breast cancer cells compared to the results reported after applying current therapies against these cancer cells [26]. This opens the door to a new treatment type against breast cancer. Aprepitant also prevented the cardiotoxicity promoted by doxorubicin (an anthracycline used to treat tumors); this is relevant since the clinical use of doxorubicin is limited due to its cardiotoxicity [27]. Thus, according to the results mentioned above, it seems that a combination therapy of aprepitant and chemotherapy will increase the antitumor activity of chemotherapeutic drugs (chemosensitization) and attenuate both chemoresistance and the harmful side effects promoted by chemotherapy (Figure 1).

Peptide antagonists may interfere with cancer mechanisms by impeding multiple routes to access their respective receptor trigger. For example, antagonists may prevent transactivation events, leading to cancer initiation and progression. This is the case for SR48692, a neurotensin receptor antagonist which inhibits RTK (receptor tyrosine kinases) activation and cancer cell growth in vitro. This antagonist also synergized when combined with Gefitinib, a tyrosine kinase inhibitor [28]. Blocking receptors with monoclonal antibodies to treat cancer has been successful, for instance, in the treatment of HER2 (human epidermal growth factor receptor 2)-positive breast cancer. However, drug resistance and adverse side effects have prompted combined therapies with tyrosine kinase inhibitors and antibodies conjugated with cargo antitumoral drugs [29]. Another example of intervention targets protease-activated receptors (PARs), a group of GPCR (G protein-coupled receptors)

activated by a proteolytic mechanism which unmasks a tethered amino acid sequence "hidden" in the extracellular N-terminus domain of the receptor [30]. PARs may be involved in diverse pathologies, including cancer. Hence, preventing proteolysis blocks the action of PARs and their pathological influence on cell function [31]. Exploring receptor peptide homodimerization and heterodimerization is worth it to ascertain the role of receptors' mutual influence on their signaling mechanisms and design procedures to control the process. Recently, it has been reported that neurokinin-2 receptor (NK-2R) heterodimerizes with NK-1R and attenuates NK-1R-dependent responses [32].

3. Arguments in Favor of Using Peptide Receptor Antagonists as Antitumor Drugs

What measures are necessary to utilize peptide receptor antagonists as antitumor agents in clinical settings? Which peptidergic system has been extensively researched and can potentially be applied in clinical practice? The substance P (SP) and neurokinin-1 receptor (NK-1R) system is currently one of the most well-studied systems. Studies have primarily focused on the proliferative and migratory effect of the undecapeptide SP on various human tumor cell lines as well as the broad antitumor action mediated by NK-1R antagonists (such as aprepitant) against different tumors in a concentration-dependent manner [11]. Although most studies have shown the above-mentioned effects of SP and NK-1R antagonists, a few studies have reported that SP did not affect cancer cell proliferation, did not counteract the antitumor impact of NK-1R antagonists, and even produced an antimetastatic action [33–35].

SP is the natural ligand of NK-1R; this receptor belongs to the family of G-protein-coupled receptors and shows seven transmembrane domains containing three extracellular and three intracellular loops. NK-1R is encoded by the *TACR1* gene [36]. Hemokinin-1, a member of the tachykinin family of peptides like SP, is also a natural ligand of NK-1R and favors the proliferation and migration of tumor cells [37,38]. A higher expression of NK-1R has been related to poor prognoses, metastasis, tumor size, and cancer stage [39–41]; a higher level of SP has been reported in the plasma of patients with cancer than in healthy individuals [19,20]; the proliferation of tumor cells in these patients increased as the expression of SP increased [42]; and the number of nerve fibers containing SP has been associated with tumor size and lymph node metastasis [43,44]. The previous data demonstrate that the SP/NK-1R system could be used as a predictive factor in cancer. Two isoforms of NK-1R, the full-length and truncated forms, have been described. It seems that tumor cells better respond to NK-1R antagonists when they express a high number of the truncated isoform, and this suggests that the expression rates of both isoforms mediate the efficacy of NK-1R antagonists; in addition, an increased expression of the truncated isoform has been associated with malignancy [45,46]. Importantly, tumor cells express more truncated NK-1Rs than the full-length isoform, and it has been reported that the expression of the latter form is inversely related to invasion, metastasis, and cell mitogenesis [39,47–50]. SP, via NK-1R, controls numerous cell signaling pathways and promotes the synthesis of second messengers, pro-inflammatory cytokines, and the activation of transcription factors [36,51]. NK-1R is involved in the viability of cancer cells but not in normal cells; the expression of SP by tumor cells is not involved in its viability; poor prognosis, tumor malignancy/size, and invasion/metastasis have been associated with a high expression of NK-1R; and SP has been shown to be released from cancer cells, nerve fibers, and immune cells located in the tumor microenvironment [11,22]. The peptide is also present in the bloodstream. The administration of NK-1R antagonists or the silencing of NK-1R in cancer cells, that is, the blockade of NK-1R by means of pharmacological or genetic mechanisms, promotes apoptosis in tumor cells. This occurs because tumor cells no longer receive the beneficial oncogenic stimulus mediated by SP, which means that cancer cells are highly dependent on this stimulus, and, without it, they die by apoptosis. Importantly, this effect does not occur in normal cells.

Some NK-1R antagonists (e.g., aprepitant, fosaprepitant) are used in clinical practice as antiemetics. Tumor cells overexpress NK-1R, which means that a higher dose of antagonist

will have to be administered than that which is used currently in clinical practice as an antiemetic (125 mg, 80 mg, and 80 mg of aprepitant, respectively, distributed over three days). That is, determining the correct/safe dose of aprepitant in clinical practice is now the question to answer, because preclinical experiments have demonstrated the broad antitumor effect of aprepitant [52]. Thus, depending on the size of the tumor overexpressing NK-1R, the dose of aprepitant will vary: a larger size, a higher dose; that is, a more significant number of NK-1Rs, a greater concentration of aprepitant. In this sense, it is known that a 100% occupancy of NK-1Rs is needed to obtain an excellent efficacy of NK-1R antagonists [53,54]. The administration of aprepitant reaching $\geq$ 70 μM concentrations induced the maximum inhibition (100%) in many human cancer cells in a study [52]. Thus, the antiemetic drug aprepitant, used in clinical practice, is one of the best NK-1R antagonist candidates to be reprofiled as an antitumor agent and then tested in clinical trials. Clinical trials must be developed to study the antitumor efficacy and tolerability/safety of high doses of aprepitant: this is a great challenge. Moreover, strategies to increase the solubility and efficacy of aprepitant must be improved, because this drug is a poorly water-soluble compound. In addition, some severe effects induced by the drug must be considered, such as the plasma level increase in corticosteroids and some chemotherapeutic drugs (slowed metabolism) and the induction of peripheral neuropathy and febrile neutropenia [55]. The drug aprepitant can affect certain compounds metabolized by the cytochrome P450 CYP34A family of enzymes because the drug acts as an inducer/inhibitor of these enzymes.

Why should we repurpose aprepitant? This is a fast/good strategy to decrease cancer patients' risk because the metabolism, safety, contraindications, side effects, tolerability, and pharmacokinetics of aprepitant are well known [56]. As indicated above, the non-peptide NK-1R antagonist aprepitant (MK-869, L-754,030, Emend) is used in clinical practice as an antiemetic (oral administration; it is safe and well tolerated in general) and exerts, in vitro and in vivo, a broad antitumor effect by inducing apoptosis in many human cancer cells and decreasing the tumor volume or cell count in many types of cancer, such as acute lymphoblastic/myeloid leukemia, breast, prostate, lung, ovarian and cervical cancers, chronic myeloid leukemia, colorectal, esophageal, larynx, pancreatic, urinary bladder and gastric carcinomas, glioblastoma multiforme, hepatoblastoma, melanoma, neuroblastoma, osteosarcoma, retinoblastoma, and rhabdoid tumors [57]. The IC_{50} of aprepitant for normal cells (e.g., fibroblasts, lymphocytes, breast epithelial cells) is much higher than that for cancer cells [5,13], which validates the argument for the safety of aprepitant. Although most of the studies published have shown a higher antiproliferative effect of aprepitant against tumor cells than against normal cells, a study has reported that, although the drug exerted an antitumor action, this action was not selective, equally affecting normal and tumor cells [58]. Aprepitant has many effects: it blocks the invasion of cancer cells, preventing apoptosis; it regulates the expression of numerous genes involved in drug resistance and cell survival; it promotes mild or moderate side effects; it augments the antitumor effect induced by both chemotherapy and radiotherapy; it counteracts the harmful effects mediated by chemotherapeutic compounds; higher doses of it produce no severe side effects; and it has been shown to exert an antipruritic effect and suppress cough in patients with lung cancer (in the two latter studies the doses administered of aprepitant where low, to induce an antitumor effect) [see 56 for review]. Additionally, aprepitant has been shown to enhance the flow of calcium from the endoplasmic reticulum to the mitochondria. It can promote a synergistic antitumor effect when used in conjunction with ritonavir. It also increases the concentration of reactive oxygen species (ROS) in the mitochondria and the expression of apoptotic markers while inhibiting the canonical Wnt pathway and reducing c-myc expression. Furthermore, aprepitant effectively blocks the neurogenic inflammation and cutaneous side effects induced by erlotinib, another antitumor agent which stimulates the release of SP. Notably, the antitumor effect of aprepitant is reduced when the NF-κB pathway is overactivated [25,59–62]. Recently, the administration of aprepitant has been suggested to overcome chemoresistance appearing after chemotherapy; this is important because chemoresistance, favoring cell proliferation and metastasis, is the cause of death

in many patients who have cancer [63,64]. Notably, the SP/NK-1R system regulates the signaling pathways related to chemoresistance (e.g., Notch 1) and the expression of genes (e.g., *HIF1alpha, FOXM1*) involved in poor prognoses, malignancy, cell proliferation, and metastasis [24]. Although NK-1R antagonists (only five of them) are exclusively used as antiemetics in clinical practice, some patents using aprepitant to treat bacterial infection, cardiomyopathy, pruritus, respiratory tract diseases, and cancer have been published (see [65] for a review). The therapeutic potential of these antagonists is minimal to date, but this may change if it is definitively demonstrated in clinical trials that they exert a safe antitumor action.

4. Conclusions and Prospects

Based on the information provided in this paper, sufficient in vitro and in vivo experimental data support conducting clinical trials to clarify the broad antitumor effect demonstrated by peptide receptor antagonists in preclinical studies. Clinical trials must be carried out promptly to determine the efficacy, safety, administration timing, drug–drug interactions, and highest safe anticancer dose of aprepitant. Utilizing a common anticancer strategy with peptide receptor antagonists (specifically, the NK-1R antagonist aprepitant) against numerous tumors is feasible. A universal combination therapy involving aprepitant and chemotherapy or radiotherapy also shows promise. It must be tested particularly in aggressive cancers that currently have limited therapeutic options and, unfortunately, short life expectancies. The importance of the NK-1R receptor has been emphasized, with some experts suggesting that it will play a crucial role in personalized medicine in the future [66].

In-depth basic and clinical studies must be developed to confirm the new antitumor strategy suggested in this paper. If the effectiveness of this strategy is confirmed in clinical trials, we will be facing a new era of medicine against cancer by treating tumors independently of tumor biology/clinical stage. What if all that was needed to exert a universal antitumor action is a dosage of aprepitant? This must be tested, and, in this sense, a dose of 25 mg/kg/day of aprepitant (administered for an extended period, depending on the response to treatment) has been suggested for further studies to observe an antitumor effect in humans [67]. It remains to be confirmed. The SP/NK-1R system participates in many physiological mechanisms and pathologies. The lack of efficacy of aprepitant observed in clinical trials to target other pathologies different from cancer may have been due to the low concentration of the drug tested and the short periods of treatment, and, hence, by increasing the dose of aprepitant and the days of its administration, the expected antitumor effect might be seen in future clinical trials. This phenomenon was observed when aprepitant was tested as an antidepressant: a low dose did not cause an antidepressant effect but a high dose did [68,69]. This could have been due to the many blocked NK-1Rs needed to obtain the specific impact desired (receptor occupancy). Finally, an important point: carcinogenesis has been induced after administering high doses of aprepitant in experimental animals, but it is crucial to comment that the above-mentioned dose of aprepitant (25 mg/kg/day) is very low in comparison to the carcinogenic doses administered in experimental animals (from 125 to 2000 mg/kg/day). First, aprepitant's safe dose/administration time with the maximal antitumor effect must be established in clinical trials. If this is determined in future studies, could this be a universal antitumor strategy (alone or combined with chemotherapy or radiotherapy) against any type of cancer? A total of 28.4 million individuals are expected to have cancer in 2040 [70]. What needs to be done is to look for new therapeutic antitumor procedures. One of these targets the peptidergic systems responsible for cell proliferation, migration, and angiogenesis mechanisms, which are crucial in diagnosing and treating tumors and in their prognosis.

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